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A Prospective Study of Cerebral, Frontal Lobe, and Temporal Lobe Volume and Neuropsychological Performance in Children with Primary Brain Tumors Treated with Cranial Radiation

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Abstract

Background—Cranial radiation (RT) is an important component in the treatment of pediatric brain tumors. However, it can result in long-term effects on the developing brain. This prospective study assessed the effects of cranial RT on cerebral, frontal lobe, and temporal lobe volumes and their correlation with higher cognitive functioning.

Methods—Ten pediatric patients with primary brain tumors treated with cranial RT and 14 age- and sex-matched healthy children serving as controls were evaluated. Quantitative magnetic resonance imaging (MRIs) and neuropsychological (NP) assessments (language, memory, auditory and visual processing, and vocabulary) were performed at baseline and at 6, 15, and 27 months following RT. The effects of age, time since RT, and cerebral RT dose on brain volumes and NP performance were analyzed using linear mixed-effects (LME) models analyses.

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Results—Cerebral volume increased significantly with age in both groups ($p=0.01$); this increase in volume was more pronounced in younger children. Vocabulary performance was found to be significantly associated with greater cerebral volume ($p=0.05$) and lower RT dose ($p=0.003$). No relationship was observed between RT dose and cerebral volume. There was no difference in the corresponding neuropsychological tests between the 2 groups.

Conclusions—This prospective study found significant relationships among RT dose, cerebral volumes, and rate of vocabulary development among children receiving RT. The results of this study provide further support to clinical trials aimed at reducing cranial RT dose in the pediatric population.

Keywords

CNS tumors; Pediatric Radiation Oncology; Neurocognitive Side Effects of RT; Volumetric MRI; Longitudinal Outcomes

INTRODUCTION

Primary brain tumors represent the most common solid tumor in the pediatric population and account for approximately 20% of all childhood cancers.^{1,2} Cranial or craniospinal irradiation (CSI) is generally required following maximal surgical resection to achieve long-term disease control in children with posterior fossa tumors. Its use, however, is associated with cognitive impairment that can affect academic performance and future employment.^{3,4} Thus as survival has improved in these children, the focus has shifted to concerns related to the long-term sequelae of treatment. Several studies have shown the contributions that age at treatment and cranial radiation therapy (RT) dose have on neuropsychological outcome and reduction of RT dose may limit the impact on intellectual functioning.^{3,4}

The etiology of cognitive dysfunction is likely multifactorial. Research has shown that RT has been associated with a reduction in the volume of normal-appearing white matter in children with medulloblastoma.^{5–9} This finding has also been shown to be dose-dependent with reduced-dose CSI associated with a decreased rate of white matter loss compared to standard dose.⁷ Furthermore, this volume reduction has been reported to contribute to deficits in attention and lower measures of intelligence and academic achievement.^{5,6,8}

In this prospective study, our objective was to assess the effects of cranial RT on total cerebral, frontal, and temporal lobe volumes in pediatric patients with primary brain tumors. We hypothesized that these pediatric patients would have reduced cortical volumes compared to their age- and sex-matched healthy controls and also decreased performance on neuropsychological testing that assess region-specific higher cognitive functioning, including language, memory, processing speed, and vocabulary.

METHODS AND MATERIALS

Patients

Ten pediatric patients with primary brain tumors treated with cranial RT were evaluated. Fourteen age- and sex-matched healthy children comprised the control group. All patients

were planned to undergo and neuropsychological assessment at four time points: following surgery but prior to the start of RT (“baseline”) and at 6-, 15-, and 27-months following RT, and at corresponding time points in controls.

All participants were free of psychiatric diagnosis based on the Diagnostic Interview for Children and Adolescents, 4th Edition (DICA-IV) at baseline and at each follow-up assessment. This prospective study was approved by the institutional review board at The Johns Hopkins Hospital and informed consent was obtained from all families participating in the study.

Brain region contouring and volume

High-resolution, T1-weighted images acquired on a 1.5 Tesla MRI scanner using 1.5-mm slices were utilized. Cerebral, frontal lobe, and temporal lobe volumes were contoured using an online MRI cross-sectional atlas of the brain to serve as a reference (www.imaaios.com/e-Anatomy) and supervised by the pediatric neuroradiologist (DL) on the protocol. The volume of each brain region was computed using Pinnacle planning system software (Philips).

Neuropsychological assessment

Neuropsychological tests were chosen based on their established relationship with the neurobehavioral functions and their association with specific brain regions under evaluation. Testing was completed under the supervision of a licensed psychologist in an outpatient setting and administered by either a trained master’s level psychology associate or postdoctoral fellow. The neuropsychological assessment was performed at the baseline (after surgery but before the start of RT) and 6, 15, and 27 months after the completion of RT for patients and at the corresponding time points for controls. We focused on tests associated with higher cognitive functioning, with established associations with regional cortical development in children, including vocabulary development (as a proxy for IQ), language, memory, and auditory/visual processing. Table 1 summarizes the neuropsychological tests and their relationship to brain function and region.

Vocabulary (IQ Estimate)—The *Peabody Picture Vocabulary Test, Third Edition* (PPVT-3) is a test of receptive single word vocabulary and verbal ability. Participants are given a word and are asked to identify it among a group of four pictures.^{10,11} It is reported correlate with the Wechsler Intelligence Scale, Third Edition Full Scale IQ at a rate of 0.90.¹¹

Language—Retrieval Fluency is a measure of verbal fluency which asks participants to name as many examples as possible from a given category and is a measure of rapid lexical retrieval and executive functioning.^{10,12}

Declarative Memory and Working Memory—Memory for Words measures auditory verbal declarative memory. Participants are asked to repeat a list of unrelated words in the correct sequence.^{10,12}

Auditory Working Memory asks participants to remember a combination of numbers and words and then reorder the numbers and words separately. It measures short-term auditory memory span and auditory working memory.^{10,12}

Bead Memory is a measure of visual-spatial working memory, and asks participants to reproduce the particular pattern of bead arrangement from memory based on a picture of beads shown earlier.^{10,13}

Auditory and Visual Processing—*Sound Blending* is a measure of phonological awareness and auditory processing. In this test, participants are asked to synthesize phonologic components of words by listening to a series of sounds and then blend them into a word.^{10,12}

Beery Visual Perception is a measure of motor-free visual perceptual skills, and asks participants to match geometric forms from one shown.^{10,14}

Statistical analysis

Linear mixed effects (LME) models were used to estimate change in: a) brain volumes and b) performance on associated neuropsychological tests (NP) between patients and controls (*Group*) and as a function of age at baseline (*Age₀*), RT dose (*Dose*), and time from baseline (*Visit*). These analyses were conducted first with respect to cerebral volume and then for regional brain volumes (frontal and temporal lobes bilaterally). Additional interactions *Group x Visit* and *Group x Age₀ x Visit*, evaluating change in brain volume with time between groups and change in brain volume with age over time between groups, respectively, were included. LME analyses of changes in NP performance additionally included corresponding brain volumes (Table 1) as main effects. For those brain-behavior associations which showed a significant relationship between brain volume and NP performance, a further LME analysis was conducted in patients to assess for dose-dependent effects on NP performance using stratifications of whole brain dose (*Dose Group*: <20 Gy, 20 Gy to <30 Gy, 30 Gy) and including interaction *Dose Group x Visit*. IBM SPSS Statistics version 19 was used to calculate the linear mixed effects regression analyses. A *p* value 0.05 was used to determine statistical significance.

RESULTS

Participants

All patients (n=10) presented with primary brain tumors at a median age at diagnosis of 9.0 (range 1.2 – 15.3) years. Patients were equally split among the sexes (males=5, females=5) and the primary brain tumors consisted of medulloblastoma (n=6), ependymoma (n=3), and a malignant glioneuronal tumor (n=1). Patients with medulloblastoma were categorized as standard- or high-risk and received either 23.4 or 36 Gy of CSI except for one patient who was treated to 28.8 Gy according to a Children's Oncology Group (COG) protocol. All medulloblastoma patients received chemotherapy as part of their initial treatment: concurrent vincristine followed by adjuvant vincristine, cyclophosphamide, cisplatin per CCG A9961 regimen B (n=2), concurrent vincristine followed by maintenance courses of combination vincristine/lomustine/cisplatin and cyclophosphamide/vincristine per COG

ACNS 0331 (n=1), concurrent and adjuvant etoposide followed by combination cisplatin/etoposide and cyclophosphamide/vincristine per POG 9631 (n=1), induction methotrexate, etoposide, cyclophosphamide, and cisplatin prior to RT followed by autologous stem cell transplant after RT per CCG 99073 (n=1), and induction etoposide, cyclophosphamide, and cisplatin followed by autologous stem cell transplant ahead of RT (n=1). Patients with ependymomas were treated with gross total resection (GTR) followed by definitive treatment to the tumor bed and therefore did not receive whole brain RT and did not receive any chemotherapy. One patient, however, presented with a myxopapillary ependymoma of the lumbosacral spine and was later diagnosed with a grade 2 ependymoma of the left temporal lobe. This was resected and treated with adjuvant whole brain RT followed by a tumor bed boost. One patient presented with a left frontal malignant glioneuronal tumor and was treated with GTR with recurrence 4 months later. He was treated with a repeat resection followed by CSI with concurrent etoposide and adjuvant cyclophosphamide, cisplatin, and vincristine per CCG 99701. Table 2 summarizes the patient characteristics.

Baseline evaluation was undertaken at a median time of 62 (range 36 – 240) days since surgery and all patients were either free of neurological findings (n = 5) or exhibited stable neurological symptoms (n = 5): left upper extremity dysmetria and gait incoordination; mild ataxic gait; persistent/occasionally inappropriate laughter; left-sided facial hemiparesis and disconjugate gaze; mild dysarthria (cerebellar mutism), dysmetria, and shuffling gait.

Eight patients completed the duration of the study; 2 patients passed away before the 15 month and 27 month time points, respectively. Among the eight patients completing the duration of the study, five completed MRI evaluation at all four time points and three completed MRI evaluation at three time points. Three, two, and two patients completed neuropsychological testing at all four time points, three time points, and two time points, respectively, among the eight patients completing the duration of the study. One patient (Patient 5), enrolled at 1.2 years of age, was able to successfully complete MRI evaluation at all four time points; this patient underwent neuropsychological testing at only the final time point due to her age.

Ages for control subjects ranged from 7.9 years to 15.6 years. It was not possible to enroll controls less than 8 years old as they would have potentially required anesthesia for MRI - this was thought to be an unreasonable risk for the purpose of a clinical trial for the “normal controls” as dictated by our IRB.

Change in Cerebral Volume

Figure 1 illustrates the different cerebral volumes of both patients and controls at each visit. Cerebral volume increased with age (inter-child; $p<0.0001$) and over time (intra-child; $p=0.012$) in both patients and controls. Overall, cerebral volumes and the rate of growth of cerebral volumes, as determined by the slope, were higher in controls than in patients, although the differences in slope were not statistically significant.

Cerebral Volume and Vocabulary Performance

Across groups and time points, a significant relationship was observed between cerebral volume and performance on the test of vocabulary (PPVT-3; $p=0.05$), with larger volumes

associated with better performance (Figure 2), and no significant interaction between *Group* and *Visit*. Given that cerebral volume increased with age and time in all children (both patients and controls), these results suggest that reduced growth rate of cerebral volumes in patients was associated with slower vocabulary development.

Cerebral Radiation Dose and Vocabulary Performance

Across visits, a significant relationship was observed between cerebral RT dose and performance on PPVT-3 ($p=0.003$), with higher RT doses associated with lower scores in patients. This finding suggests that RT dose affects performance on vocabulary measures in a dose-dependent manner (Figure 3). There were no significant interactions between *Dose Group* and *Visit*.

Changes in Regional Volumes and Associated Neuropsychological Functions

Left and right temporal and frontal lobes were assessed individually. Similar to the findings for total cerebral volume (Figure 1), bilateral frontal and left temporal lobe volumes increased with age in all children ($p<0.05$). The right frontal lobe ($p<0.05$) and the right temporal lobe ($p<0.05$) volumes differed significantly between patients and controls (controls > patients) across the four visits (Figure 4 and 5). Follow-on assessment within these regions of brain-behavior relationships (e.g. right frontal lobe and visuospatial working memory) did not disclose any statistically significant associations.

DISCUSSION

The current treatment for pediatric patients with primary brain tumors generally involves maximal safe surgical resection followed by either CSI and/or a tumor bed directed radiation therapy. Cranial RT, however, is associated with a wide range of neurological sequelae in long-term survivors. The purpose of this prospective study was to assess the effects of cranial RT on cerebral, frontal lobe, and temporal lobe volume and associations with higher cognitive functioning including language, working memory, visual processing, and intelligence.

Our results showed that cerebral volume increased with age and over time in both patients and controls and this finding is consistent with current research on brain development. One large-scale longitudinal study on pediatric neuroimaging found a linear increase in white matter with age but changes in cortical gray matter were region specific, with preadolescent peaks followed by a decline.^{15,16} The results described by Giedd et al. further showed increased total cerebral volume which appeared to be due to significant increase in white matter volume that offset the relative decrease in gray matter volume.¹⁶

We found a significant relationship between cerebral volume and performance on the Peabody Picture Vocabulary Test (PPVT-3)—an IQ estimate, with larger volumes associated with higher scores. Although the treatment of primary brain tumors in children, and medulloblastoma in particular, is associated with neurocognitive deficits, the underlying pathophysiology is unknown. A multitude of research has shown an association between cranial RT and a reduction in the volume of normal-appearing white matter (NAWM), suggesting that reduced NAWM may be responsible in part for impairments in IQ.¹² One

study comparing patients with medulloblastoma to age-matched controls treated for low-grade astrocytomas of the posterior fossa with surgery alone, found the former to have significantly lower volume of NAWM.⁸ The importance of this study was that both groups of patients were managed similarly with upfront surgical resection with the main distinguishing treatment being whether or not they received craniospinal irradiation (CSI). The same study showed that NAWM volume was significantly correlated with both Verbal IQ and Full Scale IQ in patients with medulloblastoma treated with CSI but failed to find any significant association between NAWM and any IQ score for the patients with low-grade astrocytomas.⁸

The slowing of IQ growth over time among pediatric patients is not fully understood. One longitudinal study tested two competing hypotheses related to intellectual loss among survivors of pediatric medulloblastoma: whether it was related to a loss of previously learned information or inability to acquire new information at a rate comparable to healthy subjects.¹⁷ This study showed that the patients' IQ subtest raw scores increased significantly over time following CSI, but the rate of the increase was less than expected, explaining the overall decrease in IQ.¹⁷ This was similar to our results which showed that on average, the rate of growth of cerebral volume, as determined by the slope, was lower in patients than controls though no significant difference in volume existed between the two groups. Accepting that an association exists between NAWM volume and intelligence, these results supported the authors' conclusion that deficits in IQ are due to diminished ability to acquire new information at a rate comparable to healthy controls.¹⁷

It has been widely shown that reducing cranial RT dose can limit the impact on intelligence.^{5,6} A longitudinal study evaluating brain volume changes over time in patients with medulloblastoma found that the rate of NAWM loss was 23% slower in children receiving reduced-dosed (23.4 Gy) versus conventional-dosed (36 Gy) CSI.¹⁰ These results are similar to prior studies showing a relationship between NAWM volume and IQ and that patients treated with CSI had a lower rate of growth of NAWM than controls thus explaining their overall decrease in IQ. In our study, we stratified patients into one of three groups (<20 Gy, 20 to <30 Gy, and ≥30 Gy) based on the dose of whole brain RT received. The low-dose group was comprised of patients with ependymoma who did not receive whole brain radiation but radiation to the posterior fossa tumor bed alone. The intermediate-dose group was composed primarily of patients with standard-risk medulloblastoma and the high-dose group of patients with high-risk medulloblastoma. In comparison to previous investigations into NAWM and neurocognitive outcomes in this population, a strength of our investigation is in its prospective basis and control group of healthy subjects receiving no RT, as opposed patients receiving to less RT.

Our results found a significant relationship between cerebral RT dose and performance on the PPVT, with higher doses associated with worse performance on this measure of intelligence. This relationship was based on all patients over time with no comparisons between groups at particular time points reaching statistical significance. This might be explained by the small patient numbers in each group and the resulting limited power to detect differences between groups. Our findings are consistent with similarly published data. A study comparing patients with ependymoma to those with medulloblastoma found that

patients with ependymoma, receiving posterior fossa RT only, were more likely to maintain an IQ greater than 90 than patients with medulloblastoma, receiving CSI, with the latter having a progressive decline in IQ with time following CSI.¹⁸ In another study that sought to analyze the relationship between CSI dose and intellectual outcome in children with posterior fossa tumors, the authors also found a significant correlation between full-scale IQ score and CSI dose.¹⁹ Similar to our study, patients were divided into three subgroups based on CSI doses (0 Gy, 25 Gy, and 35 Gy) with the low-dose (0 Gy) group being comprised of patients receiving posterior fossa directed RT only.

We also sought to evaluate other neuropsychological measures of higher cognitive functioning, including language, memory and processing. We found that the bilateral frontal and left temporal lobe volumes increased with age in all children similar to cerebral volume. Interestingly, the right frontal and right temporal lobe volumes differed significantly between patients and controls and this persisted over time with controls having higher volumes than patients. However, the neuropsychological tests associated with these lobar regions, bead memory and visual perception, respectively, did not differ between patients and controls. This may be due to small patient numbers. It is possible that neuropsychological deficits other than intelligence may underlie the inability to acquire new information at a comparable rate to healthy controls. Reddick et al.¹⁵ sought to determine whether problems with memory and attention were responsible for the association between reduced volumes of NAWM and declines in IQ. Their study found that the main consequence of reduced NAWM among pediatric patients was decreased attention, not memory, and this is what led to declines in IQ and academic achievement.¹⁵ While one limitation of our study was that we did not assess neuropsychological measures of attention, we similarly did not find a significant difference in memory between patients and controls which may again be due to the small patient numbers.

The major limitation of this study is related to small patient numbers. Ten patients with primary brain tumors were evaluated, further subdividing this already small group into three groups based on CSI dose. For example, we identified that baseline measures of intelligence were different between patients stratified by CSI dose even prior to radiation. Each individual group was thus likely more affected by outliers. Given that our study was prospectively accrued, and retrospectively evaluated, this limitation is one that is difficult to correct. A study by Mulhern et al. reporting on intellectual outcomes in childhood survivors of medulloblastoma, found differences between groups with regards to baseline Full Scale IQ.⁶ In their discussion, the authors recommended stratifying patients on the basis of baseline neuropsychological performance prior to randomization, as a way to reduce the initial differences between groups. This method would be an effective way to correct for the differences in baseline scores, though it will be even more important that larger patient numbers are accrued given the inherent differences in performance on such tests across the population. An additional factor to consider is that the design of the study limits interpretation to a certain extent as direct tumor effects and surgical intervention may also have a contribution to changes in neurocognitive function. It is possible that these factors may account for the differences at baseline between patients and controls that were observed. The longitudinal design helps to alleviate these confounding factors and our observation of dose-dependent effects suggests that radiation-related effects have been

captured in this study. Going forward, in addition to enrolling larger and more homogeneous populations, multiple control groups may be considered as well (e.g. patients with low-grade gliomas treated with definitive surgery only and patients with untreated brain tumors). Longer-term follow-up would also be of utility toward isolating the late effects of radiation from possible acute confounders. In future study, one could also consider enrollment of younger patients on study particularly as they are most likely to be affected by RT.

CONCLUSIONS

The cellular and molecular mechanism of cognitive dysfunction following cranial RT has yet to be fully understood. Current research has found an association between cranial RT and a reduction in normal-appearing white matter, suggesting this may be the underlying pathophysiology of intellectual impairment. The results of our prospective study found a significant relationship with cerebral volume and RT dose on measures of intelligence. This study provides further support to clinical trials aimed at reducing cranial RT dose in the pediatric population.

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Figure 1. Relationship between cerebral volume and age in patients and controls. Data from all participants at all time points and are shown with linear regression lines.

Figure 2.

Relationship between cerebral volume and performance on the PPVT-3 in patients and controls. Data from all participants at all time points are shown with linear regression lines. Standard scores were used to account for the effect of age on performance. PPVT indicates Peabody Picture Vocabulary Test.

Figure 3. RT dose in patients and its relationship to performance on the Peabody Picture Vocabulary Test. Error bars represent ± 1 standard deviation (SD). Standard scores were used to account for the effect of age on performance.

Figure 4. Right frontal lobe volume in both patients and controls at all time points. An asterisk (*) indicates a significant difference in volume between groups at visits 6 and 27. Error bars represent ± 1 SD.

Figure 5. Right temporal lobe volume in both patients and controls at all time points. An asterisk (*) indicates a significant difference in volume between groups at 27 months. Error bars represent ± 1 SD.

Table 1

Brain Regions and Corresponding Neuropsychological Tests

Hypothesized Brain Regions	Neuropsychological Function(s)	Associated Tests
Cerebrum	Vocabulary (Proxy for IQ)	Peabody Picture Vocabulary Test-3 (PPVT-3)
Right frontal lobe	Visual working memory	Bead Memory (Stanford Binet IV)
Left frontal lobe	Verbal working memory, verbal fluency	Auditory Working Memory Retrieval Fluency (Woodcock Johnson III— WJ-III)
Right temporal lobe	Visual perception	Beery Visual Perception
Left temporal lobe	Verbal fluency, phonological awareness, verbal memory	Retrieval Fluency, Sound Blending, Memory for Words (WJ-III)

Table 2

Patient Characteristics and Treatment Details

Patient no.	Sex	Age at Diagnosis (years)	Diagnosis	Whole brain RT dose (Gy)	Boost dose (Gy)	Chemotherapy
1	F	8.7	Medulloblastoma	28.8	54.0	Y
2	M	9.2	Medulloblastoma	36.0	54.0	Y
3	M	15.3	Ependymoma	36.0	54.0	N
4	F	3.8	Medulloblastoma	23.4	54.0	Y
5	F	1.2	Ependymoma	n/a	54.0	N
6	M	11.8	Malignant glioneuronal tumor	27.0	54.0	Y
7	M	12.6	Medulloblastoma	23.4	54.0	Y
8	F	8.7	Medulloblastoma	23.4	55.8	Y
9	F	3.8	Ependymoma	n/a	59.4	N
10	M	14.5	Medulloblastoma	23.4	54.0	Y

Abbreviation: NA, not available; RT, radiation therapy; y, year.