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Cognitive Mediators of Adaptive Functioning Outcomes in Survivors of Pediatric Brain Tumors Treated With Proton Radiotherapy

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Abstract

Background: Cranial radiotherapy (RT) is associated with risk for cognitive and adaptive dysfunction. Proton RT (PRT) is a technique hypothesized to spare cognition by reducing exposure to non-target brain tissue. However, little is known regarding functional outcomes in survivors of pediatric brain tumor (BT) treated with PRT. The present study examined the relationship between cognitive and adaptive outcomes in pediatric BT survivors post-PRT.

Methods: Survivors treated with either focal ($n = 33$) or craniospinal (CSI; $n = 37$) PRT completed neurocognitive evaluations approximately 5 years post-treatment. Results of intelligence testing and ratings of adaptive functioning are reported. Mediation models examined the relationship among radiation field, cognition, and adaptive functioning.

Results: The PRT CSI group demonstrated worse cognitive outcomes than the PRT Focal group across each cognitive index (Cohen's $d = .56$ to $.70$). Parent ratings of adaptive functioning were also worse in the PRT CSI group than the PRT Focal group (Global Adaptive Composite, $d = .53$; Conceptual skills, $d = .67$). Cognitive performance fully mediated the relationship between radiation field and adaptive outcomes, while controlling for group differences in tumor histology and RT dose.

Conclusions: Focal PRT survivors demonstrated generally positive outcomes with weaknesses in processing speed and aspects of adaptive functioning. CSI exposure was associated with more

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Conflict of Interest

No authors have any conflicts of interest to declare.

Data Sharing Statement

Research data are not shared.

consistently poor cognitive and adaptive outcomes. The increased risk for adaptive dysfunction in the PRT CSI group appeared due to the effects of CSI on cognition. Efforts to reduce the volume of tissue exposure to RT remain important.

Keywords

brain tumor; proton radiation; adaptive functioning; functional outcome

Introduction

Pediatric brain tumor survivors are at risk for not only suboptimal neurocognitive outcomes but also worsened adaptive functioning (1–3). Adaptive functioning refers to the practical, conceptual, and critical social skills necessary for independent living (4). Poor adaptive functioning has negative implications for future employment, independent living, personal care, and interpersonal relationships. Cranial radiotherapy (RT), and craniospinal irradiation (CSI) in particular, are associated with neurocognitive “late effects,” including declines in full scale IQ as well as attention, working memory, and processing speed (3, 5–6). However, relatively little is known regarding the effects of radiation, particularly proton radiation, on adaptive functioning and, to a lesser extent, the association of adaptive functioning with neurocognitive outcomes.

Weaknesses in adaptive functioning have been consistently documented among survivors of pediatric brain tumors (2, 7–9). Even when adaptive functioning has been reported to fall within a normative range, performance has differed significantly from healthy controls, normative means, and rates of impairment expected in the general population (1, 10–13). A number of clinical variables have been associated with worse adaptive functioning outcomes, including tumor size and location, age at diagnosis, time since treatment, and exposure to RT (7, 11, 14). Additionally, there is initial evidence within the broad pediatric literature to suggest that the relationship between clinical risk factors and adaptive outcomes may be mediated by cognitive functioning (15–17).

Advances in radiotherapy (e.g., intensity modulated RT, particle therapy) have the promise to optimize treatment outcomes while minimizing undesired side effects in pediatric brain tumor survivors. Compared to conventional photon (or x-ray) RT (XRT), proton RT (PRT) has been hypothesized to spare cognitive abilities by reducing radiation exposure to non-target brain tissue. Early findings, thus far, appear promising for potential benefits of PRT compared to modern XRT techniques in terms of preservation of neurocognitive function (18–24). However, because of the historically limited availability of PRT, the literature on adaptive outcomes following PRT is sparse. In the only published study we identified, Pulsifer and colleagues (25) reported on a diagnostically heterogeneous sample of pediatric brain tumor patients treated with PRT (n=155). They found adaptive functioning to fall within the average range at baseline and at three years post-PRT with no significant change in functioning over time. Worse adaptive functioning at baseline was associated with hydrocephalus and sensorimotor deficits. Adaptive and IQ scores were correlated at baseline.

The aim of the current study was to examine cognitive and adaptive outcomes in a diverse cohort of pediatric brain tumor survivors treated with PRT. Specifically, we hypothesized that individuals treated with CSI PRT were at an increased risk for adaptive dysfunction relative to those treated with focal PRT, consistent with the broader literature on XRT and cognition. We also explored whether cognitive functioning would mediate the association between radiation field (CSI or focal) and adaptive outcomes.

Methods

Participants and procedures

Data presented here are part of a larger study investigating long-term neurocognitive outcomes in pediatric brain tumor survivors. The study was approved by the Institutional Review Board (IRB). Eligible study participants were identified by medical chart review and consecutively enrolled. Written informed consent was obtained prior to participation.

Eligible survivors were between the ages of 5 and 20 with a history of a brain tumor treated with PRT at least one year prior to enrollment and with no evidence of active disease. All patients spoke either English or Spanish. Patients diagnosed with brain stem gliomas, high-grade gliomas, and atypical teratoid/rhabdoid tumors were excluded from participation due to our interest in long-term outcomes. The present study describes outcomes of 70 identified survivors with completed measures of adaptive functioning and neuropsychological testing at a single time point between 2011 and 2017.

Measures

Wechsler Intelligence Scale—Participants were administered the age-appropriate Wechsler Scales of Intelligence (26–31) in English or Spanish. Performance yields five summary scores. The Verbal Comprehension Index (VCI) assesses verbal reasoning skills and involves tasks such as defining vocabulary terms and explaining how two concepts are alike. The Perceptual Reasoning Index (PRI) assesses visual-spatial and picture-based reasoning skills and involves recreating block designs and identifying patterns. The Working Memory Index (WMI) assesses brief attention and short-term memory and involves remembering and sequencing auditory and visual information. The Processing Speed Index (PSI) assesses speeded responses on tasks requiring visual scanning and motor responses. Finally, performance across all measures is summarized by the Full Scale IQ (FSIQ) score. Scores are reported as age-corrected standard scores with a mean (*M*) of 100 and a standard deviation (*SD*) of 15; lower scores represent worse performance.

Adaptive Behavior Assessment System—Adaptive functioning was assessed using the *Adaptive Behavior Assessment System, Second Edition (ABAS-II; 32)* or *Third Edition (ABAS-3; 33)*. The two editions are highly correlated with corrected *r* values across adaptive domains ranging from .83 to .88 (33). The *ABAS* is a standardized, written questionnaire intended to be completed by parents or caregivers that measures adaptive behaviors necessary for independent functioning across home, school, and community settings. It is published in English and Spanish for ages 0 to 89 years. Nine subscales are summarized across four composite scores, including the Global Adaptive Composite (GAC), Conceptual

Domain, Social Domain, and Practical Domain. The Conceptual Domain summarizes skills related to communication, self-direction, and functional academics. The Social Domain summarizes skills related to social and leisure functioning. The Practical Domain summarizes skills related to community use, home living, health and safety, and self-care. Lower standard scores ($M = 100$, $SD = 15$) represent weaker adaptive behaviors and reduced functional independence.

Statistical Analyses

The demographic and medical characteristics of survivors treated with CSI or focal PRT were compared using t tests and chi square analyses. Performance on cognitive tests and ratings of adaptive functioning were compared across the PRT CSI and Focal groups using independent groups t tests. One-sample t tests were also used to compare cognitive performance and adaptive functioning to each measure's respective normative mean. Pearson correlations were used to identify significant relationships between cognitive and adaptive outcomes. Finally, mediation models were used to assess whether radiation field had a direct effect on adaptive functioning or was instead mediated by cognitive performance.

A mediation hypothesis can be tested using a series of three regression models describing the relationship among independent, dependent, and mediating variables (See Figure 1; 34). In the current study, the independent variable was defined as radiation field (i.e., CSI or focal PRT). The dependent variables were adaptive functioning outcomes measured by the *ABAS* index scores, and the mediating variables were cognitive performance across Wechsler index scores. The three regression models are completed in sequential order.

1. The first regression model (path c) determines whether the independent variable (PRT radiation field) is a significant predictor of the dependent variable (adaptive functioning). If there is not a significant relationship, the analysis ends; if there is a significant relationship, a second regression is run.
2. The second regression model (path a) assesses the relationship between the independent variable and the mediating variable (i.e., PRT radiation field and cognitive functioning). Again, if there are no significant findings, the analysis ends; otherwise, a third and final regression model is run.
3. The third model (paths b and c') includes both the independent and mediating variables predicting the dependent variable (adaptive functioning).

Mediation is said to have occurred if, in the third model, PRT radiation field is no longer a significant predictor of adaptive functioning. All regression models in the current study included covariates, which were identified as demographic and medical variables that differed between the PRT CSI and PRT Focal groups.

We corrected for multiple comparisons using the false discovery rate (FDR) approach and set the FDR threshold at 5%. Associations with p values < 0.05 but nonsignificant FDR values are reported as statistical trends. Effect sizes are reported for all comparisons. The following conventions were used to interpret small, medium, and large effect sizes: Cohen's d (0.2, 0.5, 0.8), Cramer's V (0.1, 0.3, 0.5), and r (0.1, 0.3, 0.5) (35).

Results

Demographic and clinical characteristics of the sample are reported in Table 1. The sample was balanced with respect to the number of survivors treated with CSI ($n = 37$) versus Focal ($n = 33$) PRT. At the time of evaluation, survivors were a mean age of 12.84 years old (range: 5.07–20.94 years) and were 5.40 years post-PRT (range: 1.16–9.89 years). Fifty percent of the sample was White, 30% Hispanic/Latino, 13% Black, and 7% Asian. Spanish was the primary language of five survivors (7.14%) and 11 parents completing questionnaires (15.71%). There were no significant differences on any adaptive functioning domains between parent reporters who spoke English vs. Spanish (all $p > 0.05$). Similarly, there were no significant differences between Spanish- and English-speaking patients on cognitive index scores (all $p > 0.05$).

The PRT CSI and PRT Focal groups were similar for age at diagnosis, treatment, and time of evaluation (all $p > .05$). Similarly, there were no group differences in sex, time from treatment to evaluation, tumor location (supratentorial vs. infratentorial), impaired functional status at the first clinic visit following diagnosis (e.g., Lansky/Karnofsky score), tumor diameter, history of craniotomy, or history of shunt (all $p > .05$).

As expected, tumor histology varied significantly between the PRT CSI and PRT Focal groups ($\chi^2(5) = 46.07, p < .001$). The proportion of medulloblastoma/PNET tumors was greater in the PRT CSI group, while the proportion of gliomas, ependymomas, and craniopharyngiomas was greater in the PRT Focal group. Additionally, survivors within the PRT CSI group received a significantly higher radiation dose than those in the PRT Focal group ($U = 911.50, z = 3.65, p < .001, r = .82$). There was a trend toward group differences on race/ethnicity ($\chi^2(3) = 7.88, p = .049$), with a higher proportion of White patients represented in the PRT Focal group (67%) compared to the PRT CSI group (35%).

Cognitive Functioning

Cognitive outcomes by group are reported in Table 2. Across all cognitive index scores, performance in the PRT CSI group was worse than normative expectations: FSIQ ($t(32) = -4.60, p < .001$), VCI ($t(33) = -3.52, p = .001$), PRI ($t(33) = -2.40, p = .022$), WMI ($t(32) = -3.87, p = .001$), and PSI ($t(31) = -9.00, p < .001$). Similarly, PRT CSI group means were lower than PRT Focal group means across all indexes: FSIQ ($t(64) = 2.84, p = .006$), VCI ($t(65) = 2.64, p = .010$), PRI ($t(65) = 2.57, p = .013$), WMI ($t(61) = 2.21, p = .031$), and PSI ($t(63) = 2.61, p = .011$). In contrast, performance in the PRT Focal group did not differ from normative expectations across any index except PSI ($t(32) = -4.73, p < .001$).

Adaptive Functioning Outcomes

Adaptive functioning outcomes by group are reported in Table 3. Across all adaptive index scores, performance in the PRT CSI group was worse than normative expectations: GAC ($t(36) = -5.30, p < .001$), Conceptual ($t(36) = -4.84, p < .001$), Social ($t(36) = -4.30, p < .001$), Practical ($t(36) = -5.41, p < .001$). Additionally, PRT CSI group means were lower than PRT Focal group means across the following indexes: Global ($t(68) = 2.21, p = .030$) and Conceptual ($t(68) = 2.78, p = .007$). Within the PRT Focal group, performance was

worse than normative expectations across the GAC ($t(32) = -2.51, p = .018$) and Practical ($t(32) = -2.89, p = .007$) indexes and trended toward below normative performance on the Social index ($t(32) = -2.04, p = .049$).

Correlations between cognitive performance and *ABAS* ratings by group are shown in Table 4. In both the PRT CSI and PRT Focal groups, performance on all cognitive domains was significantly correlated with global, conceptual, social, and practical adaptive functioning outcomes, with one exception. Within the PRT Focal group, working memory was not correlated with Practical adaptive outcomes. The strongest associations were between FSIQ and Conceptual adaptive skills (PRT CSI: $r = .705, p < .001$; PRT Focal: $r = .686, p < .001$) and verbal reasoning and Conceptual adaptive skills (PRT CSI: $r = .701, p < .001$; PRT Focal: $r = .672, p < .001$).

Mediation Analyses

The relationships among medical and demographic characteristics, adaptive outcomes, and cognitive performance were further explored using mediation models. An *a priori* decision was made to use radiation field (CSI vs. Focal) as the predictor of adaptive functioning. Medical and demographic variables were included as covariates if there were significant differences between the PRT CSI and Focal groups. Based on this criteria, covariates included tumor histology and PRT dose.

Radiation field was a significant predictor of Global ($B = -11.00, p = .044$) and Conceptual ($B = -12.49, p = .013$) adaptive skills, but not Social ($B = -6.20, p = .202$) or Practical skills ($B = -10.14, p = .073$). Consequently, mediation analyses were only completed using Global and Conceptual adaptive domains as dependent variables. Mediating variables included each Wechsler index score (i.e., FSIQ, VCI, PRI, WMI, and PSI).

Table 5 summarizes the results of mediation models. All models resulted in successful mediations; inclusion of cognitive test performance mediated the relationship between radiation field and adaptive functioning outcomes in every analysis, regardless of the domain of cognitive functioning.

Discussion

This study examined cognitive and adaptive functioning outcomes in a sample of 70 pediatric brain tumor survivors approximately 5-years post-PRT. Overall, survivors receiving focal PRT demonstrated generally positive outcomes, with cognitive and adaptive skills falling broadly within normal limits. The PRT Focal group demonstrated some areas of mild weakness in specific cognitive and adaptive domains. Cognitively, processing speed was a relative weakness. Adaptively, while all scores were within one standard deviation from the mean, relative difficulties were noted specifically with respect to practical and social skills.

In contrast to broadly preserved skills within the PRT Focal group, the PRT CSI group demonstrated more consistent weaknesses. Within the PRT CSI group, all cognitive and adaptive outcomes were significantly worse than normative expectations. Additionally, all cognitive variables and global adaptive skills were found to be significantly worse than

survivors within the PRT Focal group. These results are consistent with the broader literature on radiation treatment in pediatric brain tumor survivors and support our hypothesis that individuals treated with CSI PRT are at an increased risk for cognitive and adaptive dysfunction relative to those treated with focal PRT.

Somewhat unexpectedly, the PRT CSI and Focal groups did not differ across all adaptive skills domains. The PRT Focal group demonstrated relative weaknesses related to practical and social skills, and these same areas did not differ statistically from individuals with a history of CSI. Results suggest that all survivors treated with PRT demonstrate some adaptive risk, regardless of radiation field. However, relatively preserved cognitive skill in individuals receiving focal PRT may serve as a protective factor for more cognitively-based adaptive skills (e.g., communication, functional academics, and self-direction).

Results of mediation analyses support a close relationship between cognitive and adaptive outcomes. Mediation models demonstrated that the increased adaptive risk experienced by individuals receiving CSI rather than focal PRT may be due to the negative effects of CSI on cognition. These findings emphasize the continued importance of efforts to reduce the volume, or dose, of radiation to normal brain tissue. Other variables associated with adaptive dysfunction included younger age at the start of PRT, a history of shunt placement, and a Black/African American racial background. The ability to accurately interpret or generalize findings regarding racial/ethnic background is limited given small sample sizes (Black/African American $n = 9$).

There is limited information regarding adaptive functioning outcomes following PRT in pediatric brain tumor survivors. In the one prior study, adaptive skills were reported to be within the average range three years post-PRT with no significant difference across radiation fields (25). In contrast, results from the current study examining outcomes five years post-PRT on average suggest a higher risk for adaptive dysfunction. Additionally, global adaptive outcomes differed significantly based on radiation field, with survivors who received CSI PRT demonstrating worse outcomes. Divergent findings across studies may be due, in part, to differing measures and/or sampling differences. The sample described by Pulsifer and colleagues (25) was predominantly Caucasian and of a relatively high socioeconomic status, which may have contributed to a higher level of baseline cognitive and adaptive functioning. In contrast, the current study involves a more diverse sample with extended follow-up. In both studies, a close relationship between cognitive and adaptive functioning was described. Given the neurocognitive risks associated with RT, including PRT, and the association between cognitive and adaptive outcomes, it will be important for future studies to continue to investigate and describe adaptive outcomes post-PRT.

While our findings contribute to a better understanding of the functional impact of PRT in the pediatric brain tumor population and suggest generally favorable adaptive outcomes particularly for the focal PRT group, it remains unknown whether these outcomes differ from those experienced by survivors treated with modern photon approaches (e.g., intensity-modulated RT). It is challenging to compare our findings directly to historical reports from photon samples because of differences in instrumentation, sample characteristics (e.g., length of follow-up), and sampling method (e.g., most studies do not report outcomes

separately for focal and CSI groups or for irradiated and non-irradiated groups). Well designed, prospective comparative outcomes research is needed to determine the relative benefits of PRT compared to XRT.

This study is unique in our inclusion of Spanish-speaking patients and parents, a group often excluded from outcomes research in this population. While our Spanish-speaking subgroup was small, we did not find differences in outcomes between Spanish- and English-speaking patients (or parents) on cognitive or adaptive outcomes. Consideration of language and culture is important in the examination of late effects (36–37). Larger studies with samples that include more racial, ethnic, and cultural diversity are essential to gain a more comprehensive understanding of outcomes and risks in the pediatric brain tumor population.

The current study adds to the literature on outcomes in pediatric brain tumor survivors treated with PRT by describing both cognitive and adaptive functioning across an extended follow-up period of five years. Results demonstrated that cognitive dysfunction likely mediates the relationship between clinical risk factors and adaptive dysfunction. Future directions include determining with greater specificity which aspects of cognition are most closely related to adaptive risk. In the current study, all cognitive variables mediated the relationship between radiation field and adaptive functioning. With a larger sample size, it may become clearer whether specific skills (e.g., processing speed) are differentially influential. The relationship between cognitive functioning and adaptive functioning outcomes reinforce the importance of the Children's Oncology Group long-term follow-up guidelines recommending cognitive surveillance for pediatric brain tumor survivors (38). Additionally, our findings suggest adaptive functioning assessment should be part of this surveillance for all pediatric brain tumor patients post-RT, regardless of RT modality.

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Abbreviations Key

RT	Radiotherapy
XRT	X-ray or photon radiotherapy
PRT	Proton radiotherapy
CSI	Craniopsinal irradiation
VCI	Verbal Comprehension Index
PRI	Perceptual Reasoning Index
WMI	Working Memory Index
PSI	Processing Speed Index
FSIQ	Full Scale IQ

ABAS-II or ABAS-3	Adaptive Behavior Assessment System, 2 nd Edition or 3 rd Edition
GAC	Global Adaptive Composite
FDR	False discovery rate

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Visual representation of mediation models and pathways

A mediation model can be tested using three regression analyses. The first regression tests path c , which represents the total effect of an independent variable (i.e., PRT field: CSI or Focal) on a dependent variable (i.e., adaptive functioning). If there is a significant relationship, a second regression tests path a . Path a represents the effect of the independent variable on a mediating variable (i.e., cognitive performance). If this is also significant, a third regression is run to simultaneously test paths b and c' . Path c' represents the direct effect of the independent variable on the dependent variable, when controlling for mediating variables. Mediation has occurred with path c' is no longer significant.

TABLE 1

Demographics and clinical characteristics

	PRT CSI (n = 37)		PRT Focal (n = 33)		p	V
	n	%	n	%		
Sex					.518	.077
Male	23	62	18	55		
Female	14	38	15	45		
Race/Ethnicity					.049 [†]	.336
White	13	35	22	67		
Hispanic/Latino	13	35	8	24		
Black	7	19	2	6		
Asian	4	11	1	3		
Histology					<.001 [*]	.811
Glioma	1	4	14	42		
Medulloblastoma/ PNET	25	68	3	9		
Ependymoma	0	0	8	24		
Germ Cell Tumor	8	22	2	6		
Craniopharyngioma	0	0	5	15		
Other	3	8	1	3		
Tumor Location					.168	.226
Supratentorial	15	41	19	58		
Infratentorial	22	59	13	39		
Craniotomy					.811	.029
Yes	33	89	30	91		
No	4	11	3	9		
Shunt					.130	.181
Yes	14	38	7	21		
No	23	62	26	79		
Lansky/Karnofsky score, 70 ^a					.079	.222
Yes	12	36	5	17		

<u>PRT CSI (n = 37)</u>			<u>PRT Focal (n = 33)</u>			V
n	%		n	%	p	
No	21	64	25	83		
<u>PRT CSI (n = 37)</u>			<u>PRT Focal (n = 33)</u>			r
Mdn	Range		Mdn	Range	<i>b</i> <i>p</i>	
Total Radiation Dose to Tumor (cGy)						
54	45–55.8		50.4	45–60	<.001*	.82
M	SD		M	SD	p	d
Tumor Diameter (cm)						
4.90	1.81		4.55	1.70	.415	0.20
Age at Diagnosis (years)						
7.50	3.95		5.99	4.12	.123	0.37
Age at Treatment (years)						
7.80	3.93		7.04	4.24	.440	0.19
Age at Evaluation (years)						
13.00	3.76		12.67	4.78	.743	0.08
Time from RT to Evaluation (years)						
5.20	2.76		5.63	2.49	.504	0.16

Note. PRT = proton radiotherapy. CSI = craniospinal irradiation; *d* = Cohen's d. PNET = primitive neuroectodermal tumor. V = Cramer's V, effect size for associations among categorical variables.

^aThis value represents the Lansky or Karnofsky score at the first clinic visit following surgical resection, or, if no surgery occurred, the score at the first clinic visit following a brain tumor diagnosis.

^bMann-Whitney significance test

* Indicates a statistically significant association ($p < .05$ and FDR $< .05$).

[†] Indicates a trend association ($p < .05$ and FDR $> .05$).

TABLE 2

Cognitive performance outcomes on Wechsler intelligence scales

PRT CSI (<i>n</i> = 37)				PRT Focal (<i>n</i> = 33)				<u>CSI vs. Focal</u>		
M	SD	Range	CSI vs. Norm <i>p</i>	M	SD	Range	Focal vs. Norm <i>p</i>	<i>p</i>	<i>d</i>	
FSIQ	85.30	18.36	42–127	<.001 *	97.76	17.22	44–134	.460	.006 *	0.70
VCI	88.79	18.57	50–119	.001 *	99.42	13.99	57–132	.815	.010 *	0.65
PRI	90.88	22.15	47–147	.022 *	103.67	18.38	55–135	.260	.013 *	0.63
WMI	87.94	17.92	50–116	.001 *	97.60	16.58	52–132	.434	.031 *	0.56
PSI	78.03	13.85	50–105	<.001 *	87.45	15.23	50–116	<.001 *	.011 *	0.65

Note. CSI = craniospinal irradiation. PRT = proton radiotherapy. FSIQ = Full Scale IQ; VCI = Verbal Comprehension Index; PRI = Perceptual Reasoning Index; WMI = Working Memory Index; PSI = Processing Speed Index. *d* = Cohen's *d*.

* Indicates a statistically significant association ($p < .05$ and FDR < .05).

TABLE 3

Adaptive outcomes based on parent ratings on the *ABAS*

	PRT CSI (<i>n</i> = 37)				PRT Focal (<i>n</i> = 33)				CSI vs. Focal	
	M	SD	Range	CSI vs. Norm <i>p</i>	M	SD	Range	Focal vs. Norm <i>p</i>	<i>p</i>	<i>d</i>
GAC	80.85	22.02	41–120	<.001*	91.76	18.90	51–120	.018*	.030*	0.53
Conceptual	83.12	21.25	49–120	<.001*	95.73	15.93	59–120	.133	.007*	0.67
Social	86.86	18.58	55–120	<.001*	93.39	18.58	56–120	.049†	.147	0.35
Practical	80.03	22.47	40–120	<.001*	89.72	20.39	46–120	.007*	.064	0.45

Note. *ABAS* = *Adaptive Behavior Assessment System*; CSI = craniospinal irradiation; GAC = Global Adaptive Composite; PRT = proton radiotherapy. *d* = Cohen's *d*.

* Indicates a statistically significant association ($p < .05$ and FDR $< .05$).

† Indicates a trend association ($p < .05$ and FDR $> .05$).

TABLE 4
Correlations between Wechsler cognitive performance and *ABAS* adaptive outcomes

	GAC		Conceptual Skills		Social Skills		Practical Skills	
	CSI	Focal	CSI	Focal	CSI	Focal	CSI	Focal
FSIQ	.612**	.618**	.705**	.686**	.578**	.576**	.497*	.554**
VCI	.575**	.616**	.701**	.672**	.501*	.581**	.460*	.528*
PRI	.591**	.545**	.644**	.630**	.552**	.528*	.518*	.471*
WMI	.579**	.419*	.632**	.512*	.481*	.450*	.536**	.334
PSI	.522*	.494*	.522*	.481*	.393*	.383*	.536*	.544**

Note. *ABAS* = *Adaptive Behavior Assessment System*; CSI = craniospinal irradiation; GAC = Global Adaptive Composite; FSIQ = Full Scale IQ; VCI = Verbal Comprehension Index; PRI = Perceptual Reasoning Index; WMI = Working Memory Index; PSI = Processing Speed Index.

* Indicates a statistically significant association ($p < .05$ and FDR $< .05$).

** Indicates a statistically significant association ($p < .001$ and FDR $< .05$).

Cognitive mediators of the relationship between radiation field and the *ABAS* Global Adaptive Composite and Conceptual Skills Domain

TABLE 5

	Path <i>a</i> PRT Field → Cognition		Path <i>b</i> Cognition → Adaptive Skills		Path <i>c'</i> PRT Field → Adaptive Skills	
	B	<i>p</i>	B	<i>p</i>	B	<i>p</i>
FSIQ	-13.05	.008*				
GAC			0.67	<.001**	1.55	.722
Conceptual			0.71	<.001**	0.05	.989
VCI	-11.16	.013*				
GAC			0.70	<.001**	-0.32	.943
Conceptual			0.77	<.001**	-1.55	.674
PRI	-12.73	.021*				
GAC			0.57	<.001**	-1.99	.668
Conceptual			0.59	<.001**	-3.45	.393
WMI	-10.57	.028*				
GAC			0.57	<.001**	-2.79	.554
Conceptual			0.60	<.001**	-3.65	.383
PSI	-10.40	.008*				
GAC			0.70	<.001**	0.81	.863
Conceptual			0.65	<.001**	-1.56	.715

ABAS = *Adaptive Behavior Assessment System*; PRT = proton radiotherapy; GAC = Global Adaptive Composite; FSIQ = Full Scale IQ; VCI = Verbal Comprehension Index; PRI = Perceptual Reasoning Index; WMI = Working Memory Index; PSI = Processing Speed Index; B = unstandardized regression coefficient

Note. Paths *a*, *b*, and *c'* represent the three regression models used in each mediation analysis. Path *a* describes the relationship between radiation field (PRT CSI vs. PRT Focal) and the Wechsler index score. Path *b* describes the relationship between the Wechsler index score and *ABAS* adaptive outcomes. Path *c'* describes the relationship between radiation field and *ABAS* adaptive outcomes, when cognitive performance is included in the model. Mediation has occurred when the relationship represented by Path *c'* is no longer statistically significant. Covariates included in all regression models were tumor histology and total RT dose.

* Indicates a statistically significant association ($p < .05$ and FDR < .05).

** Indicates a statistically significant association ($p < .001$ and FDR < .05).