Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2015 October 1; 93(2): 400–407. doi:10.1016/j.ijrobp.2015.06.012.

Early Cognitive Outcomes following Proton Radiation in Pediatric Patients with Brain and CNS Tumors

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Abstract

Purpose—Proton radiation therapy (PRT) offers the potential of effective treatment with minimal irradiation to normal tissue, mitigating late effects in children requiring radiotherapy for brain tumors. This longitudinal study reports cognitive outcome in pediatric patients treated with PRT for central nervous system (CNS) tumors.

Methods and Materials—Sixty patients receiving PRT for medulloblastoma (38.3%), gliomas (18.3%), craniopharyngioma (15.0%), ependymoma (11.7%), and other CNS tumors (16.7%) were administered age-appropriate measures of cognitive abilities at or near PRT initiation (baseline) and afterwards (follow-up). Patients were 6 years at baseline to ensure consistency in neurocognitive measures.

Results—Mean age was 12.3 years at baseline; mean follow-up interval was 2.5 years. Treatment included prior surgical resection (76.7%) and chemotherapy (61.7%). PRT included craniospinal irradiation (46.7%) and partial brain radiation (53.3%). At baseline, mean Wechsler Full Scale IQ (FSIQ) was 104.6; means of all four Index scores were also in the average range. At follow-up, no significant change was observed in mean FSIQ, Verbal Comprehension, Perceptual Reasoning/Organization, or Working Memory. However, Processing Speed scores declined significantly (mean 5.2 points), with a significantly greater decline for subjects < 12 years at baseline and those with the highest baseline scores. Cognitive outcome was not significantly related to gender, extent of radiation, radiation dose, tumor location, histology, SES, chemotherapy or history of surgical resection.

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Conflict of Interest: Actual or potential conflicts of interest do not exist for any other author.

Presented at the American Society of Clinical Oncology, June 6, 2010, Chicago, Illinois; International Society of Paediatric Oncology, London, England, October 5, 2012; Nordic Symposium in Pediatric Proton Therapy, June 3, 2014.

Conclusions—Early cognitive outcomes following PRT for pediatric CNS tumors are encouraging, compared to published outcomes from photon RT.

Keywords

Pediatric brain tumors; Proton beam radiation; IQ; Processing speed

Introduction

Radiation therapy (RT), while part of the standard of care for many pediatric CNS tumors, is associated with negative cognitive sequelae, including decrements in overall intelligence quotient (IQ) and in specific cognitive and academic domains.^{1,2} Of particular note are declines in certain components of the overall IQ, including processing speed.^{3,4} The severity of such impairments has been associated with the dose and the volume of brain irradiated.^{5,6} Age at treatment is also an important factor, with younger patients being most affected and older patients sometimes showing little or no long-term impairment.^{4,7–10} The special vulnerability of younger patients could be due to the effects of radiation on cerebral white matter, which is rapidly developing in young children; such effects could well mediate most of the age dependence.^{10–12} Photon radiotherapy techniques have been improved with CT and MRI based planning and intensity modulation.^{5,6,13} However, long-term effects of radiation therapy remain a significant concern that could have a major influence on treatment decisions.¹⁴

Proton radiation therapy (PRT) is the most conformal form of radiotherapy available, sparing adjacent healthy tissues by reducing entrance dose and eliminating exit dose.^{15,16} Early reports of PRT in pediatric CNS tumors have found acceptable disease control and reduced endocrine and auditory toxicity;^{17–20} some promising reports of cognitive outcome have recently appeared,^{18–20} but as yet there have been no detailed reports of cognitive outcome following PRT in a large group, leaving an important gap in the literature.^{14,21}

Here, we report cognitive outcomes in a large cohort of pediatric patients with brain tumors (and one metastatic myxopapillary ependymoma) who had both baseline and follow-up evaluations at our institution after PRT. In order to obtain a sensitive indicator of cognitive outcome, the study examined changes both in overall intellectual functioning (Full Scale IQ, or FSIQ) and in its four components: Verbal Comprehension, Perceptual Reasoning/Organization, Working Memory, and Processing Speed. Because measures of all four cognitive domains are not widely available before age six years, study subjects were limited to age six and older. Outcomes are compared to published results for patients treated with photon radiation therapy.

Material and Methods

Patients and Procedures

Between September 2002 and March 2013, 106 pediatric patients were treated with PRT at XXXX for a primary brain or other CNS tumor and completed baseline and follow-up neurocognitive testing at XXXX as part of their routine clinical care. Patients came for

treatment from locations throughout the United States. Those with prior radiation or combined proton and photon treatments were excluded. Of the 106 patients, 37 were excluded due to young age (< 6 years); two due to disease recurrence at follow up, and seven due to incomplete baseline evaluation, because of scheduling difficulties (2), fatigue (3), or severe posterior fossa syndrome (2). The remaining 60 patients comprise the cohort in the study. Institutional Review Board approval was obtained for this longitudinal study of pediatric patients.

Patients were treated with proton radiation, surgery, and chemotherapy appropriate for the diagnosis and according to the current standard of care. Proton radiation dose is reported in Gy (RBE), using a relative biologic effectiveness of 1.1.^{22,23} All radiation was delivered with standard fraction sizes of 1.8 Gy (RBE) per fraction (or 1.5 Gy/fx for germinomas) in accordance with the national standard set by Children's Oncology Group protocols for target coverage.

All medulloblastoma patients received whole brain radiation, defined as craniospinal irradiation (CSI) followed by a boost to the tumor site in the posterior fossa, for a total dose of 54 Gy (RBE). Patients with craniopharyngioma, low-grade glioma, and ependymoma received radiation to the tumor site alone (partial brain radiation). Patients with germ cell tumors (N = 9) were treated with either CSI (N = 4) or partial brain radiation including a whole ventricle volume (N = 5) followed by a boost to the tumor site. Radiation treatment for all patients followed the standard protocol for our center, which includes CT and MRI-based planning utilizing proton XiO software to generate passively scattered three-dimensional (3D) conformal proton treatment plans.²³

Cognitive Assessment

Cognitive assessment was conducted at initiation of or during the course of proton radiation therapy (baseline) and at one or more scheduled outpatient visits at least one year after completion of radiation treatment (follow-up). When there were multiple follow-up evaluations, the latest results were used for analysis. Testing was done using either the Wechsler Intelligence Scale for Children-4th Edition (WISC-IV)²⁴ (ages 6–15 years) or the Wechsler Adult Intelligence Scale-3rd Edition (WAIS-III)²⁵ (ages 16 years). Both instruments yield Index scores in four cognitive domains: Verbal Comprehension (factual information, verbal knowledge, conceptualization); Perceptual Reasoning/Organization (visual-perceptual and nonverbal skills); Working Memory (including attention and concentration); and Processing Speed (mental and graphomotor processing speed). The four Index scores combine to form the FSIQ, a measure of overall cognitive functioning. The FSIQ and Index scores are age-based standard scores (SS) with a mean of 100 and a standard deviation of 15; lower scores indicate lower functioning or greater problems.

Statistics

Chi-square analysis and one-way analysis of variance (ANOVA) were used to evaluate differences between demographic and clinical variables at baseline. Paired t-tests were conducted to identify whether scores changed significantly between baseline and follow-up assessments. Repeated measures ANOVA was used to determine if cognitive outcome was

affected by gender, age at baseline (< 12 years vs. ≥ 12 years), median household income in community of residence²⁶ (a proxy indicator of socioeconomic status, or SES), hydrocephalus at diagnosis, histology, tumor location, extent of radiation (whole or partial brain radiation), CSI low dose (< 23.4 Gy) vs. high dose, treatment with chemotherapy, history of surgical resection, and presence of sensory or motor problems at follow-up. Pearson correlation was used to investigate the relationship between cognitive outcome and the time interval between baseline and follow-up. Statistical analyses were performed using SPSS version 22.0. All reported *p* values used two-tailed significance with α (alpha) set at 0.05.

Results

Demographic and clinical characteristics are summarized in Table 1. Chemotherapy as part of treatment (always completed before follow-up testing) included vincristine, cyclophosphamide, cisplatin, carboplatin, etoposide, and lomustine.

For the 28 subjects treated with CSI, the median CSI dose was 23.4 Gy (RBE) (range, 18.0 – 36.0 Gy (RBE)) and the median total dose was 54.0 Gy (RBE) (range, 30.6–54.0 Gy (RBE)); total dose was 54.0 Gy (RBE) for 23 of the 28 CSI patients. Younger patients generally received a lower CSI dose: the mean age of the low dose group was 9.9 years, compared to 14.4 years for the high dose group, a significant difference ($p = .004$). For the 32 subjects treated with partial brain PRT, the median dose was 52.2 Gy (RBE) (range, 35.7–57.6 Gy (RBE)).

No significant relationship was found between age at baseline and any of the following: gender, hydrocephalus at diagnosis, histology, history of surgical resection, treatment with whole or partial brain PRT, tumor location (supratentorial vs. infratentorial) or treatment with chemotherapy. Patients with hydrocephalus at diagnosis were more likely to have an infratentorial tumor ($p = .019$) and to receive whole brain PRT ($p = .017$), in part due to the high incidence of hydrocephalus in medulloblastoma patients (61%, 14/23), all of whom were treated with whole brain PRT.

Results from baseline and follow-up assessments are listed in Table 2 and illustrated in Figure 1. At baseline, all cognitive scores were in the average range (although the mean Processing Speed score was below the population mean). No significant relationship was found between baseline scores and histology, hydrocephalus at diagnosis, history of surgical resection, treatment with chemotherapy, gender, or median household income in the community of residence. At follow-up, FSIQ scores improved for 33 subjects (55%) and declined for 24 subjects (40%). Overall, no significant change was found from baseline to follow-up in FSIQ or in three of the four Index scores, but the mean Processing Speed score declined significantly ($p = .002$), by an average of 5.23 points. Notwithstanding the decline in standard score, raw scores actually increased for the two subtests that comprise the Processing Speed Index (Table 2), indicating that the decline was due not to a loss of skills but rather to a reduced rate of skill acquisition relative to same-age peers.

The greatest declines in Processing Speed were seen in those with the highest baseline score, a pattern noted elsewhere with FSIQ scores.^{27,28} The high-baseline group (Processing Speed Index = 100, N = 25) declined at follow-up by a mean of 14.9 points, whereas the low-baseline group (N = 35) improved by 1.7 points. The number of patients one standard deviation below the population norm (Processing Speed Index < 85) was 20 (33%) at baseline and 21 (35%) at follow-up.

The importance of patient age was investigated by dividing the subjects into two roughly equal groups based on mean age at baseline (12 years). Cognitive results differed by age group in certain areas, both at baseline and at follow-up (Table 3). At baseline, the younger patient group scored significantly higher in FSIQ ($p = .018$), Perceptual Reasoning ($p = .031$) and Processing Speed ($p = .006$). At follow-up, significant changes were seen within age groups in Processing Speed, where the younger group declined by 8.8 points ($p = .001$), and in Perceptual Reasoning, where the older group improved by 4.5 points ($p = .009$). Comparing age groups, significant differences were seen for change in Processing Speed ($p = .015$) and in Perceptual Reasoning ($p = .032$); for FSIQ, no significant change was seen within age groups, and the difference between groups fell just short of statistical significance ($p = .052$).

The time interval between baseline and follow-up was not significantly correlated with the change in Standard Score in any cognitive domain (FSIQ: $p = .072$; Verbal Comprehension, $p = .434$; Perceptual Reasoning/Organization: $p = .052$; Working Memory: $p = .673$; Processing Speed: $p = .311$).

Table 4 shows baseline and follow-up results for both FSIQ and Processing Speed with respect to several factors that have been associated with cognitive outcome following radiation therapy. Cognitive scores did not significantly differ at baseline for any of those factors. At follow-up, no within- or between-group differences were found for change in FSIQ, but there was a significant decline in Processing Speed for certain groups: patients treated with whole brain PRT ($p = .003$); those with infratentorial tumors ($p = .003$) (though note that 23 of the 27 infratentorial patients received whole brain PRT); and those in the CSI low dose group ($p = .008$) (who were on average 4.5 years younger than the CSI high dose group). The groups were not significantly different, however, in terms of change in Processing Speed scores.

No significant relationship was found between change in any of the cognitive scores and the following other variables: histology, hydrocephalus at diagnosis, history of surgical resection, treatment with chemotherapy, the presence of motor or sensory deficits at follow-up, gender, or SES (median household income of community of residence).

Discussion

The present report is the first detailed investigation of cognitive outcome in a large group of pediatric brain and CNS tumor patients treated with PRT. These results follow recent reports of cognitive outcome in much smaller samples following PRT for ependymoma (FSIQ, N =

14)¹⁸ and low-grade glioma (FSIQ, N=12)¹⁹ that found generally preserved functioning, but with some indications of decline for children age <7 years.

Overall, at a mean follow-up of 2.5 years after PRT, no significant change was seen in FSIQ or in the domains of Verbal Comprehension, Perceptual Reasoning/Organization, or Working Memory. However, there was a significant decline, of 5.2 points, in the mean Processing Speed Standard Score. The bulk of that decline was seen in younger patients (age at baseline < 12 years)—the mean score for the younger patient group declined by 8.8 points, whereas that for the older patients declined only slightly. A similar, statistically significant, relationship with age was seen in Perceptual Reasoning/Organization, but in that domain the actual change in scores was quite small. For FSIQ, the difference between age groups approached statistical significance, but there was very little change in scores.

Cognitive outcomes in this cohort did not differ significantly between patients treated with whole brain PRT (CSI) or partial brain PRT. For the 28 patients who received CSI, FSIQ declined non-significantly by a mean of 0.5 points, and in the 23 patients with medulloblastoma (all treated with CSI), the mean change was a decline of 0.1 point. For patients treated with partial brain PRT, FSIQ declined non-significantly by a mean of 0.3 points. Similar (null) results were found in all four cognitive domains, including Processing Speed (Table 4). CSI radiation dose was not significantly related to cognitive outcome in any domain; in fact, Processing Speed scores paradoxically fell by more than twice as much (9.8 points) for the low-dose group as for the high-dose group (though the difference between groups was not statistically significant). A likely explanation is the significantly younger age of the low-dose group (mean of 9.9 years, compared to 14.4 years for the high-dose group), since younger patients generally experienced greater declines in Processing Speed.

The present results for proton radiation compare favorably to earlier reports of the effects of photon RT. Those reports generally show a progressive cognitive decline that is evident at 1–2 years post-treatment and is more severe for younger age, larger volume of radiation, and higher dose.^{1,2} Medulloblastoma studies have estimated annual declines in FSIQ following treatment with photon CSI of between 1.6 and 4.3 points per year, with the better results for older children (age at diagnosis > 7–8 years).^{7,8,28,29} One study derived a quadratic model predicting an overall annual decline in FSIQ of about 2 points per year, manifesting in older children after an age-dependent delay (about 2 years for those with mean age 11 years at diagnosis).²⁷ Other studies have found relative preservation of IQ, particularly for older patients, following photon partial brain RT for low-grade glioma⁹ and ependymoma.³⁰ Some photon RT studies have reported declines in Working Memory,^{1,4} but such declines were not seen here. Reported impairments in Verbal and Performance IQ² cannot be directly compared to the present study because those scores (from the WISC-III) are no longer available in the later edition (the WISC-IV²⁴) used here; however, because the WISC-III Performance IQ includes measures of processing speed, the present results are consistent with reduction in Performance IQ following PRT.

An attractive explanation for the observed stability in cognitive measures is the clear dosimetric advantage of proton radiation.³¹ Merchant et al.³² have used modeling of dose distributions and cognitive data from a cohort of photon RT patients to predict a slower rate

of IQ decline in patients treated with PRT, due to a reduced dose of low (0–20 Gy) and intermediate (20–40 Gy) radiation to the total brain and temporal lobes. For whole brain RT, the relative benefits of proton radiation are driven by reductions in the dose delivered to areas outside of the target volume for the boost to the posterior fossa or tumor bed. Reductions in boost volume have therefore been a focus of recent studies, particularly as cognitive effects are most related to the volume receiving the highest dose.^{6,32}

The decline in Processing Speed observed in the present study is a well-known risk of RT,^{3,4,12,21} though it has been obscured in some studies because of the use of abbreviated measures. In agreement with previous reports,⁷ the decline observed here reflects not a loss of skills but a slowing in skill acquisition relative to peers. Interestingly, those most affected were individuals with high baseline scores; despite the decline in mean score, the number of those one standard deviation below the population norm ($SS < 85$) increased only from 20 to 21. The Processing Speed decrement has been related to impairment in growth of normal appearing white matter (NAWM);^{10–12} the poorer outcome of younger patients in the present study is consistent with observations showing the greatest development of NAWM before age 12 years.¹¹

The Processing Speed subtests measure the ability to complete Coding and Symbol Search tasks within a certain amount of time, and provide an indication of the rapidity with which an individual can mentally process simple or routine information accurately. While only one component of overall intelligence, Processing Speed is important in learning and academic success; impairment increases the need for educational support, including extra time on examinations and other assignments.^{24,33} The present observation of reduced Processing Speed standard scores without significant reduction in FSIQ suggests that abbreviated testing methods which calculate only an estimated FSIQ do not adequately assess patient needs and should be avoided, especially for clinical decision-making.³⁴

Overall, patients in the present study exhibited a high baseline level of cognitive functioning—the mean baseline IQ was above the mean normative level, notwithstanding the stress of CNS disease and treatments prior to PRT that may include resection and chemotherapy. It is possible that those scores are related to the overall high apparent SES of patients, whose median estimated household income (\$74,990) is higher than that of the U.S. (\$53,046).²⁶ Nevertheless, patients represent a diverse mix in SES, and no relationship was found between household income and any cognitive measure at baseline or follow-up.

Some limitations of the present study should be noted. The interval between baseline and follow-up is relatively short, important because the trajectory of cognitive change following RT is not well established, and neurocognitive effects can manifest over an extended period of time.^{27,29,30} The exclusion of patients under age six years is both a strength and limitation: doing so enabled longitudinally consistent study of the domains involved in cognitive change—information that gives insight into the physiological effects of radiation and can guide long-term treatment. However, the present sample probably exhibits better overall cognitive outcome than one including younger patients, since young age is widely associated with the greatest cognitive effects of radiotherapy. A future report will present PRT outcomes for those younger patients. Finally, the study includes only patients who

could complete the full cognitive assessment, and so excluded some (five of a possible 65) patients due to impairments at baseline, such as severe posterior fossa syndrome.

In summary, at a mean 2.5-year follow-up for 60 pediatric patients treated with proton radiation therapy for CNS tumors at mean age 12.3 years, stable scores were found in FSIQ, verbal and nonverbal intelligence and working memory, but reduced scores were found for processing speed. Patient age at diagnosis was found to be an important prognostic factor for the reduction in processing speed. These cognitive outcomes compare favorably to those reported for patients treated with photon RT.

Acknowledgments

We thank the XXXX pediatric patients and their families for participation in this study, and thank XXXX for assistance with data collection and entry.

Funding: The project described was supported by Award Number P01CA021239 from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

N.J.T. was on the medical advisory board of ProCure until 2008 and has stock options in ProCure that are currently without value. N.J.T.'s spouse continues to serve on the medical advisory board of ProCure.

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Figure 1. Wechsler Full Scale IQ and Index mean standard scores and standard error of the mean at baseline and follow-up.

Table 1

Demographic and clinical characteristics of the total sample (N = 60).

	Mean ($\pm$ SD) or N (%)
Mean Age at Baseline Testing (yr)	12.3 ($\pm$ 3.9), range 6.3–21.7
Mean Age at Follow-up (yr)	14.8 ($\pm$ 4.2)
Mean Follow-Up Interval (yr)	2.5 ($\pm$ 1.9), range 1.0–8.3
Multiple follow-up assessments (interval $\geq$ 2 yr) *	9 (15.0)
Two follow-up assessments	5 (8.0)
Three follow-up assessments	4 (7.0)
Male/Female	34 (56.7)/26 (43.3)
Race	
Caucasian	53 (88.4)
African-American	2 (3.3)
Other	5 (8.3)
Median household income in community of residence ²⁵	\$74,990, range \$40,702–\$213,423
Histology	
Medulloblastoma	23 (38.3)
Glial (astrocytoma; glioma)	11 (18.3)
Craniopharyngioma	9 (15.0)
Ependymoma	7 (11.7)
Other	10 (16.7)
Primary Tumor Location	
Infratentorial	28 (46.7)
Supratentorial	31 (51.7)
Spine **	1 (1.6)
Hydrocephalus at diagnosis	24 (40.0)
Radiation Field	
Craniospinal irradiation	28 (46.7)
Low Dose ($\leq$ 23.4 Gy)	14 (50)
High Dose ($>$ 23.4 Gy)	14 (50)
Partial brain	32 (53.3)
Surgery (prior to PRT) ***	58 (96.7)
Biopsy	12 (20.0)
Near/subtotal resection	20 (33.3)
Gross total resection	26 (43.4)
Number of prior resections	
1 resection	33
2 resections	10
3 resections	3

	Mean ($\pm$ SD) or N (%)
Chemotherapy treatment	37 (61.7)
Posterior fossa syndrome at baseline (non-incapacitating)	3 (5.0)
Motor or Sensory Problem at Baseline/Follow-up	10 (16.6)/26 (43.3)
Hearing	1 (1.6)/10 (16.7)
Motor	5 (8.3)/9 (15.0)
Vision	4 (6.7)/6 (10.0)
Multiple	0 (0)/1 (1.6)

* Minimum of two years between follow-up evaluations.

** CSI required as part of treatment

*** No surgical biopsies or resections were performed during or after proton radiation

Table 2

Cognitive scores at baseline and follow-up (N = 60)

Cognitive Domain	Baseline (Mean $\pm$ SD)	Follow-Up (Mean $\pm$ SD)	Change (Mean $\pm$ SD) (95% CI)	<i>p</i> value [†]
Wechsler FSIQ	104.6 (13.3)	104.1 (12.1)	-0.43 (7.9) (-2.47 – 1.60)	0.67
Verbal Comprehension	107.6 (12.7)	108.5 (12.6)	0.93 (6.9) (-0.85 – 2.71)	0.30
Perceptual Reasoning/Organization	104.5 (12.5)	106.0 (13.1)	1.52 (9.9) (-1.04 – 4.07)	0.24
Working Memory	102.0 (12.4)	103.9 (12.8)	1.87 (11.0) (-0.98 – 4.70)	0.19
Processing Speed	95.1 (15.8)	89.9 (11.4)	-5.23 (12.3) (-8.41 – -2.05)	0.002
Coding raw score	45.0 (17.1)	48.9 (15.2)	3.87 (16.2) (-0.33 – 8.05)	0.07
Coding scaled score [*]	8.8 (3.4)	7.9 (2.9)	-0.83 (2.8) (-1.55 – 0.10)	0.03
Symbol Search raw score	25.2 (7.3)	27.4 (9.7)	2.17 (10.4) (-0.52 – 4.85)	0.11
Symbol Search scaled score [*]	9.4 (2.6)	8.6 (2.3)	-0.82 (2.4) (-1.44 – 0.19)	0.01

IQ, Intelligence Quotient; SD, standard deviation; CI, Confidence Interval of the Difference

^{*}For scaled scores, mean = 10, standard deviation = 3[†]Statistical significance of change in mean scores at follow-up from paired t-test analysis.

Table 3

Cognitive scores at baseline and follow-up by age group (N = 60)

Cognitive Domain	Baseline SS (Mean ± SD)	Baseline difference p value *	Follow-Up SS (Mean ± SD)	Within group difference p value **	Between group difference p value **
FSIQ		.018			0.052
<12 years (N=32)	108.3 (14.8)		106.0 (13.3)	.176	
12 years (N=28)	100.3 (9.9)		101.9 (10.5)	.106	
Verbal Comprehension		.056			0.549
<12 years	108.6 (13.4)		110.0 (13.8)	.314	
12 years	106.5 (11.9)		106.8 (11.0)	.735	
Perceptual Reasoning/Organization		.031			0.032
<12 years	107.8 (13.6)		106.7 (13.8)	.585	
12 years	100.8 (10.0)		105.3 (12.4)	.009	
Working Memory		.208			0.412
<12 years	103.9 (14.1)		106.8 (13.5)	.199	
12 years	99.8 (9.9)		100.4 (11.3)	.710	
Processing Speed		.006			0.015
<12 years	100.2 (16.5)		91.4 (11.1)	.001	
12 years	89.3 (12.9)		88.1 (11.6)	.541	

IQ, Intelligence Quotient; SS, standard score; SD, standard deviation.

* Statistical significance of difference in baseline cognitive scores by age group (one-way ANOVA).

** Statistical significance from repeated-measures ANOVA of the change in test scores within age groups (within-group difference) and between adjacent groups (between-group difference).

Table 4

IQ and Processing Speed scores at baseline and follow-up for selected variables

Cognitive Domain	Baseline SS (Mean $\pm$ SD)	Baseline difference <i>p</i> value [*]	Follow-Up SS (Mean $\pm$ SD)	Within group difference ** <i>p</i> value	Between group difference ** <i>p</i> value
FSIQ					
Extent of radiation		.625			0.901
Whole-brain, CSI (N=28)	103.6 ($\pm$ 12.9)		103.1 ($\pm$ 11.5)	.722	
Partial-brain (N=32)	105.3 ($\pm$ 13.8)		105.0 ($\pm$ 12.8)	.817	
Radiation dose		.797			0.965
CSI low dose (N=14)	104.3 ($\pm$ 12.3)		103.8 ($\pm$ 12.0)	.844	
CSI high dose (N=14)	103.0 ($\pm$ 13.9)		102.4 ($\pm$ 11.3)	.761	
Tumor location		.873			0.628
Supratentorial (N=31)	104.4 ($\pm$ 14.5)		103.6 ($\pm$ 14.0)	.566	
Infratentorial (N=28)	103.9 ($\pm$ 11.7)		104.1 ($\pm$ 9.7)	.906	
Processing Speed					
Extent of radiation		.824			0.255
Whole-brain, CSI (N=28)	95.6 ($\pm$ 17.3)		88.4 ($\pm$ 11.7)	.003	
Partial-brain (N=32)	94.1 ($\pm$ 14.5)		91.1 ($\pm$ 11.1)	.129	
Radiation dose		.121			0.242
CSI low dose (N=14)	100.7 ($\pm$ 15.0)		90.9 ($\pm$ 11.5)	.008	
CSI high dose (N=14)	90.5 ($\pm$ 18.5)		85.9 ($\pm$ 11.8)	.153	
Tumor location		.810			0.135
Supratentorial (N=31)	94.3 ($\pm$ 14.1)		91.4 ($\pm$ 11.0)	.196	
Infratentorial (N=28)	95.3 ($\pm$ 17.4)		87.5 ($\pm$ 11.2)	.003	

IQ, Intelligence Quotient; SS, standard score; SD, standard deviation.

^{*} Statistical significance of the difference in baseline cognitive scores by group (one-way ANOVA).^{**} Statistical significance from repeated-measures ANOVA of the change in test scores within groups (within-group difference) and between adjacent groups (between-group difference).