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Role of Diffusion and Perfusion Imaging Measurements in Grading of Glioma and Quantitative Assessment of Temporal Change in These Measurements in Glioma Patients Undergoing Radiotherapy

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Abstract

Introduction: Conventional neuro imaging of brain tumors is anatomy based and differentiates low grade (LGG) and high-grade glioma (HGG) based on pattern recognition which at times may be difficult to comprehend. Functional MRI incorporates morphologic abnormality with physiologic alterations. Quantification of ADC (apparent diffusion coefficient) and rCBV (relative cerebral blood volume) values using functional MRI have been explored to characterize these tumors. The present study purposes to determine the temporal change in diffusion (ADC) and perfusion (rCBV) in glioma patients treated by radiotherapy.

Material and Methods: 3Tesla MRI diffusion & perfusion imaging was done postoperatively before radiotherapy (RT), during RT at 4th week & subsequently on follow-up on 18 glioma patients (LGG = 5 and HGG = 13). Quantification of $ADC_{minimum}$ (ADC_{min}), and $rCBV_{maximum}$ ($rCVB_{max}$) value was done and the temporal changes of these parameters with RT were evaluated.

Results: In pre-RT MRI, the mean ADC_{min} for LGG was significantly higher in comparison to HGG (mean ± SD, 1.10 ± 0.11; 0.83 ± 0.13, respectively, all values x 10^{-3} mm^2 sec^{-1}; t-test p = 0.00). The mean ADC_{min} for LGG during RT increased compared to baseline value and there after remained stable at the first follow-up imaging, although difference was non-significant (p = 0.33 and 0.8, respectively) while for HGG, mean ADC_{min} significantly increased during RT from baseline value and consistently increased at the time of follow up imaging (p = 0.00, p = 0.01, respectively). The $rCVB_{max}$ for LGG (1.98 ± 0.70) was significantly lower in comparison to HGG (5.07 ± 0.04). In both LGG and HGG the $rCVB_{max}$ decreased during RT from baseline pre-RT values and remained constant at the follow-up. The mean difference in $rCVB_{max}$ values was significant (LGG: p = 0 .00 & 0.03; HGG: p = 0.00 & 0.002, respectively).

Conclusion: There is a change in diffusion (ADC_{min}) and perfusion ($rCVB_{max}$) parameters in glioma patients treated by radiotherapy with values differing based on the grade of tumor, and these measurements shows a temporal change in their values with radiation response.

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INTRODUCTION

Cancer of the brain and nervous system comprise 1 to 2% of all malignancies with age standardized incidence rate per 100,000 population 4.6 worldwide and 2.85 in India.[1] The occurrence in India is found to be 5 to 10 per 100,000 population, and growing, which accounts for 2% of malignancies. Therapeutic index may be improved with the help of effective chemotherapy along with highly conformal radiotherapy targeted to areas at highest probability for tumor recurrence.

However, the use of these technologies requires the capability to identify the appropriate regions to target. There is a substantial interest in further refining therapy depends on imaging technology to augment physical examination and conventional imaging to precisely delineate the magnitude of disease and forecast patient outcome (prognosis).

Conventional contrast-enhanced T1-weighted and T2-weighted magnetic resonance imaging (MRI) used for radiation planning reflects only anatomical and morphological criteria for changes in tumor dimensions during and after completion of the treatment rather than molecular or functional properties of the tumor.

Functional imaging techniques can be employed to probe the heterogeneity of sensitivity within a tumor, assess the response of either the tumor or the normal tissues during the therapy. This information enables dynamic adaptation of treatments based on changes in the tumor and normal tissues during therapy, alter the course of treatment when no response occurs, or potential for toxicity reduction by withholding additional dose after the complete response. Functional and molecular imaging can provide metrics potentially correlated with the outcomes to the researchers.

Ultra-structural changes are known to predate morphological changes, and this is one of the main limitations of using pattern recognition in conventional imaging for response assessment.

DCE and dynamic susceptibility contrast (DSc) magnetic resonance imaging (MRI), and characterize the vascular properties in the tumor and normal organ tissue.[2-4] Such properties include blood volume, blood flow, vascular permeability, and mean transit time. They also include distribution volume and available interstitial space for the contrast agent. DWI specify tumor cellularity along with cellular structural integrity. DWI has been proposed to evaluate tumor cellularity (areas in which water movement is restricted by increased cell density have low ADC values) or tumor edema/necrosis (areas of freely moving water have high ADC values) because it measures the tissue microenvironment. The present study was done to measure the image-based biomarkers using-

a) DWI (apparent diffusion coefficient-ADC).
b) DCE (regional cerebral blood volume-rCBV)

in glioma patients prior to radiotherapy, and note the temporal changes that occur in the values during RT and follow-up after completion of radiation treatment (Figure 1).

MATERIAL AND METHODS

18 glioma patients of age between 18-70 years, with KPS ≥ 70, following a biopsy or resection referred from the department of Neurosurgery to the department of Radiotherapy were taken for study after an informed consent. Patients with history of prior radio-chemotherapy, or recurrent disease were excluded from the study. The study was approved by institute research and ethics committee. Patients were immobilized in a U-type thermoplastic cast and a contrast enhanced radiotherapy planning (RTP) CT scan of brain was done and image were co-registered with postoperative relevant MRI scan images, i.e., FLAIR (for low grade glioma, LGG), or T1w contrast images (for high grade glioma, HGG).

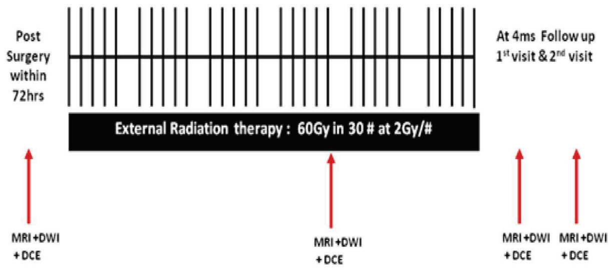

Figure 1: Schema for MR imaging in glioma patients.

Target delineation was performed on the FLAIR images in LGG and T1w contrast images in HGG based on EORTC guidelines.[5] Clinical target volume (CTV) was generated from gross tumor volume in three-dimensional (3-D) by a 1-cm expansion for LGG and a 2 cm expansion for HGG with appropriate editing for anatomical barriers to tumor spread. The planning target volume was generated from the CTV by a 0.5 cm expansion in 3-D conformal radiation therapy to a dose of 54 Gy/30 fractions for LGG and 59.4–60 Gy/30-33 fractions for HGG was prescribed to the PTV.

RT was delivered conventionally with 2–3 co-planar beams, using 0.5 or 1 cm multileaf collimator leaves to fit to the PTV usually with a 6mm out-bound fitting in the beams-eye-view on a 6MV linear accelerator (without beam shaping). Patients with glioblastoma multiforme (GBM) who could afford also received concurrent temozolamide 75 mg/m^2 daily during treatment followed by adjuvant temozolamide 150 to 200 mg/m^2 D1-5 for 6-cycles every 4-weekly.

MR Imaging Protocol: 3.0 Tesla scanner

MRI imaging was scheduled after surgery pre radiotherapy, during radiotherapy, and post radiotherapy (Figure 1). Subsequent imaging during their follow-up was done when clinical suspicion of progression or symptomatic.

MRI Machine Parameter

The MR imaging of the whole brain was performed on a 3T MRI scanner (Signa, GE Healthcare, Milwaukee, USA) using a 12-channel head-coil. The conventional MR imaging protocol included T2-weighted FSE images, T2-FLAIR images (Fluid Attenuated Inversion Recovery); and SE T1-FLAIR images. All these sequences were acquired with slice thickness = 3 mm, FOV = 240 mm × 240 mm, number of slices = 42, image matrix = 256 x 256 with no interslice gap.

DTI protocol for acquiring Diffusion weighted imaging (DWI) and calculation of ADC

DTI data were acquired using a single-shot echo-planar dual spin echo (SE) sequence with ramp sampling. A dodecahedral diffusion-encoding scheme with 10 uniformly distributed directions over the unit sphere was used for obtaining 10 diffusion-weighted images and 2 non- diffusion-weighted images. The b-factor was set to 1,000 s/mm^2, TR=8 sec, TE=100 ms and NEX=8.

DCE protocol for acquiring and calculation of relative cerebral volume (rCBV)

DCE-MR imaging was performed using a three-dimensional spoiled gradient recalled echo (3D-SPGR) sequence (TR/TE-5.0/1.4 ms, flip angle-15º, FOV-360 × 270 mm, matrix size-128 × 128, NEX = 0.5, number of phases = 32). At the fourth acquisition, Gd-DTPA (Magnevist, Berlex Schering AG Berlin, Germany) in a dose of 0.2 mmol/kg of body weight was administered intravenously with the help of a power injector (Optistar^{TM} MR, Mallinckrodt, Liebel-Flarsheim, Ohio) at a rate of 3–5 mL per second, followed by a bolus injection of 20 to 30 mL saline flush.

CBV was defined as the total volume of blood traversing a given region of brain, measured in milliliters of blood per 100 grams of brain tissue (mL/100 g). Corrected CBV map was generated by removing the leakage effect of the disrupted BBB (Figure 2). Relative cerebral blood volume is the ratio of maximum CBV correct in either the tumour or peritumoural area to that in the contralateral normal white matter in order to standardize variations in each examination. The CBV was calculated by placing region of interests (ROI, 20 to 40 mm^2) on the metric map in the tumor region seen on T1 contrast in case of high-grade glioma and on T2FLAIR in case of low-grade glioma.

Similarly, ROI were placed in all the images in which tumor was seen and mean of all rCBV_corrected were taken excluding the outliers. Figure 3 is an example of a case of glioblastoma multiforme where tumor was representative in 6 slices so ROI was placed in all 6 slices and rCBV_corrected recorded in all 6 slices and mean of rCBV corrected was thereby calculated.

Quantification of Apparent Diffusion Coefficient Calculation

MRI data was used to compute ADC values. ADC map was generated on a pixel-by-pixel basis using formula: ADC = b^{-1} In (S_0/S), where S_0 and S represent the signal intensities of the image without and with diffusion weighted gradients and b (diffusion weighting factor) was 1000 s/mm^2 in our study, and S_0 is map obtained with b = 0 and S with b = 1000 s/mm^2, and where, the diffusion weighting factor b, was

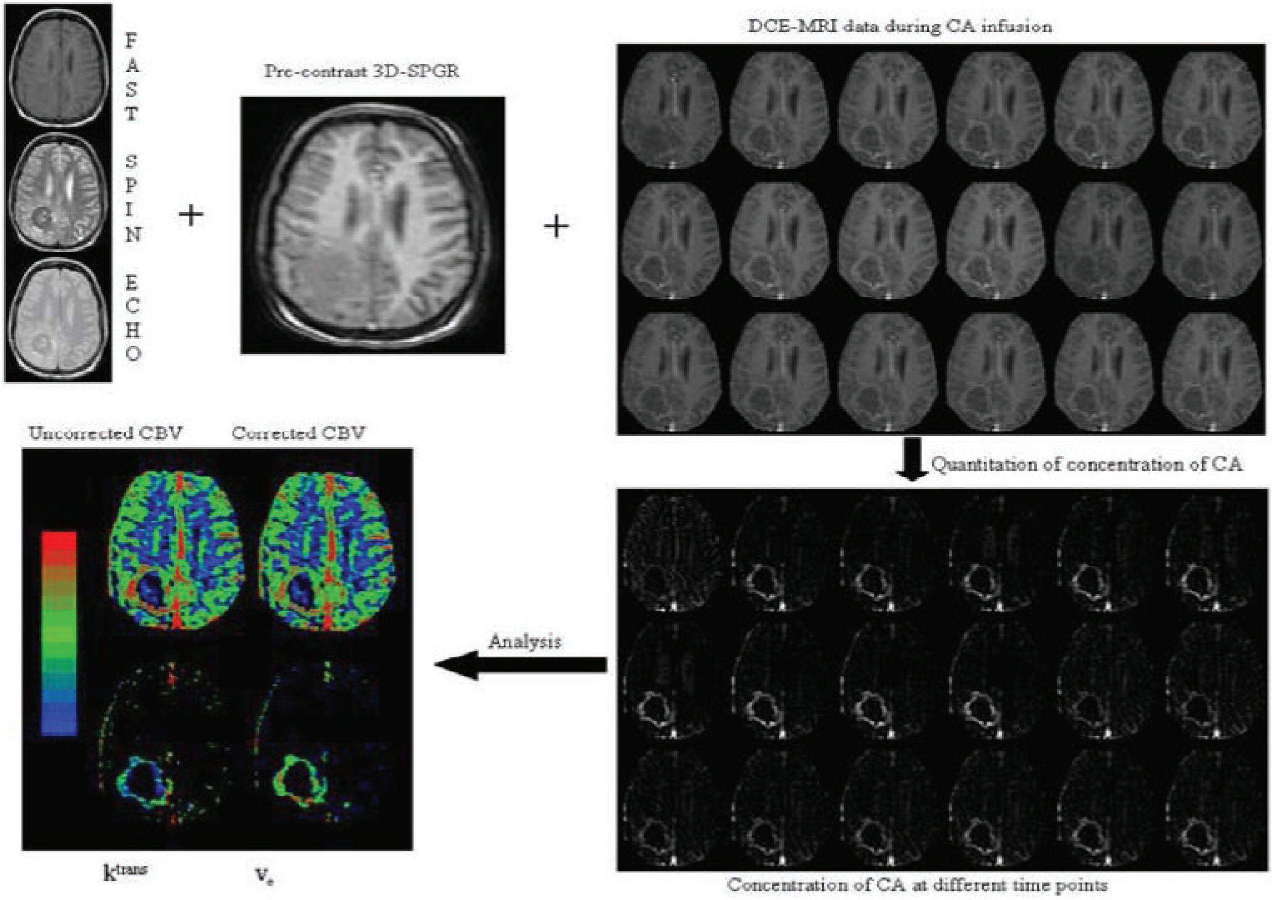

Figure 2: Diagrammatic presentation of perfusion data processing using in house developed JAVA based software.

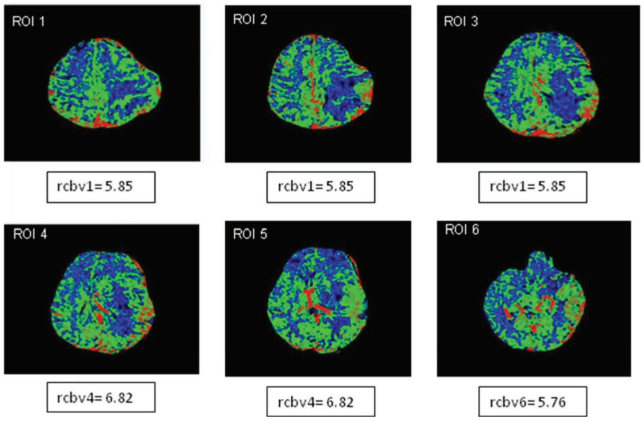

Figure 3: Placement of region of interest in case of glioblastoma in all the slices representative of tumor. Mean rCBV_corrected = 6.02.

calculated by the following formula $b = \gamma^2 G^2 \delta^2 (\Delta - \delta / 3)$, where G is the gradient strength and (δ) is gradient length. **γ** is the gyromagnetic ratio for the hydrogen nucleus and Δ is the separation in time of the two gradient pulses. Before calculation of ADC maps, an automatic de-scalping method was used for discarding the non-brain portions.

Regions of interest (ROIs) were drawn manually to obtained ADC maps in the area corresponding to the enhancing region on T1-weighted images or bright regions in a FLAIR image. ROIs of a fixed size were placed centrally to the sites corresponding to the solid-enhancing portions / relevant portions on a FLAIR image of the lesion (Figure 4). For normalization, in each patient, same-size ROIs were also drawn in the matching region of the contralateral hemisphere. The data of the minimum ADC (ADC_{min}) values on each occasion were placed with average ROI of 5, range between 3 to 10 depending on tumor visibility on T1contrast or T2 FLAIR MR images.

STATISTICAL ANALYSIS

Patient and demographic features are reported. Data is summarized using means and standard deviations (SD) and statistical significance of difference between means are reported using the t-test.

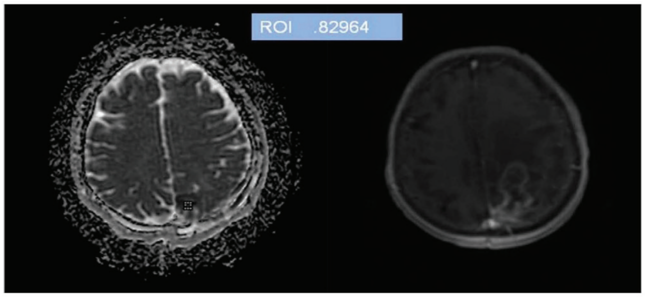

Figure 4: Placement of region of interest (ROI) seen as a small rectangle in the ADC map (left panel) in an area that corresponds to the bright signal in the tumor seen on the T1c image in a HGG (right panel). The value is read off from the Image J software, top panel.

RESULTS

The mean age of patients included was 40 ± 11 years, with male preponderance (12 males, 6 females). Of 18 patients, 5 patients had low grade glioma and 13 had high grade glioma. Mean duration of symptoms was 9-months (range 1 to 60 months). All patients had KPS of more than 80.

Treatment Details

All patients had surgery either a gross total resection or subtotal resection. For the purpose of analysis in the study patients were grouped in two categories low grade glioma (LGG, n = 5) and high-grade gliomas (HGG, n = 13). All 13 patients of high-grade glioma patients received 59.4 Gy to 60 Gy/ 30-33# while 5 patients of low-grade glioma received 54 Gy/30#.

Concurrent temozolomide could be taken by 9 patients of HGG; 3 did not take because of financial constraints. Of which, 8 patients went on to take adjuvant temozolamide while one died within one month of radiation because of progression of disease.

MRI Imaging

All 18 patients underwent pre radiotherapy MRI with diffusion and perfusion weighted images as per protocol.

MRI at 4 to 5th week of treatment during radiotherapy as per protocol could be done in 15 patients except 3 patients because of poor general condition (n=1), and administrative error (n=2).

Post radiotherapy follow up MRI could be done in 13 patients. In 5, it could not be done as succumbed to disease (n = 1), required protocol MRI sequence missing for analysis (n = 1), lost to follow up (n = 1), logistics (n = 2).

Apparent diffusion coefficient calculation:

Table 1: Temporal change in mean of the minimum ADC value of LGG vs. HGG.

ADC	Mean ± SD $1 \times 10^{-3} mm^2 s^{-1}$		
	Pre-RT	At 4-5th week	Post-RT
LGG	1.10 ± 0.11	1.51 ± 0.77	1.49 ± 0.33
HGG	0.83 ± 0.13	1.01 ± 0.26	1.09 ± 0.35
p-value	0.00	0.07	0.07

Table 2: Temporal change in mean rCBVmax value of LGG vs. HGG.

rCBV	Mean ± SD		
	Pre-RT	At 4-5th week	Post-RT
Low Grade	**1.98 ± 0.70**	**1.45 ± 0.41**	**1.57 ± 0.49**
High Grade	5.07 ± 1.29	3.10 ± 1.22	2.98 ± 1.31
p-value	0.00	0.02	0.06

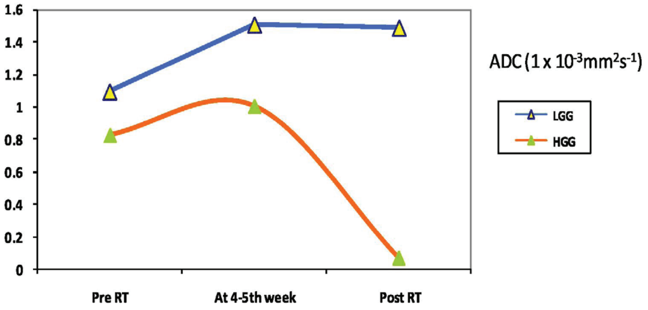

Figure 5: Temporal change in Mean of the minimum ADC value of LGG vs. HGG.

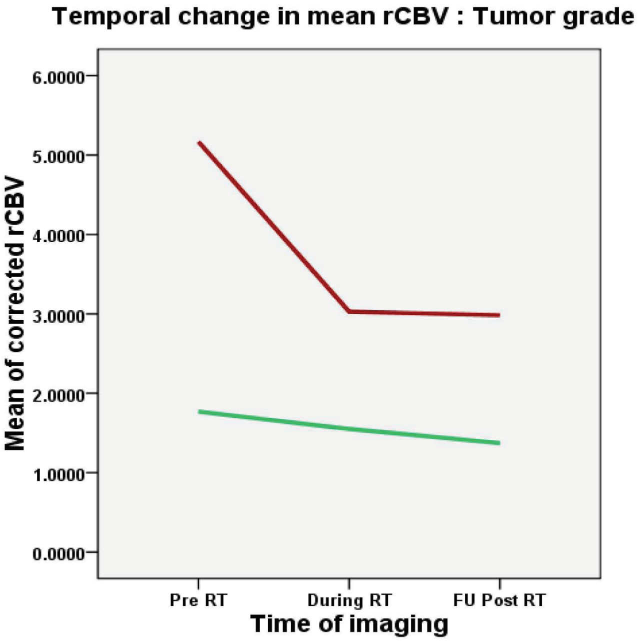

Figure 6: Temporal change in mean of the rCBVmax value of LGG (green) vs. HGG (red).

There was significant difference (p = 0.00) for mean of ADC_{min} value pre-RT, comparing low grade (1.1 ± 0.11) and high-grade glioma (0.83 ± 0.13) and this difference remained significant during RT and follow up between the two groups (Table 1 and Figure 5).

The mean ADC_{min} value in case of low grade glioma increased (1.1 ± 0.11 versus 1.51 ± 0.77) during radiotherapy and remained stable thereafter on post RT follow up (1.51 ± 0.77 versus 1.49 ± 0.33), but difference was not significant. In case of high grade glioma, the mean ADC_{min} increased (0.83 ± 0.13 versus 1.01 ± 0.26) during radiotherapy which can be explained as loss of tumor cellularity following radiotherapy and /or chemotherapy with no significant difference seen during post RT (1.01 ± 0.26 versus 1.09 ± 0.35), at median follow up of 3-month range (1-12).

Perfusion MRI / Dynamic contrast enhanced MRI

A comparative representation of the serial temporal changes following RT in the mean of the $rCVB_{max}$ values for LGG along with HGG is shown in Table 2 and Figure 6. Figure 6 and Table 2 represent the serial temporal changes in the mean rCBV values during, and post treatment from baseline. There was a significant difference between mean rCBV values for high grade vs. low grade glioma pre radiotherapy. It was higher for HGG (mean = 5.07) vs. LGG (mean 1.98). The mean rCBV decreased during 4-5th week of radiotherapy both for high (5.07 ± 1.29 vs. 3.10 ± 1.22) and low grade gliomas (1.98 ± 0.70 versus 1.45 ± 0.04) which was significant (p = 0.00, 0.03, respectively) however during follow up the mean rCBV value became stable or modestly decreased with no significant difference seen between the two groups.

Follow up and outcome

All patients of LGG were stable at the time of analysis, while 11 out of 13 HGG patients deteriorated clinically later on. MRI could not be obtained at the time of progression in 5/18 patients due to various reasons, i.e., MRI brought from outside without protocol images, patient GC very poor to be taken for MRI, finances difficulty, could not report to the hospital, logistics and therefore ADC and rCBV parameters could not be assessed.

At median FU time of 12 months median progression free survival and median overall survival among low grade glioma did not reach at the time of analysis while for high grade glioma it was 12.3 and 13.6 months, respectively.

DISCUSSION

MRI is the best investigational tool to assess brain space occupying lesion, but conventional MRI has its own limitation. Conventional MRI sometimes fails to differentiate between low- and high-grade glioma and between radiation response to radionecrosis. Functional MRI has the ability to decrease these limitations to an extent and helpful to differentiate between low-grade and high-grade glioma based on rCBV value and ADC values, impacting tumor target area during radiation planning and treatment protocol. This study was done in glioma patients to evaluate temporal changes in MRI image-based biomarkers using rCBV and ADC from baseline with radiotherapy and follow-up.

Rationale for the choice of ADC metric and comparison with literature

With increasing tumor cellularity and architectural distortion, any increase in the tortuosity of the extracellular space will additionally contribute to decreased ADC values. It would therefore, be expected that ADC values would correlate with tumor cellularity and grade.[6] In a study of 20 patients with glioma, Sugahara *et al*., showed inverse correlations between ADC values and tumor cellularity and grade, with high-grade gliomas having significantly lower ADC values than low-grade gliomas. The ADC_{min} values of HGG varied from 0.82-2.46 (mean 1.2, SD 0.5) x 10^{-3} mm^2/sec while that for LGG varied from 1.94-3.31 (mean 2.7, SD 0.7) x 10^{-3} mm^2/se.[6] Hilaro did a study on 162 patients in which the author found ADC_{min} of 1.27 ± 0.293 for low grade glioma and for high grade glioma 0.765 ± 0.768.[7] Similar to other studies in the present study, higher value of mean ADC_{min} was seen in LGG (1.01 ± 0.11) compared to that in high grade gliomas (0.828 ± 0.13).

Rationale for the choice of rCBV metric used and comparison with literature

Neoangiogenesis that is formation of new vessels, a process required for tumor growth proliferation and metastasis is charactertics of many malignant tumor. These vessels have high permeability, tortuosity and poor functionality. These vascular characterstics are poor prognostic factor determining aggressiveness of tumor. [6]

Because of the high level of histological variability within cerebral gliomas, rCBV maps of high-grade tumors are often heterogeneous, containing both high and low rCBV foci. Glioma are very heterogenous tumor so the focus of maximal CBV is taken as representative of the tumor grade. Low-grade tumors, on the other hand, tend to have homogenously low rCBV throughout the lesion. In high grade glioma high rCBV foci in uncorrected rCBV map generally represent a true positive value[8].

Radiotherapy induced endothelial changes cause radiation necrosis, small vessel injury and decrease in rCBV.[9] It was stated that normalized rCBV ratios ($rCBV_{[tumor]}$ / $rCBV_{[contralateral\ tissue]}$) is the best parameter for assessment of vascularity of tumor.[10]

Comparative study of rCBV value

Price *et al*., found good correlation between all the measures of rCBV and the MIB-1 labeling index.[11] Some previous studies (*n*≤33 patients) found a range of rCBV values from 1.11 to 1.69 and from 3.64 to 7.32 in low-grade and high-grade gliomas, respectively.[6,12]

Hilaro did a study on 162 patients in which he found $rCBV_{max}$ of 2.11 ± 1.58 for low grade, and for high grade glioma 6.30 ± 2.97.[7] A study (n = 76) showed in HGG rCBV (6.67 ± 2.31) was significantly higher than LGG (2.44 ± 0.42).[13] Similar to that of literature we found mean rCBV values of 5.06 ± 1.29 and 1.98 ± 0.69 for high-grade and low-grade gliomas, respectively as shown in Figure 6 and Table 2.

How did the ADC pattern follow with RT and that reported in literature?

Therapy-induced enhancement in ADC is a thoroughly recorded phenomenon in studies. Tumor cells undergo through apoptotic process which causes cell lysis and death of cells creating more space between cells resulting in free movement of water molecule in intracellular and extracellular compartment. Decrease in number of cells and cellularity result in increase in ADC value as shown in many studies.[14]

In the present study, it was seen that the mean of minimum ADC value for LGG increased with radiotherapy suggesting tumor cell lysis however the mean difference was not found to be significant. This could be explained by the inherent slow growing nature of the LGG with tissue compactness resulting in minimal change in the ADC value over time. On contrary, in HGG there was significant mean difference seen during and post RT ADC value compared to that of pre-radiotherapy suggesting increased cell kill and loss of cellularity with treatment intervention which sustained at median follow-up MR imaging done at three month (range 1-12-month). However most patient subsequently progressed and succumbed to disease later.

How did the rCBV pattern follow with RT and that reported in literature?

A study conducted by Sadhegi *et al*., showed a positive correlation between rCBV and both cells, and microvessel density.[15] Tumor response to radiotherapy is mediated by microvascular damage. Maximum rCBV values were significantly higher in the recurrent metastatic tumor group than radiation necrosis.[16] The rCBV values in the present study decreased both for low grade and high-grade gliomas during treatment and post-treatment follow-up suggesting microvasculature damage by radiation therapy as seen by other authors.

Whether temporal changes in ADC value & rCBV value able to predict response in Glioma patients

Although, a significant temporal change was seen in mean ADC_{min} and rCBV values during radiotherapy, both in HGG and LGG and on first follow up done at 3-months post radiation treatment however the values could not be correlated with subsequent clinical status of patient at time of progression as in majority MRI could not be obtained at progression, reasons stated above.

CONCLUSION

Functional MRI is very useful to differentiate between high- and low-grade glioma. There is a change in diffusion (ADC_{min}) and perfusion ($rCVB_{max}$) parameters in glioma patients treated by radiotherapy with values differing based on the grade of tumor. These temporal changes may be further studied in larger cohort for predicting response and outcome.

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