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GRADING OF GLIAL TUMORS BY MR PERFUSION MEAN RELATIVE CEREBRAL BLOOD VOLUME

Radio-Diagnosis

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ABSTRACT

Objective: To determine the usefulness of corrected relative cerebral blood volume in assessing the histopathological grade of cerebral gliomas. **Materials And Methods:** In order to determine relative cerebral blood volume (rCBV)(rCBV) (rCBV ratio = rCBV[tumor] / rCBV[contralateral white matter]) , 33 patients with pathologically proven gliomas (2 Grade 1, 6 Grade 2, 8 Grade 3, 17 Grade 4) underwent dynamic contrast-enhanced T2*-weighted and conventional T1- and T2-weighted imaging. rCBV maps were obtained by fitting a gamma-variate function to the contrast material concentration versus time curve. rCBV ratios between tumor and normal white matter (maximum rCBV of tumor / rCBV of contralateral white matter) were calculated and compared between four grades of glioma. **Results:** Mean rCBV ratios were 1.00 ± 0.35 for grade 1 gliomas, 2.6 ± 1.17 for grade 2 gliomas, 4.98 ± 0.76 for grade 3 gliomas and 6.54 ± 1.47 for grade 4 gliomas, and were thus significantly different;The rCBV ratio cutoff value which permitted discrimination between high-grade (gliomas) and low- grade gliomas was 2.86, and the sensitivity of this value were 93.4%. **Conclusion:** Mean rCBV is a useful and reliable technique for determining the preoperative histopathologic grade of cerebral gliomas.

KEYWORDS

INTRODUCTION

Gliomas are the most common primary neoplasms of the central nervous system, histologically varying from low grade (benign) to high grade (malignant). Their grade can be underestimated even on histopathology because even a single lesion may be histologically heterogeneous. For planning the optimal treatment strategy and assessing prognosis, accurate histologic grading is essential because treatment options are different for high-grade and low grade gliomas as high grades are usually treated with adjuvant and neo adjuvant radiation or chemotherapy, whereas low-grade gliomas are not. [1,2]

Conventional techniques can easily detect intracranial masses, but discriminating these lesions from each other and grading of tumor cannot be done.[3]Gadolinium-based MR imaging is an useful and established tool for the characterization of cerebral tumors but contrast enhancement alone is a poor differentiator between different grades gliomas therefore additional markers are required for the same.[4,5]The degree of vascular proliferation is an important marker in determining the aggressiveness and histopathological grading of gliomas.[6]

Recent advances in MR imaging techniques like perfusion MR allows us to measure the microvasculature within the brain tumors. Corrected Relative cerebral blood volume (rCBV) maps, prepared from MR perfusion images can assess the tumor vascularity both qualitatively and quantitatively.[7]

The purpose of this study was to determine the relationship between rCBV and the histopathologic grade of gliomas and to determine the corrected rCBV ratio cutoff value which can discriminate between different grades of gliomas, and the sensitivity and specificity of these values.

Table 1. Mean corrected Relative Cerebral Blood Volume Ratios of 25 Patients with High Grade Gliomas

S. no.	Age	Sex	Location	Mean rcbv	Histopath diagnosis
1	35	M	R FRONTAL	**7.53**	GBM (GRADE 4)
2	51	M	L FRONTAL	**7.84**	GBM (GRADE 4)
3	23	M	L FRONTO-TEMPORAL	**1.90**	GBM (GRADE 4)
4	35	M	L FRONTAL	**7.2**	GBM (GRADE 4)
5	70	F	L PARIETAL	**6.6**	GBM (GRADE 4)
6	70	M	R FRONTAL	**6.03**	GBM (GRADE 4)
7	65	M	R FRONTO-PARIETO-TEMPORAL	**8.36**	GBM (GRADE 4)
8	72	F	L FRONTAL	**7.10**	GBM (GRADE 4)
9	36	M	R FRONTO-PARIETO-TEMPORAL	**5.37**	GBM (GRADE 4)
10	65	F	L FRONTO – PARIETAL	**6.13**	GBM (GRADE 4)
11	58	F	L FRONTO-TEMPORAL	**6.2**	GBM (GRADE 4)
12	38	M	R FRONTAL	**6.8**	GBM (GRADE 4)
13	45	M	R FRONTAL	**7.3**	GBM (GRADE 4)
14	61	F	R TEMPORO-PARIETAL	**7.2**	GBM (GRADE 4)
15	35	F	R TEMPORO-PARIETAL	**8.1**	ASTROCYTOMA GRADE 4
16	43	M	R FRONTO-PARIETO-TEMPORAL	**5.3**	ASTROCYTOMA GRADE 4
17	6	M	ROOF OF 4TH VENTRICLE	**5.8**	MEDULLOBLASTOMA GRADE 4
18	51	F	R FRONTAL	**5.6**	OLIGODENDROGLIOMA GRADE 3
19	45	F	L FRONTO – PARIETAL	**4.8**	OLIGODENDROGLIOMA GRADE 3
20	25	M	R LATERAL VENTRICLE	**5.03**	ANAPLASTIC EPENDYMOMA 3
21	14	M	L PARIETO-OCCIPITAL	**6.5**	EPENDYMOMA GRADE 3
22	17	M	B/L LATERAL VENTRICLE	**4.5**	EPENDYMOMA GRADE 3
23	63	M	L TEMPORAL	**4.4**	EPENDYMOMA GRADE 3

24	27	M	R FRONTO-PARIETAL	**3.8**	EPENDYMOMA GRADE 3
25	28	M	L FRONTO – PARIETAL	**4.6**	EPENDYMOMA GRADE 3

Note. rCBV = relative cerebral blood volume, **L** = left, **R** = right

Table 2. Mean corrected Relative Cerebral Blood Volume Ratios of 8 Patients with Low Grade Gliomas

S.no.	Age	Sex	Location	Mean rcbv	Histopath diagnosis
1	11	M	L FRONTO - PARIETAL	**3.8**	EPENDYMOMA GRADE 2
2	12	F	R PARIETO-TEMORAL	**4.3**	EPENDYMOMA GRADE 2
3	35	M	R FRONTO-PARIETO-TEMPORAL	**2.2**	ASTROCYTOMA GRADE 2
4	16	M	ANTERIOR COMMISSURE	**1.3**	ASTROCYTOMA GRADE 2
5	51	F	L BRAIN STEM (PONS, MEDULLA)	**2.2**	ASTROCYTOMA GRADE 2
6	25	M	L FRONTO-TEMPORAL	**1.6**	ASTROCYTOMA GRADE 2
7	40	M	R FRONTAL	**1.24**	ASTROCYTOMA GRADE 1
8	45	M	L FRONTAL	**0.76**	ASTROCYTOMA GRADE 1

Note. rCBV = relative cerebral blood volume, **L** = left, **R** = right

MATERIALS AND METHOD

Patients

We retrospectively investigated 33 consecutive patients with gliomas who had undergone both conventional and perfusion MR imaging during period of one and half year period. Twenty three were male and ten were female, and their ages ranged from 6 to 72 (mean age 40) years. Only preoperative perfusion MR studies in patients with pathologically confirmed gliomas were included in our study. All patients who underwent rCBV mapping gave informed written consent under guidelines approved by the ethical committee Shree Ram Murti Smarak Institute of Medical Science, Bareilly. Before imaging, we inserted an 18- or 20-gauge IV catheter in the antecubital vein for contrast agent administration. The presence of gliomas was confirmed by surgical resection followed by biopsyin all patients. All tumors were graded according to the World Health Organization grading system [8,9] ;there were two grade 1 gliomas (astrocytoma), six grade 2 gliomas (four astrocytoma and two ependymoma), eight grade 3 gliomas (five ependymoma, one anaplastic ependymoma and two oligodendroglioma) and seventeen grade 4 gliomas (fourteen glioblastoma, two astrocytoma and one medulloblastoma). Tumors were located in the cerebral hemisphere in twenty nine cases, the brain stem in one, and the ventricles in three.

MR Imaging Studies

Cerebral perfusion studies were performed on a Siemens MRI Magnetom Skyra – 3.0 Tesla 48 channel (Berlin, Germany) using intra venous administration of gadopentetate dimeglumine (GADOSCAN, 0.1 mmol/kg; Acro life sciences; India) with dynamic tracking of bolus of contrast. Images were acquired using a first-pass gadopentetate dimeglumine–enhanced MR examinations performed using the following imaging sequences: Localizing sagittal TI-weighted images were obtained, followed by non enhanced axial T1-weighted (2000/9 [repetition time msec/echo time msec]) and T2-weighted (5520/81) images of the brain. The location and size of the tumor and the positions of the superior and inferior margins were determined from the T2-weighted images. Dynamic contrast agent enhanced T2*-weighted gradient-echo echo-planar imaging (1870/30) during the first pass of a bolus of gadopentetate dimeglumine) was then performed. Finally, post contrast axial

T1- Weighted Images Were Obtained.

Perfusion-weighted imaging was performed by using a lipid-suppressed, T2*-weighted echo-planar imaging sequence with the following parameters: repetition time, 1,870 msec; echo time, 30 msec; field of view, 220 × 220 mm; section thickness, 4 mm; data matrix, 128 x 128 matrix; and in-plane voxel size, 1.7 x1.7x 4.0 mm. Between five and seven sections were obtained to cover the entire tumor volume identified on the T2-weighted images. A section gap of 0%-30% of the section thickness was used, depending on the extent of the signal intensity abnormality on the T2-weighted images. A series of 60 multi section acquisitions was acquired at 1-second intervals.10 acquisitions were performed before contrast agent injection to establish a precontrast baseline. At the 10th acquisition, gadopentetate dimeglumine (0.1 mmol/kg) was injected with a power injector at a rate of 5 mL/sec through an 18- or 20-gauge intravenous catheter, immediately followed by a bolus injection of saline (total of 20 mL at 5 mL/sec).

Generation Of rCBV Maps

All dynamic MR images were evaluated with Siemens software on MRI console and workstations. An exponential relationship between relative signal reduction and contrast material concentration was assumed for the creation of rCBV map. To fit a gamma-variate function to the contrast material concentration versus time curve on a pixel-by-pixel basis, the non- linear regression method was used.[10,11] The rCBV of each pixel was then calculated by numerical integration of the area under the concentration-time curve (i.e. $rCBV = C_{(t)}dt$).[1] Thus, increased signal intensity on the rCBV map indicated increased rCBV, and vice versa.

Qualitative And Quantitative Analysis

For quantitative analysis, normal white matter within the contralateral hemisphere was used as the internal standard reference.[12] To determine maximum rCBV ratios, a region of interest (ROI), including at least 20 pixels, was meticulously established in the region of tumor which according to rCBV map showed maximum intensity, and also in the contralateral normal white matter. A circular ROI was drawn, and measured three times, and then its average value was recorded. rCBV ratios were calculated by dividing the mean CBV of a tumor by that of contralateral normal white matter.

Visual inspection of rCBV map images showed that the signal intensity of all tumors was higher than or similar to that of contralateral normal white matter. Thus, after visual grading, if rCBV maps depicted any intratumoral area with high signal intensity, we assigned the tumor to the high rCBV group.

Data Analysis

To assess the relationship between rCBV ratio and histologic tumor grade, we compared rCBV ratios between grade 1, grade 2, grade 3 and grade 4 gliomas using the Kruskal-Wallis and Mann-Whitney U tests. The latter was also used for comparing rCBV ratios between high-grade and low- grade gliomas. To calculate the rCBV ratio cutoff value which permits discrimination between high-grade and low- grade gliomas, and the sensitivity of this value, univariate discriminant analysis was used. For statistical computation, an SPSS statistical software package was employed, with the level of significance defined as $p < .05$.

RESULTS

Table 1 and 2summarizes the rCBV ratios of high grade and low gradegliomas respectively. These were 0.75 – 1.25 (mean, 1.00 ± 0.35) in grade 1 gliomas (fig. 1), 1.40 – 4.20 (mean, 2.60 ± 1.17) in grade 2 gliomas (fig. 2), 3.90 – 6.40 (mean, 4.98 ± 0.76) in grade 3 gliomas (fig. 3), 1.98 – 8.37 (mean 6.54 ± 1.47) in grade 4 gliomas (fig. 4) and is summarised in table 3. The overall group difference in rCBV ratio between the four grades of gliomas was statistically significant ($p = .001$, using Kruskal-Wallis test).Individual group difference in rCBV ratios were significant ($p = .012$ between grade 1 and grade 4, $p = .001$ between grade 2 and grade 4, using Mann-Whitney U test). rCBV ratio of low grade (grade 1 and grade 2) mean rCBV 2.14 ± 1.53 were significantly lower than high grade gliomas (grade 3 and grade 4) mean rCBV 5.91 ± 1.56.The rCBV ratio cutoff value which can allow us to discriminate between high grade and low grade is 2.86 . the sensitivity of the value is 93.6% (31/33).

DISCUSSION

Gliomas are the most common neoplasm of the central nervous system, and have a heterogeneous histologic spectrum from low- grade astrocytomas to high grade glioblastomas.The prognosis of patients with gliomas, particularly those with high-grade tumors, remains poor in spite of improvements in the results of surgery, radiation therapy and chemotherapy,. For planning the optimal treatment strategy, accurate determination of tumor grade is critical, and in most histologic grading systems, vascular proliferation of gliomas is a diagnostic criterion for malignancy.[13,14]

The degree of vascular proliferation is one of the most important

parameters in determining the histopathologic grade of gliomas, along with the degree of cellular or nuclear pleomorphism and the presence or absence of necrosis.[15] These neovascular channels provide a crucial pathway for tumor infiltration along the white matter tracts and commissural fibers, allowing distant tumor spread with relative preservation of the underlying cytoarchitecture of the brain.

Differentiating low-grade gliomas from high grade gliomas preoperatively with use of imaging is important for reasonbecause the management of gliomas has been widely based on the WHO histopathologic classification and grading system followed by stereotactic biopsy or surgery. However, the clinical management of the low-grade gliomas (WHO 1 and 2) depends on the clinical behaviour of these tumors and may vary from a "wait-and-watch" policy to a prompt surgical treatment,whereas high-grade (WHO 3 and 4) gliomas typically require a resection (subtotal or near-total) and adjuvant radio- chemotherapy in WHO grade 4tumors. This variable management of gliomas along with the WHO grading drawbacks indicates a need for another classification system as an addition or, potentially, replacement for histopathology in guiding treatment decisions.[16]

The degree of MR perfusion abnormality reveals the degree of micro vascularity, with or without destruction of the blood-brain barrier,whereas the presence of contrast enhancement at conventional MR imaging represents a pathologic alteration in the blood-brain barrier, with or without accompanying vascular hyperplasia.[6,17]

Perfusion MR imaging methods include the arterial spin- tagging and the first-pass contrast techniques. The former does not require the use of contrast material, but is limited by its sensitivity to motion and low contrast-to-noise ratio[18], and for these reasons it has not been widely used in modality can play an important role in the noninvasive determination of which portion of a tumor is most malignant. First-pass dynamic susceptibility-weighted, contrast-enhanced (DSC) magnetic resonance (MR) echo-planar imaging (EPI) is well established for determining relative regional cerebral blood volume (rCBV) in brain tumors.[19]

The rCBV ratios of gliomas have been described in various previous studies. Aronen et al[7] demonstrated statistically significant differences in CBV measurements between low and high- grade gliomas by using spin-echo echo-planar imaging. The findings in our study confirms these previous findings. The mean rCBV values of grade 1, grade 2, grade 3 and grade 4 gliomas were 0.75 – 1.25 (mean, 1.00 ± 0.35), 1.40 – 4.20 (mean, 2.60 ± 1.17), 3.90 – 6.40 (mean, 4.98 ± 0.76) and 1.98 – 8.37 (mean 6.54 ± 1.47) respectively which correlate with the rCBV values of the previous studies;Sugahara et al[20] found that the rCBV ratios of glioblastomas, anaplastic astrocytomas and low-grade gliomas were 4.00 16.20 (mean, 7.32), 0.98 7.93 (mean, 4.61) and 0.64 – 2.01 (mean, 1.26) respectively; according to Knopp et al[6], these ratios were 1.73 13.70 (mean, 5.07) in high-grade gliomas and 0.92 2.19 (mean, 1.44) in low-grade; Hakyemez B et al. also correlated with our results and demonstrated that the rCBV ratios of high-grade gliomas (5.76 ± 3.35) were higher than those of low-grade gliomas (1.69 ± 0.52).[21]The rCBV ratios of low and high grade gliomas ranged from 1.30 to 4.06 (mean, 2.48), and from 4.62 to 40.75 (mean, 12.07), respectively in the study conducted by Cho K S et al.[17]

We found that the rCBV ratio cut- off value which permitted discrimination between high- grade and low-grade gliomas was 2.86, with 93.6% sensitivity.

In our study, one high-grade gliomas had low rCBV, a finding which reflects a low level of neovascularity or contrast leakage through the altered blood-brain barrier. Sugahara et al.[19] reported two cases of anaplastic glioma without increased vascularity, suggesting that a lack of neovascularity within a tumor did not necessarily indicate benignancy. Our results also showed that in one of the high-grade gliomas with visually determined low rCBV, enhancement was evident at contrast-enhanced T1-weighted MR imaging, a finding which may reflect a deceptively low rCBV related to contrast leakage through the altered blood-brain barrier. Perfusion MR may underestimate the real microvascular blood volume when this is disrupted,. In a region of severe blood-brain barrier breakdown, unwanted T1 effects caused by extravasated gadolinium counteract the T2 signallowering effects of gadolinium, resulting in falsely low rCBV values.[17]

In our study one low grade glioma had high rCBV which could be explained by the fact that they might already have high-grade components at the time of the histopathologic evaluation or that rCBV is possibly higher in patients those have undergone malignant transformation. which was supported by the previous study conducted by Caseiras G. et al[22].

All our results suggest that perfusion MR imaging is a valuable technique for evaluating the histopathologic grade of gliomas. In the clinical field, however, it should be kept in mind that rCBV ratios may differ according to the imaging technique employed (i.e. the imaging sequence, amount of contrast material used for bolus injection, and duration of contrast injection).

CONCLUSION

In conclusion, dynamic contrast-enhanced T2*-weighted perfusion MR imaging performed in these 33 cases provided valuable information about the vascularity of gliomas, and led to the correct assessment of histologic tumor grade. The modality is thus a useful and dependable means of noninvasively preoperative assessing the histologic grade of gliomas and determine the appropriate treatment according to the respective grade of glioma.

Table 3. The rCBV Ratios for Each glioma grade, with Mean and SD, Extreme Values (Range) and Number of Patients Included (N) in each Group

		Mean rCBV						p-value
		N	Mean	Standard Deviation	Median	Minimum	Maximum	
Histopathological Grade	Grade-I	2	1.00	.35	1.00	.75	1.25	.0001**
	Grade-II	6	2.60	1.17	2.20	1.40	4.20	
	Grade-III	8	4.98	.76	4.80	3.90	6.40	
	Grade-IV	17	6.54	1.47	6.90	1.98	8.37	

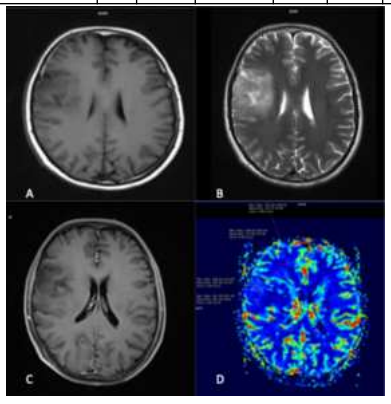

Fig.1: Astrocytoma grade 1 in a 48 year old male.

A, B. T1 and T2- weighted image shows area of altered signal intensity in the right fronto- parietal region. **C.** Contrast- enhanced T1- weighted image shows no enhancement in the above lesion. **D.** rCBV map shows the placement of ROIs for measurement of rCBV in the above lesion and shows minimally raised rCBV value as compared to normal white matter.On histopathology the above lesion proves to be astrocytoma grade 1.

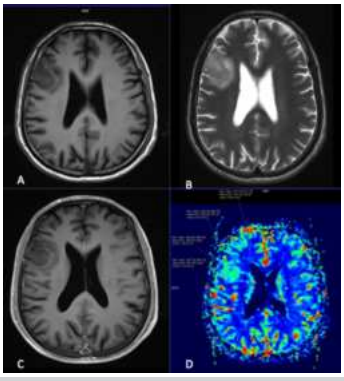

Fig.2: Astrocytoma grade 2 in a 38 year old male.

A,B. T1 and T2- weighted image shows heterogeneous area of altered signal intensity in the right fronto- parietal region with mild perilesional edema**C.** Contrast- enhanced T1- weighted image shows subtle enhancement in the above lesion. **D.**rCBV map shows the placement of ROIs for measurement of rCBV in the above lesion and shows mild raised rCBV value as compared to normal white matter.On histopathology the above lesion proves to be astrocytoma grade 2.

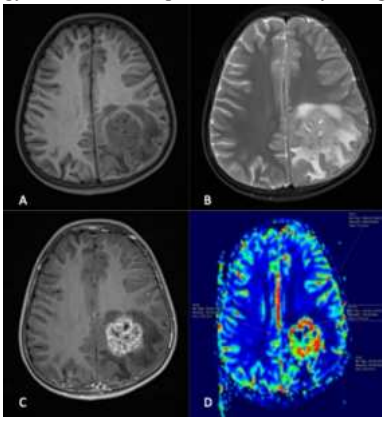

Fig.3: Ependymoma grade 3 in 14 year old male.

A,B. T1 and T2- weighted images shows a multilobulated heterogenous lesion appearing hypointense on T1 and isointense in T2 (compated to cerebral cortex) with marked perilesional edema and areas of necrosis within. C. Contrast enhanced T1- weighted image showing heterogeneous post contrast enhancement with central non enhancing areas. D. rCBF maps show perfusion MR findings of the tumoural lesions and shows moderately raised rCBV values within the lesion. On histopathology the lesion was found to be Ependymoma grade 3.

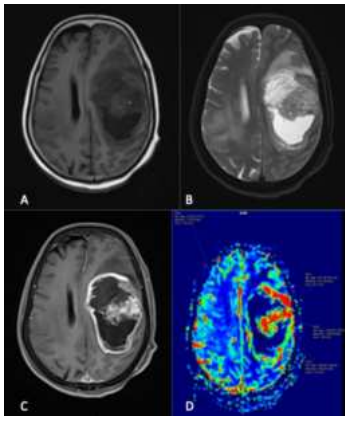

Fig.4: Glioblastoma (grade 4) in a 65 year-old female.

A,B. T1 and T2-weighted image shows a large heterogeneous signal intensity mass in the left fronto parietal cortical subcortical region with perifocal edema and necrotic area at its posterior aspect.C. Contrast-enhanced T1-weighted image shows heterogeneous contrast enhancement in the centre solid part and in periphery.D. rCBV map shows the placement of ROIs for measurement of rCBV in the tumor and in contralateral white matter shows significant high rCBV in the solid portion of the tumorand some areas in the periphery consistent with high grade glioma. Histopathological it came out to be Glioblastoma grade 4.

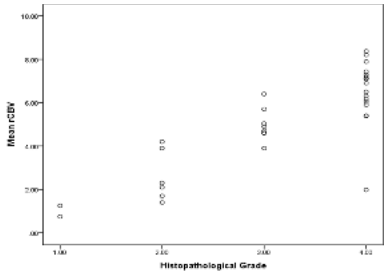

Fig. 5 Scatter plot of relative cerebral blood volume (rCBV) ratios in four grades of gliomas . The rCBV ratio is highest in grade 4 gliomas and lowest in grade 1 gliomas. A comparison of mean rCBV ratios in each tumor group shows statistically significant differences between them with one of the grade 4 glioma had low rCBV and 2 of grade 2 glioma shows more rCBV than cut off value (rCBV = 2.86) which permits discrimination between low and high grade gliomas.

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