Serial Diffusion Tensor Imaging Study in Children Receiving Cranial Radiation

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Introduction: Radiation therapy (RT) plays an important role in improving survival in childhood brain malignancies. However, radiation therapy to the brain, even if administered at relatively low doses, generates a spectrum of adverse acute, early delayed and late effects. Radiation induced injury is associated with vascular abnormalities and damage to oligodendrocytes that are responsible for axonal myelination[1]. Diffusion tensor imaging (DTI) is a non-invasive method that can provide unique information on radiation-induced white matter pathology[2-3]. A recent DTI study evaluating early delayed effects of RT in children revealed widespread abnormalities in white matter FA and ADC[4]. The aim of this prospective longitudinal study was to evaluate FA and ADC changes in specific white matter regions over a period of 15 months after completion of RT in children diagnosed with brain tumors and ALL.

Methods: Six pediatric patients (2 girls, age range 8.7-18.7 years) who received radiation to the brain were examined. The diagnoses included medulloblastoma (posterior fossa, n=2), malignant glioneuroma (frontal lobe, n=1), germinoma (suprasellar, n=1), pilocytic astrocytoma (hypothalamic region, n=1), and T-cell ALL (n=1). The control group was comprised of 27 healthy children (14 girls, age range 6.2-18.3 years). The patients were examined before completion of RT (first scan), 6 months (second scan), and 15 months (third scan) after the end of radiation therapy. Controls were examined at baseline, 6 months, and 15 months follow-ups. MRI was performed at 1.5 Tesla. DTI data were acquired with a single-shot spin echo planar sequence with 15 non-collinear diffusion gradient directions (b=1000 s/mm^2) and two b=0 s/mm^2 images. The following parameters were used: 24 axial slices, 96*96 acquisition matrix, FOV 240 mm^2, 5 mm slice thickness, no gap. FA, ADC, and color maps were calculated from raw data using the in-house developed software 'DTI Studio' .Polygonal ROIs were drawn on the color maps two times and the measurements were averaged after overlaying the ROIs on the FA and ADC maps. Examined fiber tracts included cerebral peduncle, temporal white matter (TWM), frontal white matter (FWM), anterior and posterior limb of the internal capsule, anterior white matter (AWM), temporo-occipital white matter (TOWM), superior longitudinal fasciculus, corona radiata, superior fronto-occipital fasciculus, cingulum (CING) and centrum semiovale, and genu (GCC), body (BCC), and splenium of the corpus callosum (SCC)[5]. In order to assess the dose delivered to the ROIs, the FA maps were imported into the Pinnacle Treatment Planning System (Philips Medical Systems, Madison, WI) and registered with the treatment plan using the CT simulation scan. Non-parametric Wilcoxon rank sum test and regression analysis were used for statistical evaluations.

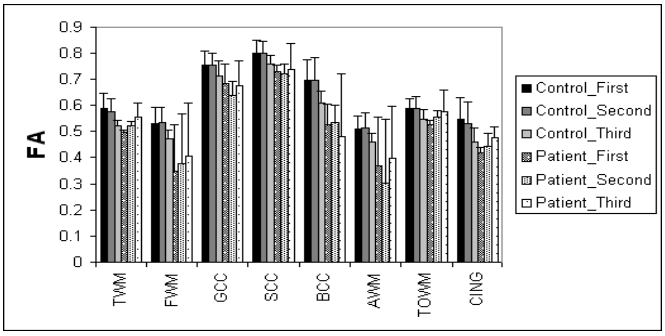

Fig 1. FA values measured at baseline, 6, and 15 months follow-ups.

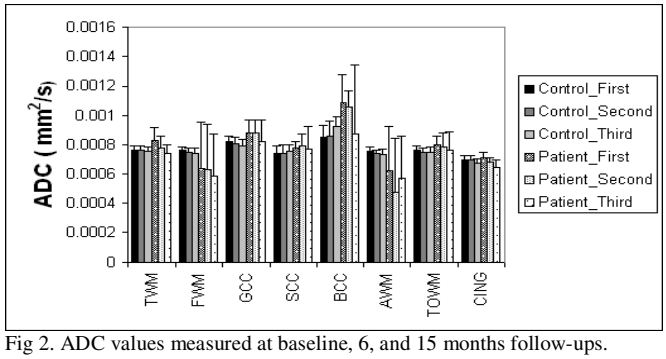

Fig 2. ADC values measured at baseline, 6, and 15 months follow-ups.

Results: At the first scan, the Wilcoxon rank sum analyses revealed highly significant differences in FA in 8 regions between the patients and controls (all $p < 0.014$) (Fig. 1). Six months after radiation, FA in patients was unchanged or increased except for genu and splenium of corpus callosum, showing a decrease in FA (Fig. 1). In the control group, the detected FA changes (average 9.2 ± 3.5%) between first and second scan were comparable to the variability determined previously for our protocol (coefficient of variation ~5%)[5]. Fifteen months after radiation, no significant differences in FA values were found between patients and control groups. Similarly as FA, ADC values were abnormal in five regions at the first scan and tended to approach to control values at the second and third scans (Fig. 2). With increasing radiation dose, FA decreased in the genu of the corpus callosum (slope $-2.4 \cdot 10^{-5}$ cGy^{-1}, $p=0.007$) and ADC increased in the splenium of the corpus callosum (slope $1.9 \cdot 10^{-5}$ cGy^{-1} mm^{2}s^{-1}, $p=0.014$).

Discussion: Despite no visible pathology in the evaluated ROIs on conventional MRI, abnormal FA and ADC values were detected in most white matter regions at the baseline scan, before the start of radiation therapy. It is therefore likely that the DTI-detected abnormality is associated with presence of malignancy, effect of chemotherapy or surgery. However, due to the small number of patients, it is not possible to separate the contribution of these effects on FA and ADC values. With the exception of a few regions (e.g. corpus callosum), FA and ADC tended to change toward control values at 6 months post-radiation, although FA and ADC values remained abnormal compared to control values. A significant effect of radiation dose on FA is consistent with radiation induced inflammation, demyelination or vascular damage. Our data at 15 months post radiation are suggestive of continuing recovery from the acute side effects of radiation, although interpretation should be cautious since currently only 6 subjects have completed the 15 month scan. In summary, the results presented here suggest that DTI is able to monitor subtle acute and early delayed changes in white matter integrity associated with RT. The clinical significance of these findings awaits correlation with neuropsychological test data and long term outcome.

References: **1.** Wong C.S., et al. Mol Interv. 4: 273-284 (2004), **2.** Khong P.L., et al. Radiology 236: 647-652 (2005), **3.** Leung L.H., et al. NeuroImage 21: 261-268 (2004), **4.** Tannazi F., et al. ISMRM (2007), #2482, **5.** Bonekamp D, et al. NeuroImage 34: 733-742 (2007).

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