Radiation Induced Changes in Perfusion Metrics in Low Grade Glioma using Dynamic Contrast Enhanced MRI

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Introduction: Changes in the cerebral blood volume (CBV) in low grade glioma (LGG) have been reported after radiotherapy (RT) using dynamic susceptible contrast enhanced (DSC) imaging[1]. Increased permeability has also been reported after radiation due to the blood brain barrier (BBB) breakdown in rat glioma model[2]. In case of increased BBB permeability, the calculated CBV from DSC data will be error prone and underestimate the true value[3]. We have used T_1 weighted dynamic contrast enhanced (DCE) imaging to see the effect of radiation therapy on perfusion indices i.e. CBV, cerebral blood flow (CBF), permeability (k^{trans}) and leakage (v_e) in patients in patients with low grade gliomas.

Materials and Methods: Ten patients (mean age = 37.2±5.65 years) with histologically proven LGG were examined using DCE MR imaging before and three months after 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-, T_1-W, post-contrast T_1-W and FLAIR images) and DTI 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 cms with appropriate editing for anatomical barriers to tumor spread. Radiotherapy (RT) to a dose of 54 Gy in 30 fractions over 6 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[4]. 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}[4]. 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[4]. Quantitative analysis of concentration time curve was performed for calculation of cerebral blood volume (CBV) and cerebral blood flow (CBF)[4]. Pharmacokinetic model was implemented for permeability (k^{trans}) and leakage (v_e) calculation[4]. Corrected CBV maps were generated by removing the leakage effect of the disrupted blood brain barrier (BBB)[4]. Region of interest (ROI) analysis, encircling the whole lesion, was performed to quantify all the perfusion indices. The statistical analysis was performed using SPSS v.12 software.

Results: The intralesional CBV, CBF, k^{trans} and v_e values before RT and three months post-RT are given in Table 1. The CBV and CBF showed a significant decrease, and k^{trans} values showed a significant increase after three months of RT (Figure 1). However, no significant change was found in v_e three months after RT.

Discussion: The CBV value quantified using DSC MRI has been questioned in case of leaky BBB[3]. The radiation induced BBB permeability changes have been reported in literature[2]. In case of leaky BBB, the obtained CBV value will be underestimated due to T1 shine-through effect[3] and might not provide the appropriate information for clinical management of patients. DCE MRI provides more accurate information of leaky BBB and has been used to remove the leakage effect from CBV. The other significance of using DCE MRI over DSC MRI in this study is to quantify all the perfusion parameters simultaneously. Different ranges of CBV values in the LGGs before and after RT have been reported in literature[1,5]. This difference suggests the role of leaky BBB which affects the CBV values quantified by DSC MRI. The decreased CBV and CBF in the tumor lesion may be due to the decreased angiogenesis in response to the radiation. Radiation might be responsible for the apoptotic death of endothelial cells and thus might inhibit the secretion of vascular endothelial growth factor (VEGF), a prime angiogenic factor. Also, the increased k^{trans} in the lesion suggests opening of the BBB after RT. However, the exact mechanism of the disruption of BBB after RT is not clearly understood. The role of both leukotrienes and bradykinin in opening of the BBB in gliomas is well known[6]. Therefore, it is likely that increased secretion of these two molecules after RT is probably responsible for increased BBB permeability. No change in the v_e suggests minimal effect, if any, of radiation on the extracellular and extravascular space. We conclude that DCE MRI is a sensitive method to document radiation-induced changes in perfusion metrics and may become a useful tool for the management of patients with brain tumors undergoing radiation therapy.

Parameter	Pre RT (mean±SD)	Post RT (mean±SD)	Difference between means of paired groups (mean±SD)	95% CI of the difference of the means of paired groups		p value
				Lower	*Upper*	
CBV	10.95±4.15	7.68±3.13	3.27±2.09	2.55	3.99	0.000
CBF	151.80±30.72	102.93±17.72	48.88±24.80	40.36	57.39	0.000
k^{trans}	0.53±0.19	0.66±0.18	-0.12±0.23	-0.20	-0.04	0.004
v_e	0.14±0.07	0.14±0.05	-0.004±0.09	-0.03	0.03	0.778

Table 1. Differences between various perfusion indices pre- and post-RT.
Unit of CBV = ml/100 gm
Unit of CBF = ml/100 gm/min
Unit of k^{trans} = min^{-1}

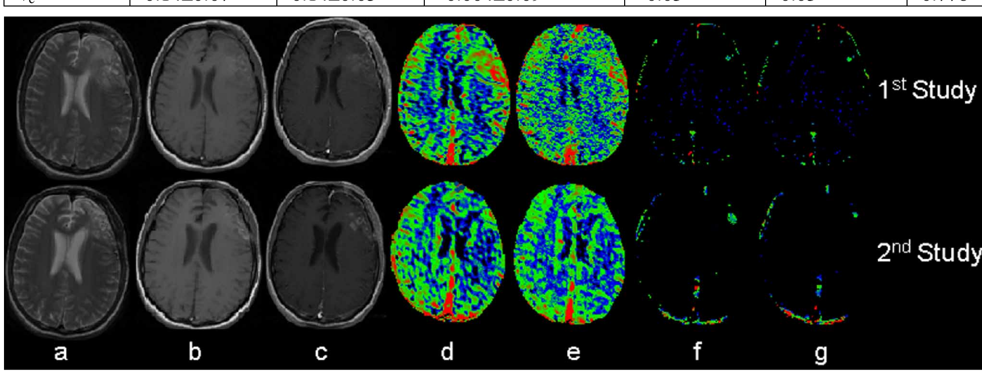

Figure . Pre (top row) and post RT (bottom row) imaging of a 36 yr old male patient suffering from frontal LGG. The T_2 W (a), T_1 W(b) and PC T1 W (c) images show a decrease in the lesion size in the post-RT scan. Post-RT, there is a decrease in both the CBV (d) and the CBF (e), while an increase is seen in the k^{trans} (f), with no change in the v_e (g).

References:
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