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Cognitive function

Diffusion tensor imaging predicts cognitive function change following partial brain radiotherapy for low-grade and benign tumors

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ABSTRACT

Purpose/objectives: Radiation injury to parahippocampal cingulum white matter is associated with cognitive decline. Diffusion tensor imaging (DTI) detects micropathologic changes in white matter. Increased radial diffusion (RD) and decreased axial diffusion (AD) correspond to demyelination and axonal degeneration/gliosis respectively. We aimed to develop a predictive model for radiation-induced cognitive changes based upon DTI changes.

Materials/methods: Twenty-seven adults with benign or low-grade tumors received partial brain radiation therapy (RT) to a median dose of 54 Gy. Patients underwent DTI before RT, during RT, and at the end of RT. Cognitive testing was performed before RT, and 6 and 18 months after RT. Parahippocampal cingulum white matter was contoured to obtain mean values of AD and RD.

Results: By univariate analysis, decreasing AD and increasing RD during RT predicted declines in verbal memory and verbal fluency. By multivariate analysis, baseline neurocognitive score was the only clinical variable predicting verbal memory change; no clinical variables predicted verbal fluency change. In a multivariate model, increased RD at the end of RT significantly predicted decline in verbal fluency 18 months after RT.

Conclusions: Imaging biomarkers of white matter injury contributed to predictive models of cognitive function change after RT.

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Changes in cognitive function have been observed following brain radiation therapy (RT) in adults [1,2], however mechanisms are poorly understood and predictive models are limited. Cognitive decline may be due in part to white matter injury caused by radiation damage to vascular and glial progenitor cells as well as chronic inflammation [3]. Previous studies have established that radiation to the hippocampus and associated structures increases risk of cognitive decline [4,5]. However, improvements in cognitive performance after partial brain irradiation have also been seen, possibly due to tumor control or test practice effects [6,7].

In this study we examined the parahippocampal cingulum, a medial temporal lobe white matter structure that is an afferent connection to the hippocampus [8]. We used diffusion tensor imaging (DTI), a magnetic resonance imaging (MRI) technique that is more sensitive to white matter microstructural changes than standard T1- and T2-weighted MRI [9]. Two measurements derived from diffusion tensor eigenvalues are radial diffusion (RD) and axial diffusion (AD). Increased RD is associated with histologic evidence of demyelination, and decreased AD is associated with axonal degeneration and inflammatory gliosis [10,11]. We have previously found that the parahippocampal cingulum shows greater diffusion changes after radiation than other white matter exposed to the same dose [12,13], and that late-delayed cognitive function changes are associated with concurrent diffusion changes in the parahippocampal cingulum [14].

In the present study, we sought to identify a *predictive* imaging biomarker of cognitive function after RT by conducting a prospective assessment of the cognitive abilities of adults with benign or low-grade brain tumors treated with partial brain RT. Patients were followed 18 months after RT to study both early-delayed (6 months) and late-delayed (18 months) effects. We hypothesized that diffusion changes in the parahippocampal cingulum consistent with white matter injury during and immediately after RT would be independent predictors of later cognitive function.

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Methods

Study design

Adults with benign or low-grade intracranial tumors were enrolled in a prospective, institutional review board approved study. All patients received a standard 6 or 7-week course of daily-fractionated RT. Functional status was assessed before RT using Karnofsky Performance Status (KPS), Folstein Mini-Mental State Examination (MMSE), and Radiation Therapy Oncology Group neurological function class. All enrolled patients had a KPS score $\geqslant 80$, MMSE score $\geqslant 27$, and neurological function class $\leqslant 2$, indicating no major functional impairments. Patients included in the current analysis had at least two time points of imaging data and no tumor progression or radiation necrosis during follow-up. Surgical resection and any complications such as hydrocephalus or hemorrhage occurred before study enrollment.

Treatment planning and dosimetry

3D-conformal or intensity-modulated radiation therapy planning was performed on computed tomography images acquired using a Brilliance 16-slice system (Philips Healthcare, Best, Netherlands). Dose values were corrected to 2 Gy per fraction equivalents using the linear-quadratic model with $\alpha/\beta = 2.5$ Gy [15]. The contribution of radiation dose to the risk of cognitive function impairment was estimated using generalized uniform equivalent dose (gEUD) calculated from the whole brain volume excluding gross target volume [16]. Our model used $a = 14$, indicating sensitivity to low-volume, high-dose areas. This parameter was determined from a maximum likelihood analysis of the Lyman normal tissue complication probability model [17] for cognitive function impairment from a dataset of 32 patients [18].

Study image acquisition

Patients underwent MRI at three time points: 1–2 weeks before RT (pre-RT), 3 weeks after starting RT (mid-RT), and within 1 week of completing RT (end-RT). At each time point, DTI, T1- and T2-weighted MR images were acquired in a single session. Due to technology upgrades, three different MRI systems were used in the study, but each patient completed imaging on a single system. Diffusion imaging parameters by system: 1.5T Signa (GE Healthcare, Milwaukee, USA), matrix 128×128, voxels $2.5 \times 2.5 \times 4$ mm, 9 diffusion directions, 2 averaged diffusion image sets, $b = 1000$ s/mm^2. 3T Achieva (Philips Healthcare, Best, Netherlands), matrix 128×128, voxels $1.75 \times 1.75 \times 2$ mm, 15 diffusion directions, 2 averaged diffusion image sets, $b = 800$ s/mm^2. 3T Skyra (Siemens Healthcare, Erlangen, Germany), matrix 220×220, voxels $1.72 \times 1.72 \times 3.9$ mm, 20 diffusion directions, 3 averaged diffusion image sets, $b = 1000$ s/mm^2.

Image pre-processing and masking

MRI pre-processing was performed using the FMRIB Software Library (FSL) (FMIRB Analysis Group, Oxford, UK) [19]. Diffusion tensor eigenvalues were calculated at each voxel, from which three parameter maps were generated: axial diffusion (AD), radial diffusion (RD), and fractional anisotropy (FA). All images were interpolated to 1 mm^3 voxels. On all image sets, abnormal tissue masks were contoured using post-contrast T1- and T2-weighted images. Volumes of tumor mass, edema, and visibly affected areas were manually contoured and excluded from registration and statistical analysis.

Within-patient longitudinal MR image registration

To improve contouring uniformity, for each patient FA images from multiple time points were co-registered to derive a within-patient template using an iterative registration method [20]. Final registration parameters were then applied to the tumor mask, AD image, and RD image from each time point, co-registering all images to the within-patient template. Non-linear registrations were performed by the FSL registration algorithm FNIRT [19,21].

Structure contouring

For each patient, the parahippocampal cingula were manually contoured on the within-patient FA template image. The structure was defined as the temporal portion of the cingulum white matter inferior to the corpus callosum. A 1-voxel erosion operation was performed on manual contours to reduce averaging error from edges (Fig. 1). The mean values of AD and RD were then calculated from contour volumes excluding the abnormal tissue masks. FA values were not used for statistical analysis to avoid biases introduced by using FA images for registration and contouring.

Cognitive testing

Cognitive testing was performed at three time points: pre-RT, 6 months after completing RT, and 18 months after completing RT. Testing included the Hopkins Verbal Learning Test (revised edition) Total and Percent Retained components of short-term and delayed verbal memory (HVLT-T and HVLT-PR), the Benton Controlled Oral Word Association Test of verbal fluency (COWAT), and Trail Making Test B of attention and task-switching (TMT-B; preceded by the simpler version Trail Making Test A). Testing was performed under the supervision of a clinical neuropsychologist (HAB). Published data were used to convert raw scores to normalized Z-scores based on age, sex, and years of education [22–24].

Statistics

Diffusion change was calculated as a percentage change from pre-RT. Thresholds for significant changes in individual DTI measurements (AD: ±3.9%, RD: ±2.9%) were determined from previously derived repeatability coefficients [25]. Cognitive test score changes were calculated as difference in Z-score from pre-RT value. Thresholds for significant changes in individual cognitive score changes were determined using the reliable change index [26]. Student's t-tests were used to assess group changes in diffusion and cognitive scores. Simple linear regression and Student's t-tests were used to determine whether changes in diffusion were significantly related to clinical variables or gEUD. Univariate and multivariate analyses were used to determine if changes in cognitive scores after radiation therapy were related to clinical variables, gEUD, baseline cognitive scores, or changes in diffusion. Clinical variables assessed included patient age, patient sex, invasive tumor (glioma), and frontal or temporal lobe location ("frontotemporal"). Univariate analysis was performed using simple linear regression or two-sample Student's t-test. Multivariate analysis was performed using linear regression models in two stages. First stage models included all predictor variables except for diffusion changes. Second stage models excluded variables from stage one with parameter significance $p > 0.10$, then added diffusion as a predictor variable. Intercepts were unconstrained in all models. All tests of significance were two-tailed with significance threshold $p \leqslant 0.05$. Correction for multiple comparisons was performed on the second stage multivariate models with Bonferroni correction. All models for one cognitive score constituted a single hypothesis family with 8 hypothesis tests (2 diffusion indices $\times$ 2 imaging