International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

Clinical Investigation

Association of Neuronal Injury in the Genu and Body of Corpus Callosum After Cranial Irradiation in Children With Impaired Cognitive Control: A Prospective Study

Kristin J. Redmond, MD, MPH,* Meghan Hildreth, BS,* Haris I. Sair, MD,† Stephanie Terezakis, MD,* Todd McNutt, PhD,* Lawrence Kleinberg, MD,* Kenneth J. Cohen, MD, MBA,‡ Moody Wharam, MD,* Alena Horska, PhD,† and E. Mark Mahone, PhD§

**Department of Radiation Oncology and Molecular Radiation Sciences and †Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University, Baltimore, Maryland; ‡Division of Pediatric Oncology, The Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland; and §Department of Neuropsychology, Kennedy Krieger Institute, Baltimore, Maryland*

Received Aug 11, 2017, and in revised form Mar 1, 2018. Accepted for publication Apr 15, 2018.

Summary

The purpose of this prospective study was to examine white matter integrity as measured by diffusion tensor imaging and the association with region-specific radiation dose and neuropsychological functioning in children undergoing cranial irradiation. These data suggest that the

Purpose: Brain radiation is associated with functional deficits in children. The purpose of this study was to examine white matter integrity as measured by diffusion tensor imaging and associations with region-specific radiation dose and neuropsychological functioning in children treated with cranial irradiation.

Methods and Materials: A total of 20 patients and 55 age- and sex-matched controls were included in the present study. Diffusion tensor imaging and neuropsychological assessments were conducted at baseline and 6, 15, and 27 months after treatment. The neuropsychological assessment included motor dexterity, working memory, and processing speed. White matter regions were contoured, and the apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were recorded for each participant. Linear mixed effects regression models were used to prospectively compare the associations among ADC, FA, radiation dose to contoured structures, and performance on the neuropsychological assessments over time.

Reprint requests to: Kristin J. Redmond, MD, MPH, Department of Radiation Oncology and Molecular Radiation Sciences, The Johns Hopkins University, 401 North Broadway, Suite 1440, Baltimore, MD 21231. Tel: (410) 614-1642; E-mail: kjanson3@jhmi.edu

This study was presented at the American Society for Radiation Oncology 2014 Annual Meeting, San Francisco, California, and at the Society for Neuro-Oncology 2014 Annual Meeting, Miami, Florida.

The present study was supported by the National Institutes of Health (grant R01 NS042851); the Kennedy Krieger Institute/Johns Hopkins University Intellectual and Developmental Disabilities Research Center (grants U54 HD-079123 and U54 HD-09123); the Institute for Clinical and Translational Research, the Johns Hopkins University School of Medicine; and the National Institutes of Health, National Center for Research Resources, Clinical and Translational Sciences Awards Program (grant UL1-RR025005).

Conflict of interest: Dr Redmond Research support, travel funding, and honorarium for speaking from Accuray received research support from Elekta AB and honorarium from AstraZeneca and has consulted for Medtronic.

https://doi.org/10.1016/j.ijrobp.2018.04.037

subcortical white matter, especially the genu and body of the corpus callosum, might be regions with increased susceptibility to radiation-induced injury, with implications for cognitive function.

Results: The mean prescription dose was 44 Gy (range 12-54). Across visits, compared with the controls, the patients showed a significantly increased ADC across all selected regions and alterations in FA in the dorsal midbrain and corpus callosum (genu, splenium, body). An increased radiation dose to the genu and body of the corpus callosum was associated with alterations in ADC and FA and reduced neuropsychological performance, most notably motor speed and processing.

Conclusions: These prospective data suggest that subcortical white matter, especially the genu and body of the corpus callosum, could be regions with increased susceptibility to radiation-induced injury, with implications for cognitive function.

Introduction

Radiation therapy (RT) is critical in the treatment of brain tumors. However, brain irradiation is associated with neuropsychological impairment (1-7). The precise mechanism of radiation-induced neurotoxicity remains unclear; however, the effect is likely multifactorial. Nevertheless, several studies have demonstrated volume loss after RT, suggesting that neuronal loss might be a key factor (8-12), with data to suggest a potential dose relationship (13) and correlation with neuropsychological functioning (14, 15).

Recent advances in imaging have led to the development of noninvasive methods to evaluate neuronal integrity in the brain. Specifically, diffusion tensor imaging (DTI) measures water movement that can be modeled at the voxel level. The tensor describes the major orientation and anisotropy. DTI evaluates the random movement of water and calculates the restriction of the molecule's diffusion (16-19). Restriction is quantified as the apparent diffusion coefficient (ADC), which depends on the presence of an intact cell membrane and the cellularity of the tissue (20). Similarly, fractional anisotropy (FA) evaluates the anisotropy of diffusion, with unrestricted movement in all directions represented by an FA of 0 (20). Ultimately, FA reflects the density of the neuronal fibers, the diameter of the axons, and white matter myelination. Thus, ADC and FA serve as sensitive and quantitative measures of neuronal injury from both tumor and therapy (21, 22).

Previous studies have used DTI to evaluate radiation injury to the temporal lobes after definitive chemo-RT for nasopharyngeal carcinoma (23, 24). Other studies have correlated the radiation dose to the temporal lobes and hippocampus with neuropsychological sequelae of brain radiation (25-29). However, although earlier studies have also suggested volume loss in the corpus callosum after brain radiation (15), no studies to date have prospectively used advanced imaging techniques to evaluate the neuronal integrity in the corpus callosum after brain RT and correlated these changes with neuropsychological testing results.

Damage or thinning of the corpus callosum has been shown to be associated with reduced functioning on tests of executive functioning, attention, working memory, processing speed, verbal fluency, and memory in a variety of healthy and patient groups, including normal aging (30), cerebral small vessel disease (31), traumatic brain injury (32), multiple sclerosis (33-38), human immunodeficiency virus (39, 40), mild cognitive impairment secondary to Parkinson disease (41), and euthymic bipolar disorder (42). Given this unique sensitivity in other neurologic diseases, we hypothesized that the corpus callosum might also be especially sensitive to injury from RT in children, resulting in associated functional deficits. The long-term goal of the present is to determine whether limiting the radiation dose to specific white matter regions might reduce the toxicity of brain RT.

Methods and Materials

Study population and eligibility

Children (n = 20) aged 5 to 18 years at the time of RT to the brain for tumors of any histologic type or undergoing cranial irradiation as part of central nervous system management for a hematologic malignancy were eligible for enrollment in this prospective observational study which was approved by the institutional review board at the Johns Hopkins University. The comparison group included 55 voluntary, healthy children with no history of psychiatric disorder, neurologic illness, or learning disability. All participants in the patient and control groups had serviceable vision.

Radiation dose to white matter structures

The white matter integrity from 6 regions of the brain, including the dorsal midbrain, temporal white matter, anterior (frontal) white matter, and the genu, body, and splenium of the corpus callosum were contoured by a single investigator using the treatment planning computed tomography scan and co-registered with T1-weighted gadolinium contrast-enhanced and fluid-attenuated inversion recovery magnetic resonance imaging studies. A vertical line abutting the posterior margin of the anterior bend of the corpus callosum was the posterior boundary of the genu; the splenium was designated by the posterior portion of the