Tumor Associated with White Matter Integrity

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Objective: Radiotherapy for pediatric brain tumor is associated with reduced white matter structural integrity and neurocognitive decline. Superior cognitive outcomes have been reported following proton radiotherapy (PRT) compared to conventional photon radiotherapy (XRT), presumably due to sparing of healthy brain tissue. This study examined long-term white matter change and neuropsychological performance in pediatric brain tumor survivors treated with XRT vs. PRT.
Participants and Methods: Pediatric brain tumor survivors treated with either XRT (n = 10) or PRT (n = 12) underwent neuropsychological testing and diffusion weighted imaging > 7 years following radiotherapy. A healthy control group (n = 23) was also recruited. Groups had similar demographic characteristics, except for handedness (p = .01), mean years of age at testing (XRT = 21.7, PRT = 16.9, Control = 15.5; p = .01), and mean years since radiation (XRT = 14.7, PRT = 8.9, p < .001). Age and handedness were selected as covariates; analyses were not adjusted for time since radiation due to redundancy with treatment group (i.e., standard of care transitioned from XRT to PRT in 2007). Participants completed age-appropriate versions of the Weschler Intelligence Scales (WAIS-IV/WISC-IV/WISC-V) and the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI and Motor Coordination subtests). Tractography was conducted using automated fiber quantification (AFQ), and fractional anisotropy (FA) was extracted from 12 tracts of interest. Linear mixed models were used to summarize group differences in FA, with tracts nested within subjects. Neuropsychological performance and tract-level FA were compared between groups using analysis of covariance (ANCOVA). Pearson correlation was used to examine associations between cognitive functioning and tract-level FA.
Results: Across all tracts, FA was significantly lower in the XRT group than the PRT group ($t(514) = -2.58$, $p = .01$), but did not differ between PRT and Control groups ($t(514) = .65$, $p = .51$). For individual tracts, FA differed significantly between treatment groups (XRT < PRT) in the left inferior fronto-occipital fasciculus (IFOF), right IFOF, left inferior longitudinal fasciculus (ILF) and right uncinate (all $t < -2.05$, all $p < .05$). No significant differences in FA were found between PRT and Control participants for any tract. All neuropsychological scores were significantly lower for XRT than PRT patients (all $p < .03$), while PRT and Control groups performed similarly on these measures (all $p > .19$). Cognitive functioning was most consistently associated with FA of the corpus callosum major forceps (4/7 domains; all $r > .33$, all $p < .04$) and the left ILF (4/7 domains; all $r > .37$, all $p < .02$).
Conclusions: Both white matter integrity and neuropsychological performance were generally reduced in patients with a history of XRT, but not in those who received PRT. The PRT group was similar to healthy control participants with respect to both FA and cognitive scores, suggesting improved long-term outcomes compared to patients receiving XRT. This exploratory study is the first to provide direct support for white matter integrity as a mechanism of cognitive sparing in PRT. Future work with larger samples is necessary to replicate these findings.

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3 Predicting Neuropsychological Late Effects in Pediatric Brain Tumor

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Survivors Using the Neurological Predictor Scale and the Pediatric Neuro-Oncology Rating of Treatment Intensity

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Objective: Pediatric brain tumor survivors (PBTS) represent a growing group of childhood cancer survivors vulnerable to adverse neuropsychological outcomes following treatment. Although the identification of risk factors has motivated the efforts to reduce the incidence of neuropsychological late effects in PBTS, most of the prior research on late effects has examined these risk factors on an individually selective basis. Given that tumor-directed treatments generally involve a multimodal approach, consisting of a combination of surgical resection, chemotherapy, and/or radiation, and that each patient may have varying degrees of neurological complications, research is needed that focuses on neurocognitive risk factors holistically. The Neurological Predictor Scale (NPS) measures neurological complications associated with neurocognitive risks (e.g., hydrocephalus) and the use of various tumor-directed treatment modalities (e.g., craniospinal radiation). The Pediatric Neuro-Oncology Rating of Treatment Intensity (PNORTI) measures the intensity of pediatric brain tumor treatments, but its association with neuropsychological late effects has not been well-established. The present study aims to 1) evaluate treatment intensity as a risk factor for the development of neuropsychological late effects; and 2) expand upon the validity and clinical utility of the NPS and PNORTI as predictive measures for the development of neuropsychological late effects in PBTS.
Participants and Methods: A retrospective chart review was completed of PBTS (n = 167, M_{age} = 13.47, *SD* = 2.80) who were at least 2 years from the end of tumor-directed treatment (surgery, chemotherapy, and/or radiation therapy) and without a multi-system genetic disorder or severe developmental delay prior to brain tumor diagnosis. Neuropsychological outcomes of interest (IQ, processing speed, working memory, verbal comprehension, and perceptual reasoning) were analyzed in relation to the NPS and PNORTI.
Results: NPS scores ranged from 1 to 11 (*M* = 5.58, *SD* = 2.28) and PNORTI scores ranged from 1 (n = 101; 62.7%) to 3 (n = 18; 11.2%). Survivors were on average approximately 6 years post-treatment (*M* = 6.13, *SD* = 3.39). Pearson bivariate correlations revealed that NPS scores were significantly correlated with IQ (r = -.20, p = .015) and processing speed (r = -.27, p = .015). Models examining the predictive utility of the NPS on neuropsychological outcomes showed that, when controlling for age at diagnosis and sex, NPS scores significantly predicted IQ [$F(3, 147) = 10.83$, $p < .001$, $R^2 = .18$, $R^2_{adjusted} = .16$] and processing speed [$F(3,88) = 5.62$, $p = .001$, $R^2 = .16$, $R^2_{adjusted} = .13$]. A one-way ANOVA showed no significant differences on neuropsychological outcomes based on PNORTI scores.
Conclusions: The findings suggest that the NPS has value in predicting IQ and processing speed above and beyond demographic variables. However, treatment intensity (PNORTI) was not associated with neuropsychological domains in our sample. Future longitudinal research should examine which specific neurological risk factors within the NPS account for the most variance in neuropsychological outcomes.

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4 Relationships Between Task-Switching Performance and Adaptive Behavior Outcomes in Survivors of Pediatric Brain Tumor

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Objective: Survivors of pediatric brain tumor (BT) experience impaired executive function (EF) and adaptive behavior (i.e. the ability to complete daily living tasks independently). The

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