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GRADING OF GLIOMAS ON THE BASIS OF MR PERFUSION DIFFUSION AND SPECTROSCOPY

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ABSTRACT

Intracranial tumors are a significant health problem. Tumors related to central nervous system (CNS) are 1-2% of all malignancies[1].among which gliomas forms 70-80% of primary tumours. Magnetic resonance (MR) is the imaging modality of choice to evaluate intracranial tumors, and it continues to have an ever expanding with its newer techniques our study is to establish a relation between rCBV(relative cerebral blood volume) and ADC(apparent diffusion co-efficient) with tumor grade for gliomas. To estimate a cutoff rCBV and ADC value for differentiation of high and low-grade gliomas, and to access the diagnostic accuracy of MR spectroscopy in grading of gliomas. A total of at least 30 patients of glioma included in the study Basic MRI sequences, perfusion, diffusion and spectroscopy done The ADC values, rCBV values obtained for different tumor grades were analyzed statistically using stata software version 11.2. RESULTS: Low grade (I + II) gliomas shows ADC values >0.804 x $10^{-3}mm^2$/sec, Grade III gliomas show ADC values 0.677-0.804x$10^{-3}mm^2$/sec while Grade IV gliomas shows ADC values <0.677x$10^{-3}mm^2$/sec Low grade (I + II) gliomas show rCBV values <2.5ml/100mg. Grade III show rCBV values 2.5-3.3ml/100mg while Grade IV gliomas show rCBV values >3.3ml/100mg.

INTRODUCTION

Gliomas are the most common primary tumors of the central nervous system (CNS), representing approximately 50% of the newly diagnosed brain tumors. Glioma is a non-specific term, used for tumors originating from glial cells which account for more than 85% of primary brain tumors [1]. Malignant cells grow, proliferate and invade normal structures of the brain seriously affecting adequate brain function Imaging plays an intergral role in intracranial tumor management. Early diagnosis facilitates better therapy making the neuroimaging approaches particularly useful in the detection and handling of these lesions. Our study aim is to establish a relation between r CBV (relative cerebral blood volume) and ADC(apparent diffusion co-efficient) with tumor grade for gliomas. To estimate a cutoff rCBV and ADC value for differentiation of high and low-grade gliomas, and to access the diagnostic accuracy of MR spectroscopy in grading of gliomas

MATERIAL AND METHODS

The study carried out in Departments of Radiodiagnosis and Imaging, Neurosurgery and Pathology for the period Jan 2013 to Dec2015. A prospective study to grade brain gliomas on the basis of MR spectroscopy, diffusion and perfusion weighted imaging done. A total of at least 30 patients of glioma included in the study. All intra-cranial gliomas (enhancing and non-enhancing) included in the study. Tumours other than gliomas, metastasis and extra-axial tumours, Post-operative, post chemotherapy, post radiotherapy cases Patients unfit to

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undergo MRI like metallic aneurysms clips, pacemakers etc were excluded from study.

All the patients underwent basic MRI sequences (T_1W, T_2W, T_2W/FLAIR) axial, sagittal and coronal plains were done as per requirement on Gyroscan Intera Nova gradient 1.5 Telsa Philips Imagining system, using a SENSE head coil (8 channel phased array coil). DWI – (diffusion weighted imaging was done with a single shot EPI sequence with a b value of 1000. ADC map was calculated by automated software on workstation (view from version 5.1) and minimum ADC values used for analysis. PWI (Perfusion weighted imaging): The patient was then given Gadobenate Dimeglumine / Meglumine Gadoterate normal a dose of 0.1mmol/Kg at a rate of 4ml/sec followed by saline flush of 20ml at a rate of 4ml/sec using pressure injector. The images of PWI were acquired using T2W / FFE dynamic sequence (susceptibility weighted imagining) to track first pass of contrast bolus through the region of interest and the dynamic showing maximum fall in the intensity was used for creating rCBV and rCBF maps and for calculating rCBV value using automated software in workstation (view Forum 5.1). Spectroscopy – single voxel spectroscopy (SVC) was done using PRESS sequence with intermediate TE of 144ms. Two spectroscopy data sets were obtained: one from the most malignant appearing area of tumor and another from the corresponding normal white matter.

RESULTS

In our study there were 12 case of grade II, 5 cases of grade III and 12 cases of grade IV glioma, there was only one case of grade I glioma. Maximum no of patients presented with seizures (n=13), the next common symptom was headache (n=12) On basic MR sequences the tumor characteristics like the appearance of tumor on T1W, T2W, FLAIR, and contrast enhanced T1W images were studied. Further characters such as cystic changes, necrosis haemorrhage, peritumoral odema were evaluated as shown in table 1 figure 1 & 2.

The most common lobe involved was right frontal lobe (n=8), next frequent lobe involved was left frontal lobe. There was overlap in ADC values for grade II and III and hence it is difficult to distinguish grade II from grade III based on ADC values alone. At a cut-off of 0.804 x 10-3 mm2/sec for ADC value to differentiate low from high grade i,e II from III, a sensitivity of 76.47%, specificity of 76.92% and accuracy of 76.67% were noted. AUC (area under curve) was 0.796. At a cut off of 0.677 x 10-3 mm2/sec for ADC, grade III and grade IV could be differentiated with a sensitivity of 94.44%, specificity of 83.33% and accuracy of 90%. AUC being 0.907 as shown in table 2.

Low grade (I + II) gliomas shows ADC values >0.804 x 10-3mm2/sec, Grade III gliomas show ADC values 0.677-0.804x10-3mm2/sec while Grade IV gliomas shows ADC values <0.677x10-3mm2/sec.Though there was overlap in rCBV values of grade II and grade III it is less than that for ADC values. Hence while differentiating grade II from grade III tumors, rCBV values are slightly better than ADC values. (AUC of ADC v/s rCBV being 0.796 and 0.823 respectively). At a cut-off of 2.5ml/100gm for differentiating low v/s high grade (grade II from grade III), a sensitivity of 94.12% and a specificity of 69.23% with accuracy of 83.33% was noted. AUC being 0.823.At a cut-off of 3.3ml/100gm (as shown in figure 3)grade III and grade IV could be differentiated with a sensitivity of 83.33% and a specificity of 67.67% with accuracy of 73.33%. AUC being 0.800.Low grade (I + II) gliomas show rCBV values <2.5ml/100mg. Grade III show rCBV values 2.5-3.3ml/100mg while Grade IV gliomas show rCBV values >3.3ml/100mg. At a cut-off of 22% for % drop low grade could be differentiated from high grade (II v/s III) with sensitivity of 88.24%, a specificity of 76.92% with accuracy of 83.33%as shown in table 3. AUC being 0.805.When differentiating low v/s high grade tumor rCBV value was slightly better than ADC value. (AUC of ADC v/s rCBV value being 0.907 and 0.800 respectively).The ADC value was better than rCBV value in differentiating grade III from grade IV.

Spectro was also taken from cystic lesions (to distinguish cystic change from necrosis) and from peritumoral edema where needed (to distinguish between primary brain tumor and metastasis).The metabolite ratios in our study were not helpful quantitatively in grading of gliomas, but presence of some peaks like lipid and lactate did help in grading. Lactate peak was found in almost all the grades though with more frequency in higher grades. Presence of lipids suggested a higher grade of malignancy.

Table 1 showing tumor characters on basic MR sequences

	Grade I	Grade II	Grade III	Grade IV
No of Cases	1	12	5	12
Necrosis	0	3	3	11
Haemorrhage	0	1	0	8
Cystic Changes	0	5	2	7

Table 2 showing summary statistics for ADC values

	No of Cases	Mean ADC Value	Standard Deviation	P 50	Range
Grade I &II	13	$0.8716\pm0.203x10^{-3}mm^2/sec$	0.203	0.845	0.491-1.3
Grade III	5	$0.8454\pm0.116x10^{-3}mm^2/sec$	0.116	0,823	0.698-0.985
Grade IV	12	$0.5704\pm0.131x10^{-3}mm^2/sec$	0.131	0.537	0.420-0.834

Table 3 showing summary statistics for rCBV

	No of Cases	**Mean rCBV**	**Standard Deviation**	**P 50**	**Range**
Grade I & II	13	2.34±0.934ml/100mg	.9340812	2.2	0.84-3.8ml
Grade III	5	4.08±2.86ml/100mg	2.866531	2.9	1.2-8.6ml
Grade IV	12	4.60±2.5ml/100mg	2.515211	3.75	2.5-11.7ml

Table 4 showing sensitivity and specificity for ADC value in the differentiation of high-grade from low grade gliomas in various studies.

Study	**Cut-off ADC value (for low v/s high grade)**	**Sensitivity**	**Specificity**
Hilario et al (2012)	$1.185x\ 10^{-3}mm^2/Sec$	97.6%	53.1%
Our present study	$0.804x10^{-3}mm^2/sec$	76.4%	76.9%

Table 5 showing sensitivity and specificity for rCBV value in the differentiation of high-grade from low grade Gliomas in various studies.

Study	**At cut-off value of rCBV**	**Sensitivity**	**Specificity**
Law et al (2003)	1.75ml/100mg	95.0%	57.5%
Weber et al (2006)	1.6ml/100mg	94%	78%
Aprile et at (2012)	3.5ml/100mg	79.4%	95.8%
Hilario et al (2012)	1.74ml/100mg	94.4%	50.0%
Roy et al (2013)	3.34ml/100mg	100%	88%
Our present study	2.5ml/100gm	94.12%	69.23%

Figure 1. Axial T1W Plain Image Showing Hypointense Mass Lesion and on Contrast Showing Homogenous Enhancement

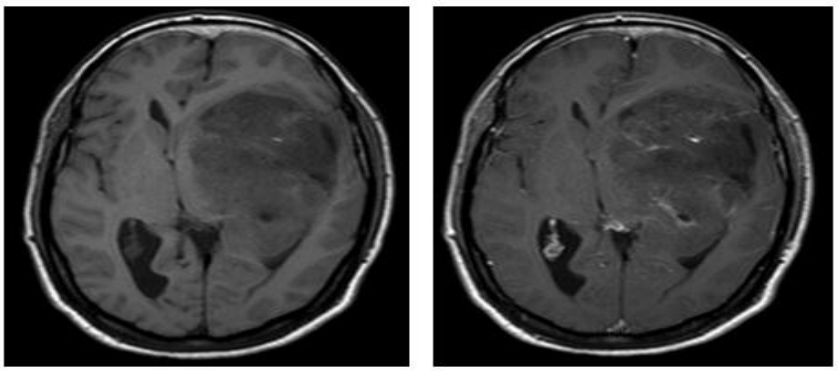


Figure 2. Axial T2W & Plair Image Showing Hyperintense Mass Lesion With Perilesional Odema and Midline Shift

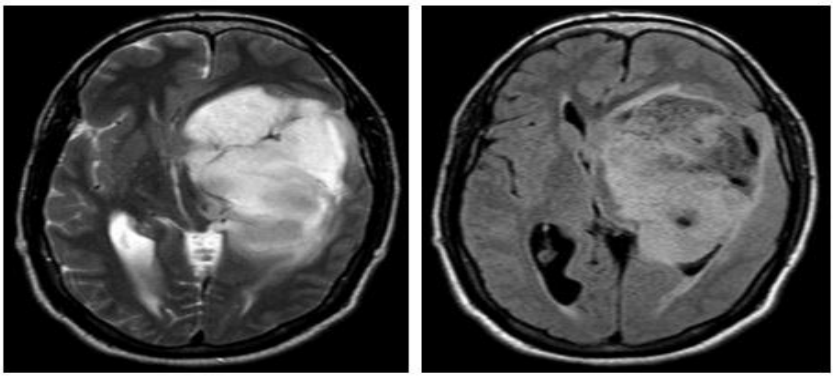
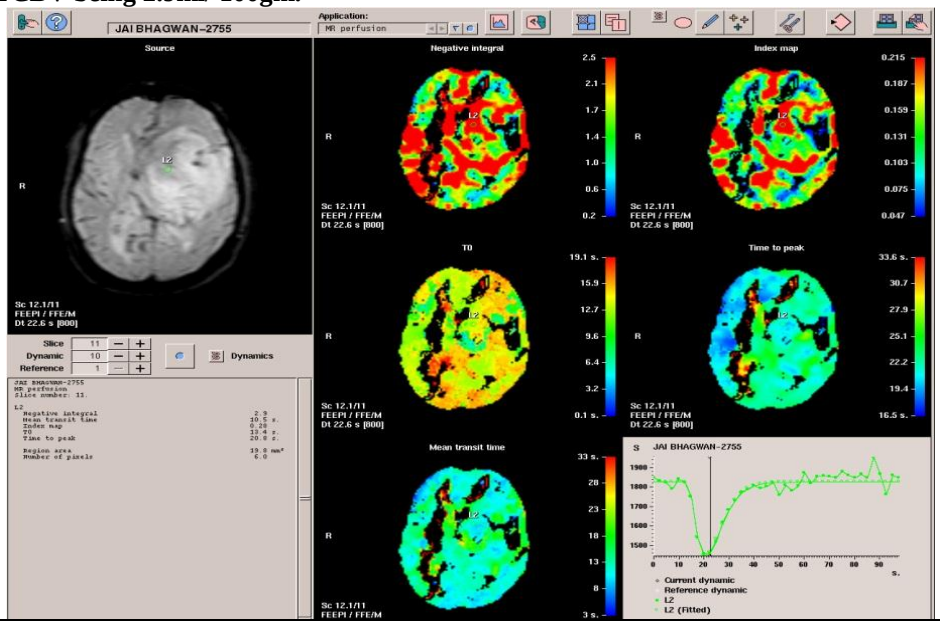


Figure 3. Axial T2*W First Pass Perfusion IME Mage Showing Color Coded rCBV Maps Along with Time Signal Intensity Curve rCBV being 2.9ml/ 100gm.



DISCUSSION

Intracranial tumors are a significant health problem. Prompt diagnosis and treatment of cerebral neoplasms are critical to decrease both morbidity and mortality.[2] New therapeutic modalities, such as image-guided surgery and anti-angiogenic agents, are becoming increasingly reliant on high quality imaging for diagnostic evaluation, treatment planning and post-treatment follow-up [3].MR imaging with its multiplanar capabilities and superior contrast resolution is now modality of choice. Most common brain tumors include glial tumors, lymphoma, medulloblastoma and hemangioblastoma. Astrocystomas are histologically heterogeneous group, having varying degrees of cellular and nuclear pleomorphism, mitotic activity, vascular proliferation, and necrosis.[4] Astrocytomas are classified into various grades, low grade astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme. Purpose of MR imaging in patients with brain tumors is the determination of location, extent, type and malignant potential of the tumor. Imaging is used for primary diagnosis, planning of treatment including biopsy, resection, radiation, and delineation of tumor from functionally important neuronal tissue. Accurate grading of astrocytoma is critical for planning therapeutic strategies, assessing prognosis, and monitoring response to therapy.[5] Diagnosis and grading mainly rely on imaging features. MR imaging findings should be evaluated for tumor crossing midline, edema, tumor signal heterogenecity, hemorrhage, border definition, cyst formation or necrosis, and mass effect. Common clinical manifestations are headache, vomiting, seizures, visual disturbances, personality change, vertigo and hemiparesis. In our study, the most common symptom were headache and seizures.

Accurate grading of gliomas is of utmost importance because the therapeutic approach and prognosis differ considerably according to tumor grade. Whereas conventional MR imaging provides information on contrast enhancement, mass effect, edema, and necrosis, it is not always accurate for the precise grading of gliomas. [6] Although previous studies have suggested that contrast enhancement alone is not sufficient to predict tumor grade because some low-grade gliomas demonstrate contrast enhancement while some high-grade tumors do not, the extent of contrast enhancement has been traditionally used as a mark of malignancy. Advanced MR imaging techniques such as diffusion and perfusion MR imaging have demonstrated utility for the grading of brain tumors[6].

DWI allows assessing the cellularity of tumors in a noninvasive form because cellular and subcellular elements impede water mobility and quantitative information from the restriction of water molecule movement can be observed in calculating the ADC. Thus, brain neoplasms with higher cellularity or with a higher grade show a significant reduction in ADC values[43]. In our study, we found a significant difference in the minimum ADC value for differentiating the low- and high-grade gliomas ($P<0.001$). These findings are similar to those reported previously by Lee et all [7](n = 16), Kono et al [8] (n-17), and Clli et al [9](n=31), with high-grade gliomas showing a significant reduction in ADC values and incrased signal intensity on DWI. Our findings also agree with those demonstrated by Yamasaki et al which suggests in inverse relationship between ADC and grade of glial tumors. In the study conducted by Hilario et all they found that at a cut-off ADC value of 1.185x 10-3 mm2/s for the discrimination of high and low grade

gliomas sensitivity was 97.6% and specificity was 53.1%. Comparison between Hilario et al (2012) and our study is shown in table 4.

CE-MRI only represents a pathological alteration in the blood-brain barrier (with or without concomitant angiogenesis), whereas the degree of perfusion MR abnormality can truly reflect the degree of angiogenesis (with or without destruction of the blood-brain barrier).[10] Therefore, the advantage of perfusion MRI over contrast enhanced MRI is in depicting tumor angiogenesis and hence in pre-operative grading. Moreover, because large cerebral gliomas are often histopathologically heterogeneous, areas with higher rCBV values, which may be regarded as greater tumor vascularity, can be selectively targeted by stereotactic biopsies to reduce tumor under-grading. This is especially true for nonenhancing gliomas with relatively intact blood – brain barrier. On the contrary, for high grade enhancing gliomas with concomitant breakdown of the blood-brain barrier, the first pass of contrast material may leak into extravascular space, and thus susceptibility effects may be decreased between intravascular and extravascular space near the disrupted blood-brain barrier, which is considered to cause the underestimation of the true tumor vascularity. In anaplastic tumors, peritumoral areas demonstrate not only altered capillary morphologic findings but also scattered tumor cells infiltrating along newly formed or pre-existing but dilated vascular channels. In low grade gliomas, on the other hand, the peritumoral region contains less infiltrating tumor cells. This interpretation is consistent with elevated blood volume preceding the appearance of enhancement, which reflects blood-brain barrier breakdown. Information regarding heterogeneity of peritumoral region in terms of vascularity as depicted by PWI can be effectively used for better estimation of true brain tumor size pre-operatively. We however did not calculated rCBV values in peritumoral edema. In the study conducted by Hilario et al, at a cut-off of rCBV 1.74ml/100mg to differentiate low grade from high grade, sensitivity was 94.4% and specificity was 94.4% and specificity was 50.0%. Aprile et al found that at a cut-off 3.5ml/100mg for rCBV sensitivity was 100% and specificity was 95.8%. Comparison of cut-off values between various studies is shown in table 5.

Though the metabolite ratios in our study were not helpful quantitatively in grading of gliomas, presence of some peaks like lipid and lactate did help in grading. There are some limitations to our study. The sample size of 30 is quite small. Stereotactic biopsies were not targeted by rCBV or ADC maps. Moreover there is the possibility of histopathologic misdiagnosis attributable to sampling error in the pathologic examination because of the histologic heterogencity of tumor tissues. It is widely known that a given individual glioma, usually of high grade, often contains a continuum of histologic features of grades II-IV and tumor grading ins dependent on the site of tumor biopsy or resection and thus subject to smapling error or under sampling.

CONCLUSION

To conclude MRI forms main modality for imaging of gliomas always include diffusion, perfusion and spectroscopy while doing the imaging of gliomas that the selection of ROI should be from area of maximum hypointensity on ADC maps and maximum signal loss of PWI. The biopsy has to be done from area of maximum hypointensity on ADC maps and maximum signal loss of PWI. Spectroscopy is very useful differentiate tumors from metastases.

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