

ASSESSMENT OF STRUCTURAL INTEGRITY OF NORMAL BRAIN TISSUES IN CRANIOPHARYNGIOMA PATIENTS AFTER PROTON THERAPY

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TARGET AUDIENCE: Imaging scientists and clinicians who have interests in assessment of normal tissue injury following cancer treatment.

BACKGROUND AND PURPOSE: Childhood craniopharyngioma is a brain tumor that typically arises in the suprasellar region. It is often managed by surgical resection followed by radiation treatment. Proton beams have been recently used for treatment of this tumor in an effort to reduce side effects associated with irradiation (1). Compared to conventional radiation using photons, protons advantageously deliver less dose to normal tissues, expected to give favorable structural and functional outcomes. The purpose of this work is to monitor structural changes in normal-appearing white matters of craniopharyngioma patients after proton therapy. We used diffusion tensor imaging (DTI) for this assessment, which has been reported as a useful marker for detecting white matter alterations induced by radiation treatment (2).

METHODS: A total of ten craniopharyngioma patients (baseline age 3-19 years, 2 males) recruited to an institutional prospective study were included in this work. DTI data were acquired at baseline before proton therapy and follow-ups of 3 and 6 months from the start of irradiation. DTI scans were performed on a 1.5T MR scanner (Avanto; Siemens Medical Solutions) using a double spin echo pulse sequence with the following scan parameters: TR/TE=10,000 ms/100ms; FOV=230 × 230 mm²; matrix = 128 × 128; slice thickness = 3 mm; b-value=1,000 mm²/s; and the number of averages=4.

We used FSL (FMRIB, Oxford, UK) to calculate DTI-derived parameter maps including fractional anisotropy (FA) and radial diffusivity (RD). All DTI parameter maps were first spatially registered to the baseline. Then, they were normalized to a standard space (MNI) by a nonlinear deformation so that the same regions-of-interest (ROIs) identified in the standard space could be commonly used for all patient images. The CT and the associated dose distribution were also spatially normalized to the standard space using a T1-weighted high resolution image (1.25 × 0.82 × 0.82 mm³) as an intermediate.

We manually identified five white matter ROIs in the standard space that tend to receive high doses: pons, midbrain, posterior and anterior limb of the internal capsule (AIC and PIC), and genu of the corpus callosum (GCC). The average DTI parameter values at each ROI were calculated. A pairwise t-test was performed for group comparisons between baseline and the follow-up data. The dependency of DTI parameter change on dose and age-related effect was tested by a linear model for each ROI: $nDTI = \beta_0 + \beta_1 \times dose + \beta_2 \times age$, where $nDTI$ indicates DTI parameter normalized by the baseline value, $dose$ is the average dose to the given ROI, and age is the baseline age.

RESULTS: The doses to the identified ROIs ranged from 19.3 Gy to 54.6 Gy, showing variance across patients and brain regions. Figure 1 shows the mean and standard deviation of dose to each region. The doses to different ROIs were not the same as each other (one-way ANOVA, $p=0.013$). Midbrain tended to receive higher dose than the other regions possibly because of its proximity to the target volume.

Figure 2 compares the baseline DTI parameter values (Time=0) with those at the follow-ups (Time=3 or 6 months). We observed a reduction of FA and an increase of RD at 3 months after the radiation treatment (pairwise t-test, $p<0.05$ for all ROIs). The mean percentage changes ranged from -3.3% (Pons) to -5.0% (AIC) for FA and from 2.2% (Pons) to 11.6% (GCC) for RD. On the other hand, the DTI parameters at 6 months were not significantly different from the baseline values (pairwise t-test, $p > 0.06$ for all regions) except for FA of pons ($p=0.043$).

The DTI parameter changes were weakly related to dose and age. Only few tests reached statistical significance ($p<0.05$). The FA reduction in the pons tended to be greater with higher dose ($\beta_1 < 0$, $p=0.092$ for 3 month data and $p=0.030$ for 6 month data). The normalized FA in the PIC showed a positive relation with baseline age ($\beta_2 > 0$, $p=0.035$), indicating smaller FA reduction for older patients.

DISCUSSION: We focused on FA and RD in this work based on previous reports suggesting that these two parameters are most sensitive to the radiation-induced white matter changes (3,4). The reduction of FA and increase of RD implied compromised structural integrity of white matter contributed by demyelination (5). However, the changes were relatively mild compared to those previously reported based on photon therapy (3,4). Furthermore, the data at the 6 month follow-up suggested that the alteration has recovered. We did not observe a strong correlation between DTI parameter changes and dose possibly due to the mild change and small number of patients. Other potential confounding factors that may have affected our findings include surgical effect and proton delivery uncertainties.

CONCLUSION: The DTI data suggested that the short-term (<6 months) change in normal-appearing white matters of craniopharyngioma patients is mild after proton therapy. Longer follow-up with a larger number of patients will be helpful to confirm this observation.

REFERENCES: (1) Beltran et al. *Int J Radiat Oncol Biol Phys*, 82:e281-e287, 2012; (2) Khong et al. *AJNR Am J Neuroradiol*, 24:734-740, 2003; (3) Nagesh et al. *Int J Radiat Oncol Biol Phys*, 70:1002-1010, 2008; (4) Hua et al. *Int J Radiat Oncol Biol Phys*, 82:2047-2054, 2012; (5) Song et al. *Neuroimage*, 17:1429-1436, 2002.

