

Regional variation in white matter diffusion index changes following chemoradiotherapy: A prospective study using tract-based spatial statistics

Christopher H Chapman¹, Mohammad Nazem-Zadeh¹, Oliver Lee², Matthew Schipper¹, Christina I Tsien¹, Theodore S Lawrence¹, and Yue Cao^{1,3}

¹Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, United States, ²Department of Biostatistics, University of Michigan, Ann Arbor, MI, United States, ³Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, United States

Purpose:

Chemoradiotherapy for brain neoplasms is limited by neurocognitive impairment. The pathogenesis of this toxicity is poorly understood, however, brain white matter is known to be especially radiation sensitive.¹ It is not known what regional variation there is in white matter degradation and how this might relate to neurocognitive impairment. Using diffusion tensor imaging, our aims are to identify regional variation in white matter degradation following chemoradiotherapy, and investigate the use of specific diffusion indices for distinguishing pathological processes.

Methods:

Fourteen brain metastasis patients receiving whole brain radiation therapy with or without chemotherapy underwent diffusion tensor imaging before radiation therapy (pre-RT), after completion of radiation therapy (end-RT), and one month following radiation therapy (one month post-RT). Interval changes in fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD) were analyzed using voxelwise tract-based spatial statistics. Mean changes within fourteen volumes representing the major supratentorial white matter structures were also determined, and variation in pre-RT to end-RT FA changes between structures was analyzed using repeated-measures ANOVA and post hoc *t*-tests. Significance level was $\alpha = 0.05$ after correction for multiple comparisons.

Results:

Between pre-RT and end-RT, 87.8% and 64.6% of white matter voxels showed significant decreases and increases in FA and RD, respectively. Especially large FA and RD changes were seen in the fornix, inferior and superior cingula, and corpus callosum (Fig. 1). There were similar findings for pre-RT to one month post-RT changes. From pre-RT to one month post-RT, significant AD decreases were seen in 12.9% of white matter voxels, especially in the superior cingula and the superior longitudinal fasciculi. There was a high amount of spatial overlap between significant FA and RD changes and significant FA and AD changes, but there was virtually no overlap between significant AD and RD changes (Fig. 2). Repeated-measures ANOVA revealed highly significant differences between structures in pre-RT to end-RT FA changes. Post hoc comparisons showed that the inferior cingula had a significantly greater pre-RT to end-RT FA decrease than nearly all other structures.

Conclusions:

Widespread changes in FA and RD were seen following treatment, likely representing early demyelination.² These changes were prominent in two components of the limbic system, cingula and fornix, which may be relevant to treatment-induced neurocognitive impairment.³ AD decreases likely representing axonal degradation and/or astrogliosis.² The lack spatial of overlap between RD and AD changes implies that these indices reflect distinct pathologic processes. Demonstration of preferential white matter damage in the limbic circuit supports proposals to spare these radiation-sensitive structures⁴ and the further development of imaging biomarkers for treatment-induced neurocognitive impairment.⁵ The temporal and spatial independence of AD and RD changes supports existing evidence that these indices are associated with distinct pathological processes.

Figure 1. Pre-RT to end-RT significant FA changes.

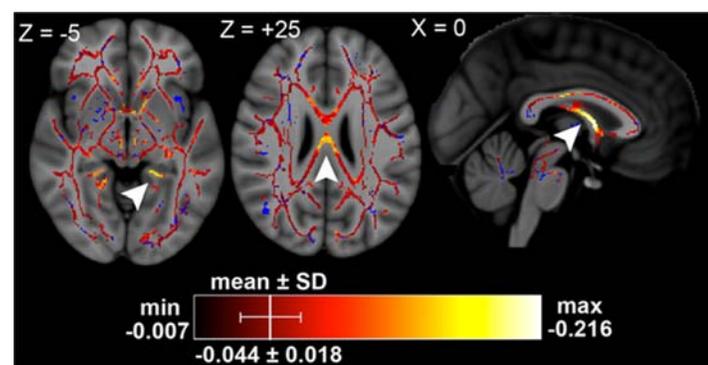
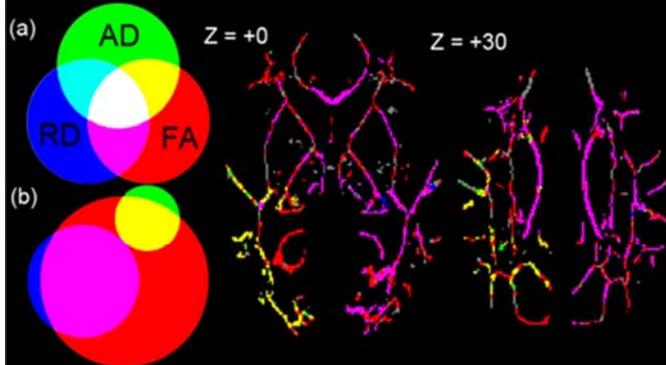


Figure 2. Pre-RT to one month post-RT diffusion index overlap.



References:

1. Okada, S. & Okeda, R. Pathology of radiation myelopathy. *Neuropathology* **21**, 247–265 (2001).
2. Wang, S. *et al.* Longitudinal diffusion tensor magnetic resonance imaging study of radiation-induced white matter damage in a rat model. *Cancer Res* **69**, 1190–1198 (2009).
3. Lautin, A. *The Limbic Brain*. (Kluwer Academic Publishers: New York, NY, 2002).
4. Marsh, J. C., Godbole, R., Diaz, A. Z., Giolda, B. T. & Turian, J. V. Sparing of the hippocampus, limbic circuit and neural stem cell compartment during partial brain radiotherapy for glioma: A dosimetric feasibility study. *Journal of Medical Imaging and Radiation Oncology* **55**, 442–449 (2011).
5. Chapman, C. H. *et al.* Diffusion tensor imaging of normal-appearing white matter as biomarker for radiation-induced late delayed cognitive decline. *Int J Radiat Oncol Biol Phys* **82**, 2033–2040 (2012).