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Regional susceptibility to dose-dependent white matter damage after brain radiotherapy

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ABSTRACT

Background and purpose: Regional differences in sensitivity to white matter damage after brain radiotherapy (RT) are not well-described. We characterized the spatial heterogeneity of dose–response across white matter tracts using diffusion tensor imaging (DTI).

Materials and methods: Forty-nine patients with primary brain tumors underwent MRI with DTI before and 9–12 months after partial-brain RT. Maps of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were generated. Atlas-based white matter tracts were identified. A secondary analysis using skeletonized tracts was also performed. Linear mixed-model analysis of the relationship between mean and max dose and percent change in DTI metrics was performed.

Results: Tracts with the strongest correlation of FA change with mean dose were the fornix (−0.46 percent/Gy), cingulum bundle (−0.44 percent/Gy), and body of corpus callosum (−0.23 percent/Gy), $p < .001$. These tracts also showed dose-sensitive changes in MD and RD. In the skeletonized analysis, the fornix and cingulum bundle remained highly dose-sensitive. Maximum and mean dose were similarly predictive of DTI change.

Conclusions: The corpus callosum, cingulum bundle, and fornix show the most prominent dose-dependent changes following RT. Future studies examining correlation with cognitive functioning and potential avoidance of critical white matter regions are warranted.

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Radiation therapy (RT) is standard of care for most primary and metastatic brain tumors. However, RT can damage healthy brain tissue, leading to neurocognitive deficits in verbal and nonverbal memory, executive function, and attention and problem-solving [1]. Pathogenesis of this process involves white matter damage driven by vascular injury, demyelination or axonal injury; parenchymal injury characterized by gliosis or neuroinflammation; impairment of hippocampal neural stem cell function; and possibly cortical thinning [2,3].

Despite advances in precision and conformality of RT delivery, there is little evidence regarding regional sensitivity of the brain to radiation on which to base applications of these technologies. There are no accepted regional dose constraints for white matter in fractionated partial brain RT. Maximum dose constraints exist for brain parenchyma in general, without distinguishing between cortex, white matter, and deep gray matter structures. Based on evidence that radiation impairs hippocampal neural stem cell differentiation [4], avoidance of the hippocampus during whole-brain RT for brain metastases has gained some traction and has been associated with improved memory preservation [5]. However, even without hippocampal damage, injury to its afferent and efferent white matter pathways may still result in memory decline or other cognitive impairment.

Radiation damage to white matter has been studied using diffusion tensor imaging (DTI), a non-invasive method of measuring the diffusion of water at the cellular level. DTI models the overall motion of water as an ellipsoid using a tensor model, with quantitative metrics allowing the study of white matter or axonal structures. Generally, DTI changes have been found to be progressive and occur after some threshold or in a dose-responsive manner [6–8]. Studies have generally focused on one or a few selected white matter regions. Pediatric patients have been found to have lower fractional anisotropy (more white matter disruption) in frontal lobe, temporal lobe, and periventricular white matter after

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radiation [9–11]. Other studies of adults have looked at only particular regions, such as the corpus callosum, parahippocampal cingulum, brain stem, and limbic circuit [8,12,13]. Many of these studies included patients receiving whole brain RT with a constant dose across the entire brain [9–13].

We previously analyzed DTI metrics of white matter damage after RT and found progressive, dose-dependent changes even at low doses and at time points early on after RT [14]. However, it is unclear which white matter regions of the brain are the most sensitive to radiation injury. Such insights would inform efforts toward cognitive-sparing RT. In this study, we sought to characterize the spatial heterogeneity of dose–response to DTI metrics across white matter tracts using an atlas-based approach. The cohort consists of primary brain tumor patients receiving partial brain RT, to explore dose response and sensitivity across the entire white matter of the brain and across a range of probative doses.

Materials and methods

Study design

Study patients were treated with photon-based fractionated partial brain RT from January 2010 to December 2014. A total of 49 patients met criteria of MRI and DTI imaging [15] at pre-RT (or within one week of RT start) and one year post-RT (9–12 months) time points. Most patients were treated to 60 Gy in 30 fractions. Other dose schedules were converted to a total 30 fraction equivalent dose using biologically equivalent dose principles [16] and an α/β ratio of 2 Gy [14]. Treatment and demographic factors are shown in Supplementary Table 1. This study was approved by our institutional review board.

MRI acquisition

MR imaging was performed on a 3T Signa Excite HDx scanner (GE Healthcare, Milwaukee, Wisconsin) equipped with an 8-channel head coil. The imaging protocol included a 3D volumetric T1-weighted inversion recovery spoiled gradient-echo sequence (echo time [TE]/repetition time [TR] = 2.8/6.5 ms; inversion time [TI] = 450 ms; flip angle [FA] = 8 degrees; field of view [FOV] = 24 cm; $0.93 \times 0.93 \times 1.2$ mm) and a 3D T2-weighted FLAIR sequence (TE/TR = 126/6000 ms; TI = 1863 ms; FOV = 24 cm; $0.93 \times .093 \times 1.2$ mm). Diffusion data were acquired with a single-shot pulsed-field gradient spin-echo-planar imaging sequence (TE/TR = 96 ms/17 s; FOV = 24 cm, matrix = $128 \times 128 \times 48$; slice thickness = 2.5 mm) at $b = 0$, 500, 1500, and 4000 s/mm^2, with 1, 6, 6, and 15 unique gradient directions for each b-value, respectively.

Image processing and registration

All image data were preprocessed using in-house algorithms developed in MATLAB (Mathworks, Natick, Massachusetts). Anatomical scans were corrected for distortions due to gradient nonlinearities using a spherical harmonic representation of the gradient fields [17]. Diffusion scans were corrected for spatial distortions associated with gradient nonlinearities, susceptibility (using a separate opposite phase-encoding polarity acquisition) [18], and eddy currents (using a post-acquisition correction algorithm) [19]. The diffusion tensor at each time point was calculated using mono-exponential fitting and data from all diffusion weightings ($b = 0$, 500, 1000, 4000 s/mm^2). We analyzed four main diffusion metrics, each computed as a map at each time-point [14]. These diffusion metrics are defined in detail previously [14]: mean diffusivity (MD) represents the average mobility of water molecules and is sensitive to edema; fractional anisotropy (FA) is an expression of the degree of directional bias and hence a marker of microstructural white matter integrity; axial diffusivity (AD) represents diffusion along the white matter axon and is thought to be sensitive to axonal injury; radial diffusivity (RD) represents diffusion perpendicular to axonal orientation and is a marker of demyelination [20,21].

Weighted averages of T1 and T2 FLAIR images were calculated to account for edema and other pathology during registration of diffusion images. Pre-RT MRI images were linearly co-registered to the CT simulation images used in radiation treatment planning. The quality of this registration was confirmed visually slice-by-slice, and the resulting transformation matrix was used to resample the delivered radiation dose distribution to the MRI volume space. To avoid bias to one time point [22], MRI volumes from each time point were non-linearly registered to the MNI152 standard-space T1-weighted average structural template image, a normal brain atlas, using FSL's FNIRT, a standard nonlinear registration algorithm which implements a "sum-of-squared differences" cost function [23,24]. Tumor and surgical beds/scars were censored from consideration during the registration [3,14]. Successful registration was confirmed via visual inspection. The resulting deformation fields were applied to the diffusion images and pre-RT dose map.

Regions of interest analysis

With all patient diffusion scans in MNI space, regions of interest were defined using ICBM-DTI-81 white-matter labels atlas [25]. Paired structures were considered as two observations of one region. Twenty-one ROIs were identified. Representative tracts are shown and labeled in Fig. 1. A censoring mask including tumor, tumor bed, surgical cavity, surgical scars, and any T2 FLAIR edema hyperintensity was manually drawn for each patient and for each time point separately. To guard against the inclusion of non-white matter due to small registration errors or misalignment of the ICBM-DTI-81 hand-drawn labels with our actual subject anatomy, we excluded voxels with a baseline FA of less than 0.2 on the basis these may not represent well-defined white matter tracts [26].

Skeletonized analysis

Skeletonization of white matter tracts, as with FSL's Tract-Based Spatial Statistics, is a common method of aligning FA images from multiple subjects via projection onto an alignment-invariant tract representation (the "mean FA skeleton") [26]. This process may compensate for local registration errors and improve the sensitivity, objectivity and interpretability of analysis of multi-subject diffusion imaging studies [27]. We undertook a secondary analysis of skeletonized white matter tracts to determine if our findings were reproducible with this method.

A mean of the FA images of all subjects was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to the group. Each subject's aligned FA data were then projected onto this skeleton by assigning the maximum FA value perpendicular to the skeleton to the nearest skeleton voxel [26]. The same projections were also applied to all MD, AD, and RD maps to generate skeletonized forms of these maps as well.

Statistical analysis

Mean dose ranges to each tract are shown in Supplementary Fig. 1, and voxel size of each tract pre- and post-RT is shown in Supplementary Table 2. Mean values for MD, FA, AD, and RD were obtained for each region of interest. We used R [28] and *lme4* [29] to perform linear mixed effects analyses fit using maximum