Time-dependent clearance of ATM & H2AX foci in PC3 & DU145 after 4Gy

117 **Diffusion Tensor Imaging: A Possible Biomarker for Early Prediction of Delayed Radiation-Induced Neurocognitive Changes in Cerebral Tumor Patients**

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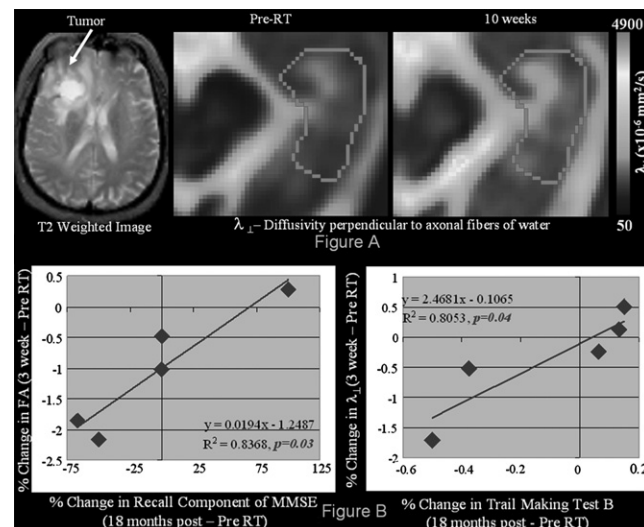
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Purpose/Objective(s): Cranial radiation therapy (RT) is known to affect the central nervous system resulting in delayed neurological complications and deficits in long-term survivors. We hypothesize that structural degradation in cerebral tissue after RT will evoke deficits in neurocognitive functions involving a large neural network.

Materials/Methods: Twenty-five patients with low and high grade gliomas or benign lesions treated with RT participated in an IRB approved MRI study. The biologically corrected doses ranged from 50 to 81 Gy. The MRI protocol included T1, T2 and diffusion tensor imaging (DTI). Temporal changes in normal-appearing tissue were assessed pre, during, and up to 18-months post RT. Four DTI indices were calculated: (i) Mean diffusivity of water D, (ii) fractional anisotropy of diffusion, FA, an indicator of white matter integrity, (iii) diffusivity perpendicular ($\lambda_\perp$) to the fiber long axis, a measure of myelination and (iv) diffusivity parallel ($\lambda_{||}$ to the long axis, a measure of axonal injury. Neuropsychological tests included the Trail Making Test, and Folstein Mini-Mental State Exam (MMSE).

Results: In normal-appearing gray and white matter tissue of the ipsilateral and contralateral hemispheres of the tumor, $\lambda_\perp$ and $\lambda_{||}$ increased by 15% and 10% respectively by 3 months post-RT, signifying global and diffuse effects of RT, and suggesting dose-dependency. Further analysis of radiation-induced injury to large white matter fibers of the corpus callosum indicated demyelination evident from the substantial increase in $\lambda_\perp$ (22%) and only 5% in $\lambda_{||}$ 3 months post RT. Demyelination progressed up to 9 months post RT. In addition to global gray matter degradation, specific structural injury was seen in the hippocampus, which is implicated in learning and memory. Even in the contralateral hippocampus remote from the tumor (pink outline Fig. A) and remote from high radiation dose an 18% increase in $\lambda_\perp$ was noted 1 month post RT, suggesting radiation can affect distant structures. Neurocognitive measures were obtained up to 18 months for five patients; the % changes in FA and $\lambda_\perp$ at week 3 during RT were significantly correlated with the % change in (i) memory component of MMSE and (ii) Trail Making performance at 18 months (Fig. B), indicating sensitivity of DTI to subtle structural changes which in turn affect the neural networks with subsequent neurocognitive decline.

Conclusions: Our data suggest that early detection of neurostructural changes in normal tissue offer a window of opportunity for interventional therapy to minimize neurotoxocity and neurological deficit.

Figure A

Figure B