Cranio-spinal radiation produces long term compromise of white matter tracts in childhood brain tumour survivors.

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TARGET AUDIENCE. This study is targeted at researchers and clinicians whose interests are paediatric neurological injury and white matter.

PURPOSE. Children treated with cranial radiation exhibit declines in both global white matter (WM) volume and cognitive function.[1,2] What remains unknown is the impact of radiation on specific white matter tracts. We sought to determine the condition of WM microstructure within specific tracts of childhood cancer survivors. Our work provides insight into the developmental trajectories of WM tracts following treatment for pediatric brain tumours.

METHODS. Longitudinal MRI data were obtained from a cohort of 34 healthy children (HC), and 68 childhood cancer survivors who had received one of three treatment types: surgery-only (SO), cranial-spinal radiation (CSR), and focal radiation (FR). MRI measurements were obtained using a 1.5T MRI scanner with an 8 channel head coil from the Hospital for Sick Children (GE), BC Children's Hospital (Siemens), and Alberta Children's Hospital (Siemens). A 3D-T1 FSPGR gradient echo, inversion recovery-prepared sequence (TE/TR = 4.2/10.056 ms, T1 = 400 ms, Slice thickness = 1.5 mm) and a diffusion-weighted single shot spin sequence (EPI readout: 25-31 directions, b = 1000 s/mm2, TE/TR = 85.5/15,000 ms, Slice Thickness = 3 mm) were acquired. The inferior longitudinal fasciculi (ILF), inferior fronto-occipital fasciculi (IFOF), optic radiations (OR), and uncinate fasciculi (UF) were delineated bilaterally using probabilistic tractography (Probtrackx, FSL; Figure 1). Changes in fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD) over time since diagnosis were modelled as a function of treatment, controlling for type of scanner. To allow for longitudinal comparisons a "time since diagnosis" variable was created for HC by referencing time to the patient groups.

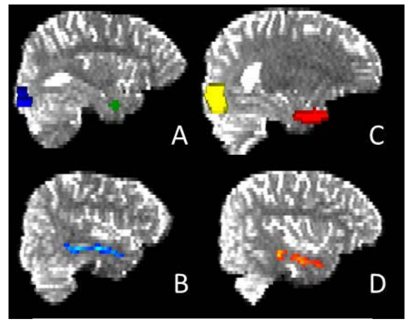

Figure 1. ILF regions of interest (A,C) and tracts (B,D).

RESULTS. Patients treated with CSR displayed declines in FA over time within the left OR, left IFOF and right ILF as compared to healthy controls (P<0.05). Over time, these patients also exhibited greater increases in RD than HC in left UF, right ILF, and right OR (Figure 2; P<0.05). All patient groups displayed increasing MD within the right OR: slopes were significantly different from HC (P<0.01). Those treated with SO displayed positive trajectories significantly higher than HC within RD of the left UF (P<0.05). Lastly, within the CSR group, significant increases were found over time in RD of the OR (bilaterally), IFOF (bilaterally), and the left ILF (P<0.05) as well as decreases in FA of the left IFOF and bilateral ILF (P<0.05).

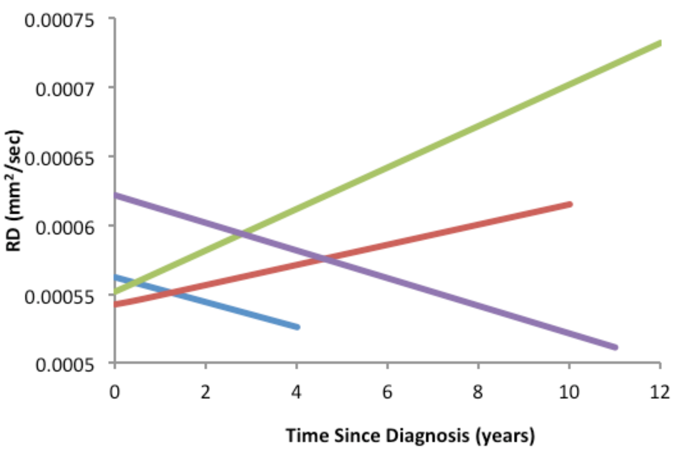

Figure 2. Radial diffusivity changes in right OR over time. HC=blue; SO=red; CSR=green; FR=purple.

DISCUSSION. CSR has a greater negative effect on WM microstructure potentially due to larger doses of radiation and a greater area of brain exposed to radiation. Although SO and FR groups showed fewer deficits than the CSR group, it is interesting that SO and FR groups display supratentorial deficits when insults are localized to infratentorial structures. **CONCLUSION.** To our knowledge, our investigation provides novel evidence for the longitudinal effect of radiation treatment for brain tumours in children. Potential research should focus on methods of refining treatment protocol to provide an optimal prognosis with decreased long-term effects of treatment on childhood brain tumour victims.

REFERENCES. 1. Khong PL, Kwong DL, Chan GC, et al. Diffusion-tensor imaging for the detection and quantification of treatment-induced white matter injury in children with medulloblastoma: a pilot study. AJNR AM J Neuroradiol. 2003; 24(4):734-740. 2. Moxon-Emre I, Bouffet E, Taylor MD, et al. Impact of craniospinal dose, boost volume, and neurological complications on intellectual outcome in patients with medulloblastoma. J Clin Oncol. 2014;32(17):1760-1768.