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Original Research Article

Analyses of regional radiosensitivity of white matter structures along tract axes using novel white matter segmentation and diffusion imaging biomarkers

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ABSTRACT

Background and purpose: Brain radiotherapy (RT) can cause white matter damage and downstream neurocognitive decline. We developed a computational neuroimaging tool to regionally partition individual white matter tracts, then analyze regional changes in diffusion metrics of white matter damage following brain RT.
Materials and methods: RT dose, diffusion metrics and white matter tract structures were extracted and mapped to a reference brain for 49 patients who received brain RT, and underwent diffusion tensor imaging pre- and 9–12 months post-RT. Based on their elongation, 23 of 48 white matter tracts were selected. The Tract-Crawler software was developed in MATLAB to create cross-sectional slice planes normal to a tract's computed medial axis. We then performed slice- and voxel-wise analysis of radiosensitivity, defined as percent change in mean diffusivity (MD) and fractional anisotropy (FA) as a function of dose relative to baseline.
Results: Distinct patterns of FA/MD radiosensitivity were seen for specific tracts, including the corticospinal tract, medial lemniscus, and inferior cerebellar peduncle, in particular at terminal ends. These patterns persisted for corresponding tracts in left and right hemispheres. Local sensitivities were as high as 40%/Gy (e.g., voxel-wise: $-39 \pm 31\%$/Gy in right corticospinal tract FA, $-45 \pm 25\%$/Gy in right inferior cerebellar peduncle FA), $p < 0.05$.
Conclusions: Tract-Crawler, a novel tool to visualize and analyze cuts of white matter structures normal to medial axes, was used to demonstrate that particular white matter tracts exhibit significant regional variations in radiosensitivity based on diffusion biomarkers.

1. Introduction

Brain radiotherapy is standard of care for most primary and metastatic brain tumors. However, the decline of neurocognitive function is an unfortunate sequelae among brain tumor patients treated with radiotherapy, likely driven in part by damage to white matter, cortex, and neurogenic stem cell niches [1]. In particular, radiation-induced damage to normal-appearing white matter has been studied using advanced diffusion imaging [2–6], with evidence associating diffusion biomarkers of white matter damage with neurocognitive decline after brain radiation. How to prevent such neurocognitive decline in terms of selective avoidance of white matter regions is unclear. The QUANTEC report [7] on radiation dose-effects in the brain stipulates constraints for radiation necrosis, but acknowledges that there is limited data on constraints to avoid neurocognitive decline. It encourages the use of advanced neuroimaging to identify signatures of microstructural damage and relate these imaging biomarkers to functional changes.

We have previously reported on radiation-induced damage to white

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matter following brain RT for primary brain tumors [8]. Specifically, using diffusion tensor imaging, it was demonstrated that changes in water diffusion characteristics correlate with dose and that these changes are observed for the full dose range, including < 10 Gy [5]. We further investigated whether these changes vary regionally across the brain [4]. Overall, 21 structures were identified and mean values for fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) were calculated for each structure for scans acquired before and 9–12 months after RT. These changes were shown to correlate with maximum and mean dose for some, but not all structures, with the corpus callosum, cingulum bundle and fornix showing the most pronounced dose-response. Traditionally, diffusivity metrics are averaged over the volume of the structure, and so any information on spatial variation of the sensitivity of the tract along its principal (primary) axis is lost. Studies employing a more sophisticated along-tract analysis have been reported in the neuroimaging literature. For example, the superiority of along-tract analysis of diffusion imaging metrics over the tract-averaged approach has been demonstrated in a study of children with fetal alcohol spectrum disorders vs typically developing controls [9]. The emphasis of the along-tract analysis of FA and MD following brain radiotherapy is different. Literature, including our preliminary results [10], suggests that diffusion tensor imaging predicts decline in cognitive function [11]. If differential radiosensitivity along the tract axis is demonstrated, this would pave way to tract-geometry driven, rather than tract-averaged-driven constraints to guide radiotherapy planning.

In order to determine how radiation sensitivity measures change along a tract, the tract must first be correctly partitioned, which is a complex procedure. In the case of perfectly cylindrical geometry, this problem can be solved by a basic rotation of the volume. However, tracts are often curved in 3-dimensional space and so traditional parallel (axial, sagittal, coronal) slice planes neither uniformly subdivide a tract nor provide a true representation of a local cross-section. In the extreme case of curved tracts which subtend an angle > 180°, parallel slicing would sometimes result in these tracts being sampled in two disconnected locations at once, regardless of any possible rotations. Computation of an anatomical central axis to calculate normal-tissue metrics to correlate with the risk of radiation-induced complications has been attempted for reasonably well shaped structures. Hoogeman et al. [12] used the minimum distance field approach to define the axis of a rectum to guide digital unfolding of the rectal wall. White matter tracts present a more complicated challenge as they are not necessarily cylindrical, and vary in size and shape.

In this report we describe a novel method to define the tract axis, and use this method to explore differential sensitivity to radiation along the axes for 23 white matter tracts.

2. Material and methods

2.1. Study design

A detailed description of the study patients and MRI image preprocessing can be found elsewhere [4]. In brief, 49 patients with pre- and post-RT MRI imaging were selected for analysis. The MRI acquisition protocol consisted of a T1-weighted, T2-weighted FLAIR, and a diffusion-weighted sequence. Diffusion data (TE, 97 ms, TR, 1700 ms; diffusion time, ~90 ms; matrix, 128 × 128 × 48; resolution (mm), 1.875 × 1.875 × 2.5) were acquired with b = 0, 500, 1500, and 4000 s/mm^2. One instance of the non-diffusion weighted images (b = 0 s/mm^2) was acquired, while 6, 6, and 15 unique gradient directions were acquired for b = 500, 1500, and 4000 s/mm^2, respectively. Anatomical scans were corrected for distortions arising from gradient nonlinearities [13] while diffusion-weighted scans were corrected for distortions arising from static field inhomogeneity [14] using in-house algorithms. A diffusion tensor was fit, per-voxel, to the diffusion data, from which the mean diffusivity (MD) and fractional anisotropy (FA) were extracted. The anatomical scans were used to register the patient data set, including the MD and FA maps, into the standard space, from which the white matter tracts could be segmented using the JHU-ICBM 1 mm atlas [15–17]. RT planning data, including the planning CT and volumetric calculated dose, were also non-linearly registered to the standard space. The quality of the final registrations was manually assessed by visual inspection. Overall, 48 tracts (left and right) were automatically segmented using a non-linear registration to the JHU-ICBM atlas [18]. The study was approved by the institutional review board.

Tumor, tumor bed, surgical cavity, and surgical scars were manually censored on each patient. A white matter mask was computed from the T1-weighted sequence at the baseline time-point using automatic segmentation software [19]. In order to avoid partial volume effects from gray matter and CSF at the edges of the volume, the mask was shrunk to its six-connected voxels (voxels whose six face neighbors were also white matter) [5].

2.2. Fractional anisotropy and mean diffusivity analysis

A computational neuroimaging tool, Tract-Crawler, was developed in MATLAB (Mathworks, Natick, MA) to create slice planes for individual white matter tracts in the brain normal to the tract's computed medial axis. This software requires the definition of terminal points of a tract, and therefore only tracts where clear identification of these points was possible could be used. Following a visual examination, 23 of 48 white matter tracts were selected for this analysis, as described in Table 1. These data demonstrate that the selected tracts are indeed

Table 1
Medial axis lengths for each of the 23 tracts analyzed and maximum and mean tract diameters, calculated from the cross-sectional area assuming circular geometry.

Tract	Length along Medial Axis (mm)	Maximum Diameter (mm)	Mean Diameter (mm)
Fornix (column and body of fornix)	31	5	3
Corticospinal Tract L/R	37	9	5
Medial Lemniscus L/R	21	7	5
Inferior Cerebellar Peduncle L/R	37	5	4
Superior Cerebellar Peduncle L/R	29	6	5
Anterior Corona Radiata L/R	54	14	11
Sagittal Stratum (includes inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) L/R	53	9	6
Cingulum (cingulate gyrus) L/R	107	6	4
Cingulum (hippocampus) L/R	51	5	3
Fornix (cres) L/R	43	6	4
Superior Longitudinal Fasciculus L/R	81	12	8
Superior Fronto-Occipital Fasciculus L/R	28	5	4