LONG TERM EFFECT OF RADIOTHERAPY ON ADULT SURVIVORS OF CHILDHOOD BRAIN TUMOR PATIENTS: A NEUROIMAGING STUDY

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INTRODUCTION

With current aggressive surgery, radiotherapy and chemotherapy, long-term survival rates of childhood brain tumors have increased 36% over a twenty-year period [1]. Despite improved a survival rate with successful treatments, a significant number of patients have left with neurocognitive and endocrinologic deficits. Several studies have revealed that radiotherapy often results in significant brain function restrictions, such as intellectual and emotional functions, comparing to healthy controls [2]. Recent studies have suggested the importance of age at diagnosis, radiotherapy, white matter (WM) integrity, memory and emotional functioning in predicting childhood adaptive outcomes within the first five years of diagnosis [3]. However, the role of these and other factors in predicting longer term adult outcomes (over 10 years) have received limited attention and is poorly understood. Specially, it is not clear if such restrictions are related to specific brain white matter (WM) integrity changes. This study reports the findings in quantitative evaluation of WM microstructure damages using diffusion tensor imaging (DTI). The observed changes in DTI then were correlated with brain function restrictions in long-term adult survivors so that we better understand the progression of microstructure damage underlying the brain functioning decline by recognizing complications of radiotherapy.

MATERIALS AND METHODS

<u>*Subjects and Methods:*</u> The study was approved by the Institutional Review Board. 15 adult survivors with pediatric brain tumor (average 23.6 y, 47% female) were enrolled in the study, which included astrocytoma (n=5), choroid plexus papilloma (n=1), pilocytic astrocytoma (n=2), and medulloblastoma (n=7). They were subgroup survivors with radiotherapy (RT) (n=8) and without radiotherapy (NRT) (n=7). Additional 15 matched controls were recruited. The Vocabulary and Similarities subtests of Wechsler Abbreviated Scale of Intelligence (WASI) were used to estimate verbal cognitive abilities in all subjects. All DTI and structural MRI were recorded on a Siemens 3T MRI scanner (Siemens Trio). DTI was performed in the axial direction with 60 slices, 30 gradient directions and 2 mm thickness without gap covered the entire brain. For structural MRI, axial 3D T_1-weighted multiplanar magnetization prepared rapid gradient echo (MPRAGE) imaging with TR = 45 ms and TE = 15 ms was used with a field of view (FOV) of 240 mm, matrix of 256 × 256, and slice thickness of 1 mm with the same section location with 60 slices and no gap.

<u>*Image and Data Analysis:*</u> FSL program (FMRIB Center, University of Oxford, UK) was used for analyzing DTI data. We used Threshold-Free Cluster Enhancement (TFCE) for finding clusters of difference on the maps of fractional anisotropy (FA), mean diffusivity (MD) and radial (RD) and principal axial (PD). FA, MD and RD & PD measurements were obtained in different clusters of each individual based on Tract-Based Spatial Statistics (TBSS) voxel-wised statistical analysis. For statistic analysis, mean FA, MD, RD, PD values in clusters between NRT and RT, between controls and survivors, between controls and RT/NRT groups were compared and correlated with the WASI verbal IQ scores using SPSS. Outcomes with $P < 0.05$ were considered statistically significant.

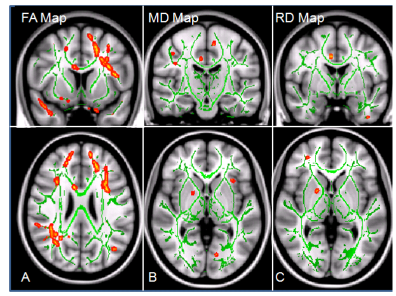

Fig. 1: Differences between survivors with and without radiotherapy were found in areas with red-yellow color in FA (A), MD (B) and RD (C) maps. The color maps are overlapped on the white matter skeleton

RESULTS AND DISCUSSIONS

We found the survivals in radiotherapy group demonstrated significantly decreased FA in the frontal (forceps minor, superior and inferior fronto-occipital fasciculus, anterior thalamic radiation, uncinate fasciculus, cingulum) and temporal (inferior and superior fronto-occipital fasciculus) WM tracts [**Fig. 1A**] compared to those measured from the survivals without radiotherapy. A significant increase of MD in survivals with radiotherapy comparing to survivors without radiotherapy was found in frontal and temporal WM (superior fronto-occipital fasciculus) as well as cingulum [**Fig. 1B**]. Additionally, RD values were significantly higher in survivals with radiotherapy than those in survivals without radiotherapy in the frontal inferior fronto-occipital fasciculus, uncinate fasciculus, anterior thalamic radiation [**Fig. 1C**]. No significant differences were found in PD values between the two groups, suggesting that FA value is more sensitive than PD values for radiotherapy effect. Compared to survivors without radiotherapy group, the survivals with radiotherapy group had significant lower FA, higher MD, and higher RD in the above reported regions [**Fig. 2**].

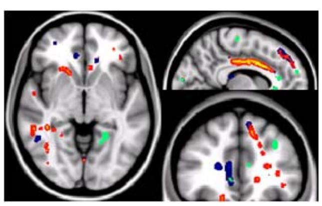

Fig. 3 There were different FA values in color areas from comparison of two groups. Red-yellow: RT Vs controls. Blue: all survivors Vs Controls. Green: NRT Vs controls.

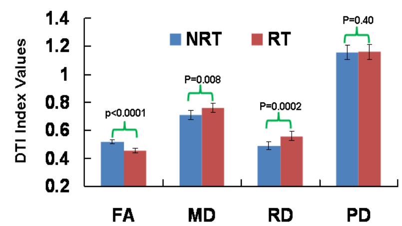

Fig. 2 Example of one area with inferior fronto-occipital fasciculus revealed decrease of FA, increased MD and RD, but no significant differences were found in PD values between the two groups.

We also compared other different groups using FA map obtained from TBSS. More different areas were found in RT group versus controls **[red-yellow colors in Fig. 3]** than that in either all survivors **[blue color]** or NRT group **[green color]** versus matched controls. All different areas were colored in **Fig. 3.**

Verbal abilities were found more impaired in RT group. Lower WASI verbal IQ scores correlated with lower FA and higher MD and RD in specific WM areas, such as inferior fronto-occipital fasciculus in right frontal and temporal WM, forceps minor, superior fronto-occipital fasciculus, and anterior thalamic radiation in left frontal WM. One example of such relationship in the inferior fronto-occipital fasciculus of right temporal WM was presented in **Fig. 4**.

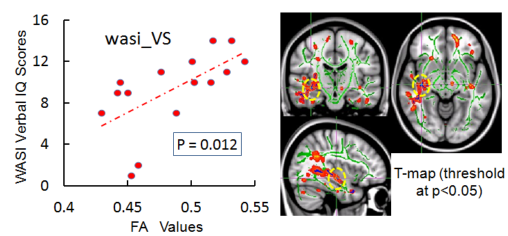

Fig. 4 Positive relationship between FA value on the Inferior fronto-occipital fasciculus (dashed circle with yellow color) and verbal IQ scores are presented.

The findings from this study suggest that micro-structural WM abnormalities in long-term survivors with radiotherapy group may contribute cognitive dysfunctions. These results strongly indicate that there is a relationship between radiation treatment and the change in brain tissue integrity, suggesting the importance of further investigation of the association between radiation and quantitative assessment of specific areas with WM abnormalities. Survivors in RT group had significantly lower performance relative to survivors in the NRT group.

CONCLUSIONS

The results demonstrated reduction of WM integrity related to radiotherapy in long-term survival rates of childhood brain tumors. It also suggested radiotherapy might contribute to cognitive challenges and low IQ scores.

References: [1] Pollack, I.F. & Jackacki, R.I. *Nat. Rev. Neurol*. 2011 [2] Oeffinger, K.C., et al. *N Engl J Med.* 2006 [3] Brinkman, T.M. et al. *Neuro-Oncology.* 2012