Serial Diffusion Tensor Imaging to Characterize Radiation Induced Changes in Normal Appearing White Matter following Radiotherapy in Patients with Adult Low Grade Gliomas (WHO grade II)

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Introduction: Diffusion tensor MR imaging (DTI) has been widely used for the detection of WM abnormality in various disease conditions.[1] Quantitative evaluation of changes in normal appearing white matter (NAWM) of brain tumor patients receiving radiotherapy (RT) have been described using DTI metrics i.e. fractional anisotropy (FA) and mean diffusivity (MD).[2] However, data on DTI metrics in NAWM irradiated to varying doses are scarce and in one recent study, confounded by the addition of chemotherapy to RT.[3] Besides FA and MD, other DTI metrics i.e., linear case (CL), planar case (CP) and spherical case (CS) may provide additional information associated with WM injury as modeled by various groups.[4] This study assessed the utility of various DTI metrics to characterize the threshold for detection and temporal evolution of changes in NAWM of adults with low grade glioma (LGG) treated with RT.

Materials and methods: With informed consent five patients [mean age (SD)=41.6 (11.78) years], with histopathologically proven WHO grade-II glioma, were immobilized in a thermoplastic three-point fixation mask and following placement of MR compatible fiducial markers, underwent standard radiotherapy treatment planning (RTP) MR scans which include both conventional and DTI imaging in the same sitting. Conventional MRI and DTI images were acquired on a 1.5 Tesla GE MRI scanner using standard quadrature birdcage head coil. Conventional MRI included T2 [Repetition time (TR)/Echo time (TE)/Number of excitation (NEX)=6sec/85msec/1), T1 (TR/TE/NEX=1000msec/14msec/1), fluid attenuated inversion recovery (FLAIR) (TR/TE /NEX=9sec/120msec/1, inversion time (IR) = 2200msec) and post contrast T1 (TR/TE/NEX=1000msec/14msec/1) weighted images. DTI data were acquired using a single-shot echo-planar dual SE sequence with ramp sampling. The b-factor was set to 1,000 s/ mm^2, TR=8secs, TE=100ms, NEX=8. All the conventional and DTI images were acquired in axial plane with image matrix size of 256×256, field of view (FOV) of 240×240 mm, slice thickness of 3 mm with no inter-slice gap. Patients were imaged again at 3, 8 and 14-months after completion of RT for a total of 18 studies. Five normal healthy volunteers also underwent for the DTI imaging.

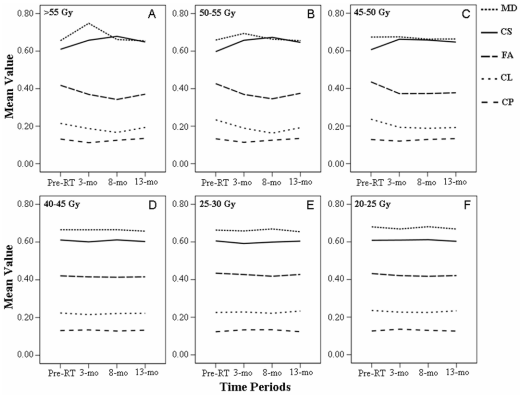
***Radiotherapy planning*:** The FLAIR and the b0 DTI images were transferred using DICOM protocol to the treatment planning system (TPS) (Eclipse version 8.0, Varian Medical Systems, Palo Alto, CA). The b0 DTI images were co-registered with the FLAIR RTP images using the fusion software on the TPS. Target delineation was performed on the FLAIR images. The Planning Target Volume (PTV) was expanded from gross tumor volume (GTV) in 3-D by 1.5 cm with appropriate editing for anatomical barriers to tumor spread. RT to a dose of 54Gy/30 fr/6 weeks was delivered conventionally with 2-3 co-planar beams to the PTV with 6MV photons from a linear accelerator. The 95% isodose line aimed to cover the PTV in all cases and dose heterogeneity within the PTV was restricted to -5% to +7% of the prescribed dose. Isodose distribution at 5Gy intervals was visualized in all the slices of FLAIR and the corresponding b0 DTI images. The b0 DTI images with isodose distribution were exported for relative quantitative analysis. Subsequent follow up FLAIR / b0 DTI images were also co-registered with the RTP reference image on the TPS.

***Data processing*:** Data processing was performed using in house developed JAVA based software.[5] Regions of interest (ROIs) analysis for calculation of various DTI derived metrics (FA, MD, CL, CP, and CS) was done for the dose bins from 20Gy to >55Gy with the exception of 30-35 and 35-40Gy bins. For each DTI metric studied in the 5 patients, the number of measurements on the baseline and 3 subsequent studies were 237 (>55Gy), 192 (50-55Gy), 75 (45-50Gy), 69 (40-45Gy), 72 (25-30Gy) and 82 (20-25Gy) for a total of 727 data points. Independent samples t-test was performed between pre RT base line and each follow up study. One way ANOVA was applied to see the time dependent changes in the DTI metrics. Bivariate Pearson's correlation between various DTI metrics was also performed.

Results: In none of the patients, treatment induced WM changes could be visually identified in the post RT sequential studies using standard T2-W or FLAIR sequences. Compared to pre RT values, FA values declined progressively at 3 and 8-months and recovered at 14-months (to values identical to those at 3 months) for dose bins > 55Gy and 50-55Gy. For the 45-50Gy bin, following a significant decline at 3-months, no further decline was seen at 8-months and a non-significant recovery was seen at 14-months. For dose bins of 40-45Gy, 25-30Gy and 20-25Gy, no changes were seen at any time points following RT for any of the DTI metrics. CL mirrored the pattern of FA (r =0.77, P=0.000) with the lone exception for the 45-50Gy bin, where following a significant decline at 3-months, values remained unchanged at 8 and 14-months. CS inversely correlated with FA (r = -0.73, P=0.000), displaying a pattern identical to FA i.e. an increase at 3 and 8-months and a decline at 14-months (to levels identical at 3-months) for >55Gy and 50-55Gy bins, while the increase seen at 3-months for the dose bin of 45-50Gy remained unchanged at 8 and 14-months. Compared to pre RT values, MD increased and CP decreased at 3-months, but returned to base line values at 8 and 14-months for >55Gy and 50-55Gy bins but not at 45-50Gy bins, where, no changes were observed. The FA, MD, CL, CP and CS values in the normal volunteers were 0.43±0.12, 0.67±0.07, 0.23±0.10, 0.13±0.04 and 0.62±0.09 respectively. These were identical to base line data of the patients.

Discussion:

The threshold of detection of radiation changes was 45-50Gy using FA, CL and CS while it was 50-55Gy when using MD and CP. Two major pathways has been described that lead to the development of early delayed white matter damage.[6] One is associated with specific damage of the myelin sheath due to the radiation injury to the oligodendroglial cells and other with breakdown of blood brain barrier (BBB). It has also been reported that all the early demyelinating events were associated with the increased capillary permeability.[7] We suggest that the decrease in FA by 3-months is associated with axonal demyelination and is consistent with the findings of previous studies that have shown reduction in anisotropy in disease processes that affect myelin or axonal integrity. Increased CS and MD values at 3-months probably reflect increased extracellular water content due to the increased capillary permeability. At 8-months, the FA and CL continued to decrease with increased CS in the dose bins of >55Gy, 50-55Gy suggests that demyelination continued to occur along with increased capillary permeability even after 8-months following RT. Graded opening of BBB over a period of time after localized X-irradiation has been reported.[8] This might be the possible explanation of increased CS associated with decreased FA and CL at 8 months following RT. Others have reported reversibility both in the FA and MD values after 8-months following RT and chemotherapy.[2] However, in the present study only MD and CP values normalized 8-months following RT. By 14-months, the FA, CL and CS showed reversibility in the affected dose bins; the reversibility being significant only in the dose bins of >55Gy and 50-55Gy compared to the 8-month assessment suggests that recovery of WM injury and repair of BBB occur to a greater extent for 50-55Gy and >55Gy compared to the 45-50Gy dose bin. However, none of these values normalized by 14-months following RT. We conclude that 45-50Gy is about the threshold for detection of change in DTI metrics upto 14-months following RT. Further, FA along with CL and CS are more sensitive compared to MD and CP. This study may form the basis for designing protocols for evaluating a quantitative effect of RT dose *vs.* WM distortion and its recovery as a function of time.



Graph showing changes in various DTI metrics for the different dose bins before RT, and at 3, 8, and 14 months post RT.

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