The Effect of Radiation on Normal Appearing Gray and White Matter after Treatment for Low Grade Gliomas using Dynamic Contrast Enhanced MRI

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Introduction: Radiation induced perfusion changes that include changes in cerebral blood volume (CBV) in normal regions of brain have been reported[1]. In this preliminary study, by using T_1 based dynamic contrast enhanced magnetic resonance imaging (DCE-MRI), and comparing the pre-treatment and three-month post-treatment perfusion indices, we have tried to evaluate the dose dependent effect of radiotherapy (RT) on perfusion indices i.e. CBV, cerebral blood flow (CBF), permeability (k^{trans}), leakage (v_e) in normal appearing white matter (NAWM) and normal appearing gray matter (NAGM), in patients treated for low grade glioma (LGG). We also tried to ascertain if a threshold dose level exists below which no apparent changes in perfusion indices are demonstrable after radiotherapy.

Materials and Methods: Ten patients (Mean age = 37.2±5.65 years) with histologically proven LGG were examined using DCE MRI before and after three months of RT. All the patients gave their informed consent before the DCE MR study. All patients underwent a post-op, MRI - Radiotherapy Treatment Planning (RTP) scan following immobilization in a thermoplastic face mask with fiducial markers. Data acquisition consisted of conventional (T_2-W, T_1-W, post-contrast T1-W and FLAIR images), and DCE imaging. The T_2 or FLAIR images were transferred using DICOM protocol to a RTP system in which the gross tumor, as visualized by the high signal intensity, was contoured in axial slices. The Planning Target Volume (PTV) was expanded from the T_2-W/FLAIR gross tumor volume in 3-D by 1 - 1.5 cm with appropriate editing for anatomical barriers to tumor spread. Radiotherapy (RT) to a dose of 54 Gy in 30 fractions over six weeks was delivered conformally with 2-3 beams to the PTV with 6MV photons from a linear accelerator. The 95% isodose line covered the PTV in all cases and dose heterogeneity within the PTV was restricted to -5% to +7% of the prescribed dose. All patients underwent the same sequences in a follow up MR scan three months following completion of RT.
DCE MRI was performed using sequential multi-section multiphase (n=32) three dimensional spoiled gradient recalled echo sequence (TR/TE-5/1.4, flip angle-15º, (FOV)-360×270mm, slice thickness-6mm, matrix size-128×128) with a temporal resolution of 5.2s for 12 slices covering the lesion[2]. The contrast (Gd-DTPA, 0.2 mmol/kg) was injected at the 4th acquisition. Fast Spin echo T_1W and fast double spin echo PD and T_2W imaging was performed to quantify voxel wise pre-contrast tissue T_{10}[2]. Images were registered for voxel wise analysis and de-scalped manually. The absolute tissue T_{10} value was used to generate concentration time curve from signal intensity-time curve[2]. Quantitative analysis of concentration time curve was performed for calculation of CBV and CBF[2]. Pharmacokinetic model was implemented for k^{trans} and v_e calculation[2]. Corrected CBV maps were generated by removing the leakage effect of the disrupted blood brain barrier (BBB)[2].
Before region of interest (ROI) analysis was undertaken, dose bins were identified on axial slices of interest by generating isodoses at intervals of 5Gy. Elliptical ROIs of 4×4 pixels were placed in the NAWM and NAGM in the corresponding areas of both pre RT and post RT image acquisitions. The perfusion indices in these corresponding ROIs selected were evaluated using anatomical landmark-based matching to ascertain changes post treatment. Evaluation was done for the dose bins from 20 Gy to >55 Gy, with class intervals of 5 Gy. Statistical analysis was performed using the t-test on the SPSS v.12 statistical software.

Results: The pre- and post-RT CBV, CBF, k^{trans} and v_e values in corresponding NAWM and NAGM ROIs for different dose bins are reported in Tables 1 and 2. The CBV values decreased significantly in the >55 Gy, 50-55 and 45-50 Gy bins while the CBF values decreased significantly in the >55 and 50-55 Gy bins. We did not find any difference in the k^{trans} and v_e in both NAWM and NAGM for all selected ROIs in different Gy bins, before and after RT – both pre- and post-RT k^{trans} and v_e values were close to zero.

Discussion: In the doses and fraction sizes of RT used, i.e. 54Gy/30fx/6weeks @1.8Gy/fx, which is the commonly accepted upper limit of many intracranial structures viz. the optic chiasm and brain stem, and therefore has found acceptance for the treatment of both low grade gliomas, and other benign lesions such as meningiomas, pituitary adenomas, craniopharyngiomas and acoustic neuromas, all of which share the common feature of prolonged life expectancy. It appears that at three months post-RT, the BBB is not disrupted to a significant extent, as measured by the insignificant change in the k^{trans} value, or these indices measured are not sensitive enough to pick up any presumed damage. However, fall in CBV/CBF suggests that regional perfusion is compromised and perhaps endothelial damage (apoptosis) and/or reduced caliber of vessels (thrombosis) is a possible explanation. Whatever be the basic pathophysiology of reduced blood volume/flow, the study suggests that below 45 Gy, even changes in CBV/CBF are not readily apparent. Clearly, these observations may have impact on radiation doses considered safe as of today. Follow-up studies with longer time periods may reveal the evolution of these changes with time, and time-trend graphs may help us to devise better RT, and follow up MRI protocols.

Dose Bins (Gy)	Pre-RT CBV (mean±SD)	Post-RT CBV (mean±SD)	Mean difference	p-value	Pre-RT CBF (mean±SD)	Post-RT CBF (mean±SD)	Mean difference	p-value
>55	2.97±0.69	1.88±0.41	1.09	0.000	33.58±5.40	28.47±3.47	5.11	0.000
50-55	2.99±0.70	1.98±0.42	1.01	0.000	33.06±4.63	29.54±3.74	3.53	0.000
45-50	2.97±0.60	2.16±0.43	0.80	0.000	33.04±4.19	31.68±4.01	1.36	0.129
40-45	2.96±0.24	2.97±0.36	-0.01	0.912	32.84±3.42	33.30±3.65	-0.46	0.705
35-40	No ROI could be placed due to sharp gradient between isodose lines.							
30-35	2.99±0.48	2.97±0.15	0.02	0.911	33.31±2.91	33.97±3.25	-0.66	0.718
25-30	2.97±0.39	2.97±0.60	0.005	0.984	32.83±3.25	33.34±3.06	-0.51	0.722
20-25	2.92±0.44	2.98±0.71	-0.06	0.690	33.03±4.54	33.40±2.77	-0.37	0.701

Table 1. Post-RT changes in CBV and CBF in NAWM according to dose bins.

Dose Bins (Gy)	Pre-RT CBV (mean±SD)	Post-RT CBV (mean±SD)	Mean difference	p-value	Pre-RT CBF (mean±SD)	Post-RT CBF (mean±SD)	Mean difference	p-value
>55	11.28±2.28	8.80±1.80	2.49	0.000	71.10±7.08	63.52±5.96	7.57	0.000
50-55	11.13±2.23	9.23±1.78	1.90	0.000	70.74±7.47	65.67±7.41	5.07	0.000
45-50	11.34±2.31	9.55±1.81	1.78	0.000	70.55±7.55	69.25±6.11	1.30	0.372
40-45	11.46±1.89	11.55±2.13	-0.09	0.892	71.18±6.21	70.84±4.79	0.35	0.855
35-40	No ROI could be placed due to sharp gradient between isodose lines.							
30-35	11.14±1.87	11.42±1.28	-0.28	0.766	69.90±3.68	70.21±2.71	-0.31	0.871
25-30	11.46±1.95	11.32±1.97	0.14	0.874	71.13±2.51	70.67±7.65	0.45	0.861
20-25	11.11±1.75	11.24±2.17	-0.13	0.804	71.34±8.4	71.75±6.43	-0.41	0.832

Table 2. Post-RT changes in CBV and CBF in NAGM according to dose bins.

Unit of CBV = ml/100gm
Unit of CBF = ml/100gm/min
Unit of k^{trans} = min^{-1}

References: 1. Wenz F et al. AJR 1996;166: 187-193; 2. Singh A et al. 2006, Seattle; ISMRM: 1538.