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Long Term Effects of Radiation Therapy on White Matter of the Corpus Callosum: A Diffusion Tensor Imaging Study in Children

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Abstract

Background—Despite improving survival rates, children are at risk for long-term cognitive and behavioral difficulties following the diagnosis and treatment of a brain tumor. Surgery, chemotherapy and radiation therapy have all been shown to impact the developing brain, especially the white matter.

Objective—The purpose of this study was to determine the long-term effects of radiation therapy on white matter integrity, as measured by diffusion tensor imaging, in pediatric brain tumor patients two years after the end of radiation treatment, while controlling for surgical interventions.

Materials and Methods—We evaluated diffusion tensor imaging performed at two time points: a baseline three to twelve months after surgery and a follow-up approximately two years later in pediatric brain tumor patients. A region of interest analysis was performed within three regions of the corpus callosum. Diffusion tensor metrics were determined for participants (N=22) who underwent surgical tumor resection and radiation therapy and demographically matched with participants (N=22) who received surgical tumor resection only.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of Interest: None

Results—Analysis revealed that at two years post treatment, the radiation treated group exhibited significantly lower fractional anisotropy and significantly higher radial diffusivity within the body of the corpus callosum compared to the group that did not receive radiation.

Conclusion—The findings indicate that pediatric brain tumor patients treated with radiation therapy may be at greater risk of experiencing long-term damage to the body of the corpus callosum than those treated with surgery alone.

Keywords

diffusion tensor imaging; brain tumor; radiation; white matter; corpus callosum; children

Introduction

The incidence of pediatric central nervous system (CNS) tumors has been on the rise over the last 40 years with 1.9 cases per 100,000 in 1973 [1] and 5.4 cases per 100,000 for children under 19 years by 2013 [2]. Survival rates for pediatric CNS tumor patients have also been on the rise, largely due to improved diagnostic techniques and therapeutic approaches. The five-year survival rate for primary brain tumors in patients below 19 years at diagnosis was 66% from 2000-2004; however, by 2013, the rate increased to 73% [2].

Gross total tumor resection remains the gold standard of treatment. In many cases, however, complete tumor resection is not possible. Subsequently, the multi-pronged approach of surgery, chemotherapy, and radiation therapy is commonly employed in the treatment of CNS tumors. Approximately 200,000 patients of all ages receive partial or whole brain radiation therapy for the treatment of primary or metastatic brain tumors every year in the United States of America (USA) [3]. However, the usage of radiation therapy for the treatment of pediatric CNS tumors comes at some cost in terms of neurodevelopmental morbidity. Research shows that children treated with radiation therapy are susceptible to radiation-induced cognitive impairment, a condition characterized by poor behavioral, emotional, and cognitive outcomes. Deficits in intelligence quotient (IQ), scholastic development, memory, attention, and information processing speed have all been reported [4-9]. These sequelae have been found in children who received both diffuse and focal radiation therapy [7, 8, 10, 11]. Longitudinal studies show that children treated with radiation therapy for brain tumors exhibit an elevated risk for a poorer quality of life compared to their healthy siblings; they are less likely to be employed or to be able to engage in complex motor tasks, such as driving a car [8]. Survivors also have an increased risk of developing academic difficulties, with many requiring remedial classes in mainstream schools or placement in special-needs classrooms [7, 8, 10].

Radiation therapy can have a profound effect on the brain. Vascular damage, multifocal hemorrhage, edema, neuroinflammation, astrogliosis, and neuronal cell damage are common findings [12, 13]. Cellular damage is not limited to neurons, but extends to glial cells, with oligodendrocytes being particularly vulnerable. Oligodendrocytes have high metabolic demands and mitochondrial content, making them sensitive to the oxidative stress caused by radiation [14, 15]. Damage to oligodendrocyte progenitor cells and fully differentiated

oligodendrocytes with subsequent white matter necrosis due to axonal demyelination and degradation has been observed [3, 14, 16, 17].

Diffusion Tensor Imaging (DTI) is a magnetic resonance imaging (MRI) technique useful for characterizing white matter integrity. DTI relies on the diffusion characteristics of water to depict white matter tracts in the brain. Without barriers, the random, Brownian movement of water molecules is isotropic or uniform in all directions. The presence of membranes, fibers, myelin, and other such barriers, create anisotropic water diffusion, which is greater in one direction than others.

DTI studies have shown that radiation therapy has a negative effect on white matter integrity [18, 19] and that this radiation therapy-induced decline in white matter integrity is associated with poor cognitive outcomes [20]. However, many of these studies focused on white matter changes within the first year following the commencement of radiation therapy. Many patients who receive radiation therapy do so after undergoing surgical tumor resection and little work has been done to account for the possible effects of surgical intervention. The purpose of this study was to determine the long-term effect of radiation therapy on white matter integrity, as measured by diffusion tensor imaging, in pediatric brain tumor patients two years after the end of radiation treatment, while controlling for surgical interventions. This study evaluated the hypothesis that children treated with surgery and radiation therapy, with and without chemotherapy, will exhibit reduced white matter integrity compared to those treated with surgery only.

Methods

Study Participants

This study is part of a longitudinal project focused on cognitive, behavioral, socio-emotional, and imaging outcomes following pediatric brain tumor treated with or without radiation. Participants included pediatric brain tumor patients recruited from Neuro-Oncology clinics at four different urban medical centers: Cincinnati Children's Hospital Medical Center in Cincinnati, Ohio; Dayton Children's Hospital in Dayton, Ohio; Nationwide Children's Hospital in Columbus, Ohio; and Kennedy Krieger Institute in Baltimore, Maryland (Table 1). During recruitment, 271 patients who had recently undergone brain tumor resection were screened for inclusion in the study. Thirty patients were ruled out due to severe pre-existing conditions or ineligible tumors, which included glioblastoma multiforme and intrinsic brain stem glioma. Patients suffering from these tumors were excluded because their poor prognosis is not ideal for inclusion in a longitudinal study. An additional 93 patients were excluded due to severe post-surgical complications and 35 patients were excluded due to a history of neurofibromatosis type 1, a genetic disorder that is associated with functional and cognitive difficulties outside of the occurrence of tumors. Of the 113 eligible potential participants, 44 declined to participate and the remaining 69 were enrolled into the study. Informed assent and parental consent was obtained for all individual participants included in the study. Participants were separated into two groups on the basis of tumor treatment. The radiation therapy group (RT) included participants who underwent surgical tumor resection and adjuvant radiation therapy, with or without chemotherapy. The comparison group comprised participants who received surgical

tumor resection and no radiation therapy (No-RT). Members of the No-RT group were group matched to members of the RT group based on age and MRI scanner type, evaluated at a post-surgical baseline and a 2-year follow-up time point. Table 2 reconciles participant enrollment numbers with participant imaging numbers included in this analysis.

Image Acquisition

Imaging was conducted from August 2005 until August 2011 on three types of MRI scanners: a Trio 3 Tesla scanner (Siemens Medical Solutions, Malvern, PA, USA), a Signa 1.5 Tesla scanner (General Electric Healthcare, Chicago, IL, USA), and a Signa 3 Tesla scanner (General Electric Healthcare, Chicago, IL, USA). DTI data from two examinations were evaluated. Baseline imaging was conducted 3-12 months after surgery and follow-up imaging was acquired 2 years (+/- 3 months) after baseline. The baseline time point was selected to ensure the resolution of any acute neurosurgical effects, such as edema, for all participants, while preceding the onset of any delayed late-effects of radiation therapy in the RT group. The DTI protocols for the participants in the study are listed in Table 3.

Image Processing

Variations in tumor location and surgical resection cavities made atlas-based image processing impractical as the transformations created severe image distortions for some participants. This analysis employed a region of interest (ROI) based approach with 3 ROIs constructed to extract DTI metrics. They included the genu, body, and splenium of the corpus callosum. With our limited sample size, these three regions were chosen because of the strong association with cognitive performance and the technical factors associated with defining white matter tracts. Data were analyzed using DTI Studio and ROI Editor software packages [21]. Images were checked for artifacts; slices exhibiting severe distortions were excluded. To maximize the integrity of the diffusion tensor maps, image masks were created to minimize distortion from the background noise of the scans. Also, due to the small sample size, we limited our tensor calculation to three diffusion metrics: fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD). The diffusion maps were saved in the "Analyze" format in DTI Studio and re-opened in ROI Editor for ROI drawing. For each DTI dataset, the diffusion maps were simultaneously imported into ROI Editor and ROIs were manually drawn onto the axial plane of the FA map (Figure 1). A minimum FA threshold of 0.2 was set for each voxel before the acquisition of ROI values to ensure that only areas of white matter were recorded in each ROI. Any voxels falling below this threshold in the FA map were excluded from all three diffusion maps when the ROI values were calculated.

Statistical Analysis

The three diffusion metrics for each participant ROI were imported into SigmaPlot [22] for statistical analysis. Student's t-tests were used to compare the change in diffusion metrics between the No-RT group and the RT group at the two time points. Paired t-tests were used to compare within the two groups over time. Cohen's d value and effect size correlations were determined using group mean and pooled standard deviation values.

Results

Analysis of the post-surgical baseline data did not reveal any statistically significant differences in diffusion metrics for the genu, splenium and body of the corpus callosum between the No-RT and the RT groups (Table 4). For the majority of the RT participants, baseline imaging occurred 1-6 months after completing radiation therapy (median value 1.2 months). At the 2-year time point, the RT group exhibited significantly lower FA and significantly higher RD in the body of the corpus callosum compared to the No-RT group (Table 4). Conversely, no significant group differences in FA or RD were observed in the genu or splenium of the corpus callosum, and no significant group differences were observed for AD within any of the 3 ROIs at the post-surgical baseline or 2-year time point (not shown). To assess within group changes over time, we restricted our analysis to the body of the corpus callosum. Participants, 14 in each group, with both imaging studies performed on the same scanner type, were compared. Within the RT group, FA of the body of the corpus callosum exhibited significantly lower values and RD exhibited significantly higher values at the 2-year time point compared to that from post-surgical baseline (Table 5).

Discussion

Pediatric brain tumor patients treated with radiation therapy, with or without chemotherapy, exhibited significantly reduced white matter integrity of the body of the corpus callosum compared to those treated without radiation therapy more than 2 years after the end of their treatment, while no such differences were observed between the two groups of patients within the first 3-12 months following treatment. This pattern of findings suggests that radiation therapy may confer greater long-term damage to white matter than surgery alone.

FA increases with CNS maturation because increasing axonal structure, membrane integrity, and myelination creates a preferred diffusion direction [23]. Damage to axonal structures, membranes, and myelination reduces the coherence of the preferred main diffusion direction, thus decreasing FA. AD is sensitive to changes in the diffusion of water parallel to the long axis of white matter tracts [23-25, 26] and reflects changes in axonal integrity. RD is best suited for measuring the degree of axonal myelination because it provides information about the diffusion characteristics of water perpendicular to the long axis of white matter tracts [27-29]. Strong evidence indicates that increases in RD are indicative of white matter demyelination; as the amount or quality of the myelin around an axon decreases, it becomes easier for water to diffuse through the walls of the axon, causing an increase in RD.

Decreases in FA [18, 19, 30-32] and increases in AD, and RD [18, 33] have been observed in brain tumor patients treated with radiation. Unfortunately, the literature is sparse when it comes to the effects of surgery and chemotherapy on white matter integrity. One study found that pediatric brain tumor patients treated with surgery alone and those treated with surgery, chemotherapy, and radiation therapy both experienced reductions in the FA of the body of the corpus callosum after treatment, but these reductions were only significant in the radiation therapy patients [19]. Similar to the current study, the surgery-only patients were

diagnosed with pilocytic astrocytomas while those receiving surgery, chemotherapy, and radiation therapy had medulloblastomas.

A potential confounder in the current study is tumor location. At the post-surgical baseline timepoint, there is a mismatch of infratentorial and supratentorial tumors. The surgical effects upon the corpus callosum of a supratentorial primitive neuroectodermal tumor (PNET) differ from those of posterior fossa medulloblastoma. For both the baseline and two-year timepoints of the current study, the radiation therapy group included one patient with a supratentorial PNET. The more severe disease course or the addition of chemotherapy also may have affected the white matter integrity. Pediatric brain tumor patients receiving chemotherapy consisting of, but not limited to, vincristine and carboplatin without surgery or radiation therapy have been observed to experience significant decreases in the FA of the corpus callosum [34]. The possibility that chemotherapy affected the white matter integrity of the RT group cannot be ruled out by our study.

As the largest neural fiber bundle in the human brain with more than 200 million nerve fibers connecting the left and right cerebral hemispheres, the corpus callosum plays an indispensable role in our ability to coordinate movements, communicate, and engage in critical thinking. The white matter integrity of the corpus callosum, as measured by DTI, is positively related to information processing speed [35-38] which in turn mediates and reasoning ability [39].

Group variability with respect to scanner usage, tumor location and treatment course, specifically, chemotherapeutic regimes, are key limitations which ultimately resulted in the primary limitation of this study, the small sample size. The study sites consisted of multiple centers designed to support enrollment for the broader neurobehavioral aims. Our overall study design allowed for recruitment of a RT group participant at one site and a No-RT participant at another site. Unfortunately, not every location used scanners with the same vendor or the same magnetic field strength. To minimize the research burden on participants, the research imaging was usually added on to the routine clinical imaging examination. Also, one site had the initial study-designated MRI scanner replaced during the course of the study. DTI sequence parameters, such as field strength, have a significant effect on the signal to noise ratio and the determined diffusion metrics. To account for technical differences in the parameters, each comparison group matched numbers of participants with DTI data acquired on a particular scanner type.

Although significant changes have been observed in the genu and splenium of the corpus callosum in similar studies [18, 20], such findings did not occur in this study. The effects of age and dose could explain our lack of findings in genu and splenium. Nagesh et al. found in the genu and splenium of the corpus callosum in adults (60 years median, range 23 to 75 years), treated with biologically corrected doses of 50-81 Gy, a linear, dose-dependent increase in RD and AD starting at 3 weeks and continuing to 32 weeks from the start of radiation therapy [18]. With the current study, the age at baseline is lower (median 10 years, range 3 to 16 years) and the total radiation dose is within a smaller range (median 54 Gy, range 45-59.4 Gy). A lack of statistical power could also be magnified by the partial volume effect. Partial volume effect reflects intra-voxel heterogeneity arising from different

structures [40-42] and impacts DTI values for the ROIs [43]. The values of larger fiber tracts are inherently more accurate than those of smaller tracts because they are averaged from a larger number of voxels. The partial volume effect causes voxels on the periphery of ROIs, which are in close proximity to structures of differing diffusion characteristics, to be “contaminated” by the values of their neighbors.

Increased intracranial pressure, ventriculomegaly, hydrocephalus and treatment with shunting could also impact the white matter integrity [44-46]. However, our groups were balanced to minimize potential effects. At baseline, each group had a nearly equivalent number of patients with and without hydrocephalus and with shunts (1 per group). Post surgery, three patients had a shunt inserted, one in the radiation group, two in the surgery only group. However, the shunts did not cause artifact within the ROIs for the current study.

The imaging examinations were carried out for the majority of participants on 1.5 Tesla scanners. This limited the visualization of other white matter tracts and the ability to perform tensor calculations on crossing white matter fibers. The corpus callosum was among the easiest tracts to visualize and reproducibly draw ROIs within, as these structures are myelinated early in development and was tumor free in our study population.

A baseline time point of 3-12 months after surgery was chosen to allow for the resolution of post-surgical volume changes and edema. This may have come at some expense in terms of accounting for white matter damage as it has been shown that surgery alone can cause significant decreases in the FA of the rostral body of the corpus callosum before the commencement of radiation therapy in pediatric brain tumor patients. Once these patients undergo radiation therapy, those with surgically affected body of the corpus callosum exhibit a significantly greater reduction in FA than those without surgically affected body of the corpus callosum [32].

Conclusion

The findings from this study suggest that pediatric brain tumor patients treated with radiation therapy may be at greater risk of experiencing long-term damage to the body of the corpus callosum than those treated without radiation therapy. This damage may occur through axonal demyelination.

Acknowledgments

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Figure 1.

Fractional anisotropy maps shown within the axial plane to illustrate the regions of interest drawn in the study. A. Shown in blue, the genu and in white, the splenium of the corpus callosum. B. The tracing, shown in yellow, illustrates the body of the corpus callosum. Color coding for fiber directions: red, right to left; blue, inferior to superior; green, anterior to posterior.

Table 1
Group Demographic and Tumor Related Variables

Variable	Baseline		Two Year	
	No-RT (n=22)	RT (n=22)	No-RT (n=14)	RT (n=14)
Gender (male/female)	15/7	19/3	11/3	12/2
Age at baseline (y) [m (sd)]	10.14 (4.39)	9.68 (3.77)	10.07 (4.32)	10.07 (4.03)
Location				
Cincinnati	16	15	11	8
Dayton	-	1	-	1
Columbus	4	4	1	3
Baltimore	2	2	2	2
Scanner				
GE Signa 1.5 Tesla	15	15	11	11
GE Signa 3 Tesla	2	2	2	2
Siemens 3 Tesla	5	5	1	1
Tumor Type				
Glioma	18*	3	13	1
ATRT	-	1	-	1
Choroid Plexus Papilloma	1	1	-	1
Craniopharyngioma	1	1	-	-
Ependymoma	-	2	-	1
Germ Cell	-	3	-	3
Dysembryoplastic Neuroepithelial Tumor	1	-	1	-
Medulloblastoma/PNET	-	11	-	7
Meningioma	1	-	-	-
Tumor Location				
Infratentorial	8	14	7	7
Supratentorial	14	8	7	7
Primary Lesion Size (mm ³) [m (sd)]	1286.52 (1302.40)	1300.78 (870.6)	1692.38 (1443.21)	1343.87 (886.29)
Chemotherapy	Total 1	Total 16	-	Total 10
Platinum Based	1	13	-	9
Vincristine	1	13	-	9
Type of Radiation				
CR	-	1	-	1
CSRT	-	12	-	9
Focal	-	8	-	4
Total Radiation (Gy) [M (SD)]	-	53.19 (4.43)	-	52.75 (4.55)

ATRT atypical teratoid rhabdoid tumor, CR cranial radiation therapy, CSRT craniospinal radiation therapy, Gy gray, m arithmetic mean, mm³ cubic millimeter, No-RT no radiation therapy group, PNET primitive neuroectodermal tumor, RT radiation therapy group, sd standard deviation

* Within the No-RT group, all astrocytomas were classified as low grade with the majority as pilocyticastrocytomas.

Table 2

Loss from Enrollment: Available Imaging for Analyses

Timepoint	Group	Initial	Deceased	Dropout	Lost to follow-up	Technical malfunction	Unable to match demographic variables ^a	Total
Baseline	No-RT	39	1	4	1	3	8	22
	RT	30	1	2	3	1	1	22
2 Years	No-RT	30	0	3	4	0	9	14
	RT	23	3	1	4	0	1	14

No-RTNo-radiation therapy group, RTradiation therapy group

^aMembers of the No-RT group were matched to members of the RT group based on age and scanner type.

Table 3

DTIA cquisition Parameters

Scanner	Sequence	TR (ms)	TE (ms)	Voxel Size (cm)	Directions
GE Signa 1.5T	2D SE EPI	12000	81	3×3×3	15
GE Signa 3T	2D SE EPI	6000	71-87	3×3×3	25
Siemens TRIO 3T	2D SE EPI	6000	87	2×2×2	12

cm centimeter, GE General Electric, ms milliseconds, TTestra, TE echo time, TR repetition time, 2-D SE EPI two dimensional, spin echo, echo planar imaging
b values for all scanners: 0 and 1000 s/mm²

Diffusion Metric	Post Surgical Baseline (<i>n</i> = 44)						Two Year Follow-up Imaging (<i>n</i> = 28)						
	RT			No-RT			RT			No RT			
	<i>n</i>	mean	sd	<i>n</i>	mean	sd	<i>p</i>	<i>d</i>	<i>n</i>	mean	sd	<i>p</i>	<i>d</i>
FA Body	22	0.69	0.11	22	0.69	0.099	0.83	-0.069	14	0.61	0.091	0.005	-1.16
FA Genu	22	0.80	0.070	22	0.79	0.058	0.60	0.16	14	0.77	0.047	0.17	-0.52
FA Splenium	22	0.76	0.079	22	0.75	0.097	0.62	0.16	14	0.77	0.075	0.87	0.057
RD Body	22	0.00668	0.00026	22	0.00663	0.00024	0.48	0.21	14	0.00089	0.00024	0.017	0.97
RD Genu	22	0.00046	0.00019	22	0.00048	0.00017	0.75	-0.010	14	0.00052	0.00010	0.43	0.32
RD Splenium	22	0.00054	0.00022	22	0.00057	0.00034	0.72	-0.11	14	0.00051	0.00020	0.89	-0.054

Student t-tests were used to compare the change in diffusion metric (FA or RD) for a given ROI (genu, splenium or body of the corpus callosum) *between* the RT and No-RT groups at each time-point (post-surgical baseline and two year follow-up imaging). Participant groups were matched based upon age and MRI scanner type.

d Cohen's Effect size, FA fractional anisotropy, n number of participants within the group, $No-RT$ no radiation group, P statistical significance p-value (<0.05 , considered statistically significant and noted in bold), RD radial diffusivity, RT radiation therapy group, SD standard deviation

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