ISSN: 2577 - 8005

Research Article

Medical & Clinical Research

Role of Contrast Perfusion Weighted Magnetic Resonance Imaging in Grading of Brain Tumors with Histopathological Correlation

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Submitted: 26 Aug 2024; **Accepted**: 02 Oct 2024; **Published**: 15 Oct 2024

Citation: Bardhan, V., Sharma, P., Arora, R., Kishore, S. (2024). Role of Contrast Perfusion weighted Magnetic Resonance Imaging in Grading of Brain tumors with Histopathological Correlation. *Med Clin Res, 9*(10), 1-07.

Abstract

Background: *Traditional MRI sequences provide precise anatomical information about brain tumors. But these sequences can't quantitatively evaluate vascular physiology, or capture tumor biology at the molecular level; which is important for tumor grading, therapeutic assessment, and prognostication. Furthermore, non-enhancing parts of the tumor affected brain, which generally indicates peri-tumoral brain edema with infiltrative tumor cells, is not visible on conventional MRI sequences. Perfusion weighted Magnetic Resonance Imaging (PW-MRI) techniques such as Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) and Dynamic Susceptibility Contrast Magnetic Resonance Imaging (DSC-MRI) have shown promise as imaging biomarkers for glioma therapy, since these new sequences can also provide information about vascular hemodynamics. Our study was first prospective study from Himalayan belt of India, wherein we tried to assess the role of PW-MRI in the grading of brain tumors, with histopathological correlation.*

Aim and Objective: *To compare tumor perfusion and histopathological tumor grading, in evaluation of brain tumor especially gliomas.*

Material and Method: *40 patients who were referred to Department of Radiodiagnosis for evaluation of brain tumor, and who gave informed consent, were included in this prospective study, done over a period of 18 months. All patients underwent MRI, followed by surgical resection.*

Observation and Result: *In our study, diagnostic accuracy was 90% for mean rCBV (lesion) (cut off: 7 by ROC), mean rCBF (lesion) (cut off: 13.9 by ROC), and rCBF ratio (cut off: 2.9 by ROC); for differentiating benign versus malignant brain tumor. rCBF ratio was found to be best diagnostic parameter with sensitivity of 96%, specificity of 80%, positive predictive value of 89%, negative predictive value of 92%, diagnostic accuracy of 90%, area under ROC curve=0.909, and p value<0.001.*

Conclusion: *We come to conclusion that high grade brain tumor display higher CBF, than do low grade brain tumor. Three parameters showed good diagnostic accuracy, which includes rCBF ratio, mean rCBF (lesion), and mean rCBV (lesion). These parameters can be used to predict the grade of the brain tumor, with good diagnostic accuracy.*

Keywords: Glioma, Perfusion, Relative cerebral blood flow (rCBF), Relative cerebral blood volume (rCBV)

1. Introduction

The abnormal growth of cells within the brain is referred to as brain tumor. Meningioma is the most frequent benign primary brain tumor in adult, while glioma is the most common primary malignant brain tumour. Malignant brain tumors are considered uncommon because they only account for 1% to 2% of all malignancy in adult.

Treatment for brain tumors is currently changed based on the tumour's stage, which is primarily assessed with histopathologic grading system. As a result, several investigations are being conducted to see if different imaging modalities might predict the molecular subtype of brain tumor, with probable survival benefit; due to ability to select appropriate treatment according to molecular subtype of brain tumor.

To locate and characterize brain malignancy, Magnetic Resonance Imaging (MRI) is the imaging modality of choice. Gliomas are the most frequent primary brain tumors in adults, ranging from pilocytic astrocytoma to glioblastoma multiforme (GBM) [1-

3]. Glioma associated neovascularization, is a common tumor characteristic that plays a role in a variety of biological processes, including tumor growth, invasiveness, and therapeutic resistance [4]. For better glioma care, it is essential to visualize tumor vascularity.

Traditional MRI sequences provide precise anatomical information about brain tumors. But these sequences can't quantitatively evaluate vascular physiology, or capture tumor biology at the molecular level; which is important for tumor grading, therapeutic assessment, and prognostication [5-8]. Furthermore, non-enhancing parts of the tumor affected brain, which generally indicates peri-tumoral brain edema with infiltrative tumor cells, is not visible on conventional MRI sequences. Due to this limitation, neurosurgeons find it difficult to resect brain tumors completely, based only on conventional MRI sequences [9,10]. Perfusion weighted Magnetic Resonance Imaging (PW-MRI) techniques such as Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) and Dynamic Susceptibility Contrast Magnetic Resonance Imaging (DSC-MRI) have shown promise as imaging biomarkers for glioma therapy, since these new sequences can also provide information about vascular hemodynamics [11,12]. PW-MRI is quickly broadening it's application range, by noninvasively investigating the link between imaging parameters and brain tumour vascularity. Our study was first prospective study from Himalayan belt of India, wherein we tried to assess the role of PW-MRI in the grading of brain tumors, with histopathological correlation.

2. Aim and Objective

To compare perfusion imaging grading and histopathological vascular density, in evaluation of brain tumor especially gliomas.

3. Material and Method

40 patients who were referred to Department of Radiodiagnosis for evaluation of brain tumor, and who gave informed consent, were included in this prospective study, done over a period of 18 months. Patient with ongoing treatment for brain tumor, or patient with past history of treatment for brain tumor, or patient with history of recurrent brain tumor, or patient who failed to give informed consent, or patient with renal dysfunction (estimated glomerular filtration rate, eGFR<30ml/min/1.73m2), or patient with history of allergy to contrast media were excluded from this study. All patients underwent MRI, followed by surgical resection. All MRI scans were done on 3T MRI (GE Discovery 750 W, GE Healthcare USA) with dedicated brain coil. Multiplanar Conventional MRI T1, T2, T2 FLAIR, DWI/ADC, SWI, and DSC sequences were obtained. The images were analysed using the workstation provided with the MRI scanner. Parameters like cerebral blood volume (CBV), mean transit time (MTT), cerebral blood flow (CBF) and peak height (PH) recovery were evaluated.

- Contrast: gadolinium based contrast agent
- Dose: 0.2ml/kg

Calculation of DSC perfusion was done by signal intensity curve, after the pass of the bolus contrast agent. CBV was proportional to the area under the contrast agent concentration - time curve. MTT was estimated from the concentration-time curve, utilizing a standardized measurement such as the width of the perfusion curve, at half of the maximum height. CBF was easily calculated given its relationship to the product of CBV and MTT. PH was calculated as S0–Smin, where S0 was pre-contrast bolus baseline signal intensity and Smin was minimum signal intensity obtained during the first pass bolus phase of contrast. PSR was calculated as (S1–Smin/S0 –Smin), where S1 was the average post-bolus signal intensity.

Non-model-based "semi-quantitative" indices such as the initial area under the curve (IAUC) was derived from the dynamic data.

4. Stastical Analysis

Microsoft Excel spread sheet was used to enter the data. All precautions were taken to make sure that there was no error in data entry. In categorical variables, frequency and percentage were used as descriptors. Mean ± standard deviation was used for continuous variables. Using the Chi square test, we compared proportions. The Mann Whitney U test and students t test were used to compare the means of the two groups as applicable.

5. Observation and Result (Figure 1, Table 1-4)

40 patients were included in study population, with 3 (7.5%) patients having histopathological grade I, 12 (30%) patients having histopathological grade II, 13 (32.5%) patients having histopathological grade III, and 12 (30%) patients having histopathological grade IV. 15 patients had low grade brain tumor, and 25 patients had high grade brain tumor. The mean age (years) in low grade brain tumor was 38.00 ± 16.05, and 44.24 ± 17.22 in high grade brain tumor. There was no significant difference between the groups in terms of age in years (p=0.256).

In low grade tumors, 6 (40%) patients were in age group of 18-30 years, 4 (26.7%) patients were in age group of 31-40 years, 2 (13.3%) patients were in age group of 51-60 years, 2 (13.3%) patients were in age group of 61-70 years, and 1 (6.7%) patient was in age group of 41-50 years.

In high grade tumors, 7 (28.0%) patients were in age group of 18-30 years, 7 (28.0%) patients were in age group of 41-50 years, 4 (16.0%) patients were in age group of 41-50 years, 3 (12.0%) patients were in age group of 31-40 years, 2 (8.0%) patient was in age group of 61-70 years, 1 (4.0%) patient was in age group of 71-80 years, and 1 (4.0%) patient was in age group of 81-90 years. There was female preponderance in low grade (8 out of 15 patients), and male preponderance in high grade (16 out of 25 patients) brain tumor. Mean rCBV (lesion) was 6.58 ± 8.04 in low grade brain tumor, and 23.18 ± 16.81 in high grade brain tumor. rCBV ratio was 3.69 ± 2.88 in low grade brain tumor, and 9.32 ± 5.01 in high grade brain tumor.

Mean rCBF (lesion) was 10.71 ± 16.33 in low grade brain tumor, and 43.51 ± 26.86 in high grade brain tumor. rCBF ratio was 2.05 ± 1.90 in low grade brain tumor, and 7.83 ± 4.40 in high grade

brain tumor.

13 (86.7%) patients with low grade on histopathological grading, were correctly labelled as low grade on contrast perfusion weighted MRI; while 2 (13.3%) patients with low grade on histopathological grading were wrongly labelled as high grade on contrast perfusion weighted MRI. 24 (96.0%) patients with high grade on histopathological grading, were correctly labelled as high grade on contrast perfusion weighted MRI; while 1 (4.0%) patient with high grade on histopathological grading were wrongly labelled as low grade on contrast perfusion weighted MRI.

In low grade brain tumor category, 4 (26.7%) patients had low grade astrocytoma, 3 (20.0%) patients had astrocytoma, 3 (20%) patients had oligodendroglioma, 2 (13.3%) patients had pilocytic astrocytoma, 1 (6.7%) patient had ependymoma, 1 (6.7%) patient had low grade oligodendroglioma, and 1 (6.7%) patient had subependymal giant cell astrocytoma (SEGA).

In high grade brain tumor category, 7 (28%) patients had glioblastoma, 6 (24%) patients had anaplastic astrocytoma, 5 (20%) patients had anaplastic oligodendroglioma, 4 (16%) patients had astrocytoma, 2 (8%) patient had secondary glioblastoma multiforme, and 1 (4%) patient had oligodendroglioma.

In low grade brain tumor category, 3 (20.0%) patients had histopathological grade I, and 12 (80%) patients had histopathological grade II. In high grade brain tumor category, 13 (52.0%) patients had histopathological grade III, and 12 (48%) patients had histopathological grade IV.

When we compared contrast perfusion weighted MRI with histopathological grading, then we found concordant result in 13 (86.7%) patients and discordant result in 2 (13.3%) patients of low grade brain tumor. When we compared contrast perfusion weighted MRI with histopathological grading, then we found concordant result in 24 (96.0%) patients and discordant result in 1 (4%) patients of high grade brain tumor.

In our study, diagnostic accuracy was 90% for mean rCBV (lesion) (cut off: 7 by ROC), mean rCBF (lesion) (cut off : 13.9 by ROC), and rCBF ratio (cut off : 2.9 by ROC); for differentiating benign versus malignant brain tumor.

rCBF ratio was found to be best diagnostic parameter with sensitivity of 96%, specificity of 80%, positive predictive value of 89%, negative predictive value of 92%, diagnostic accuracy of 90%, area under ROC curve=0.909, and p value<0.001.

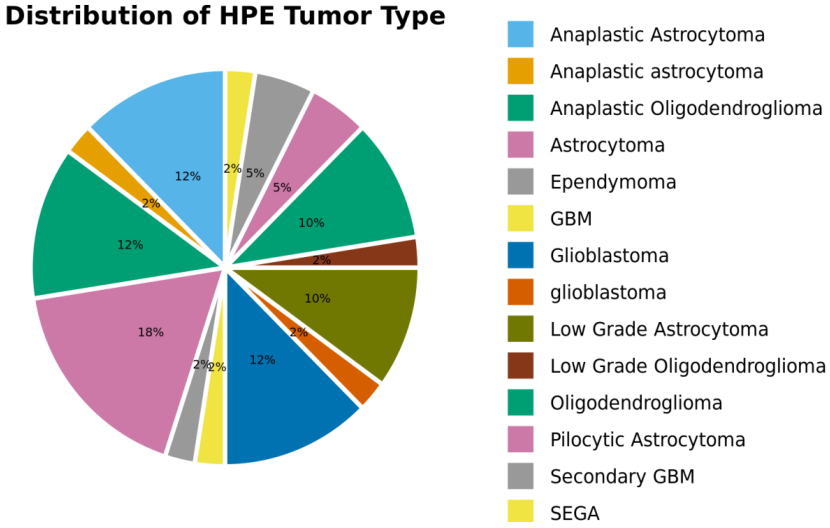

Figure 1: Distribution of Brain Tumors according to Histopathological Analysis

Histological Grade	Frequency	Percentage	95% CI
I	3	7.5%	2.0% - 21.5%
II	12	30.0%	17.1% - 46.7%
III	13	32.5%	19.1% - 49.2%
IV	12	30.0%	17.1% - 46.7%

Table 1: Distribution of Brain Tumors according to Histological Grade

Parameters	Histological Tumor Grade		p-value
	Low Grade (n = 15)	High Grade (n = 25)	
Age (Years)	38.00 ± 16.05	44.24 ± 17.22	0.256[1]
Age			0.546[2]
18-30 Years	6 (40.0%)	7 (28.0%)	
31-40 Years	4 (26.7%)	3 (12.0%)	
41-50 Years	1 (6.7%)	7 (28.0%)	
51-60 Years	2 (13.3%)	4 (16.0%)	
61-70 Years	2 (13.3%)	2 (8.0%)	
71-80 Years	0 (0.0%)	1 (4.0%)	
81-90 Years	0 (0.0%)	1 (4.0%)	
Gender			0.283[3]
Male	7 (46.7%)	16 (64.0%)	
Female	8 (53.3%)	9 (36.0%)	
Mean rCBV (Lesion)* **	6.58 ± 8.04	23.18 ± 16.81	<0.001[4]
Mean rCBV (WM)	1.52 ± 0.58	2.90 ± 2.20	0.081[4]
rCBV Ratio* **	3.69 ± 2.88	9.32 ± 5.01	<0.001[4]
Mean rCBF (Lesion)* **	10.71 ± 16.33	43.51 ± 26.86	<0.001[4]
Mean rCBF (WM)	4.18 ± 3.45	6.08 ± 3.89	0.108[4]
rCBF Ratio* **	2.05 ± 1.90	7.83 ± 4.40	<0.001[4]
MTT	11.03 ± 3.33	13.53 ± 5.57	0.083[1]
BAT	22.13 ± 6.08	21.80 ± 12.91	0.214[4]
Tmax	2.65 ± 1.18	2.86 ± 1.98	0.737[4]
TTP	33.60 ± 8.83	33.94 ± 12.85	0.625[4]
Radiological Grade* **			<0.001[3]
Low Grade	13 (86.7%)	1 (4.0%)	
High Grade	2 (13.3%)	24 (96.0%)	
HPE Tumor Type* **			<0.001[2]
Anaplastic Astrocytoma	0 (0.0%)	5 (20.0%)	
Anaplastic astrocytoma	0 (0.0%)	1 (4.0%)	
Anaplastic Oligodendroglioma	0 (0.0%)	5 (20.0%)	
Astrocytoma	3 (20.0%)	4 (16.0%)	
Ependymoma	1 (6.7%)	0 (0.0%)	
GBM	0 (0.0%)	1 (4.0%)	
Glioblastoma	0 (0.0%)	5 (20.0%)	
glioblastoma	0 (0.0%)	1 (4.0%)	
Low Grade Astrocytoma	4 (26.7%)	0 (0.0%)	
Low Grade Oligodendroglioma	1 (6.7%)	0 (0.0%)	
Oligodendroglioma	3 (20.0%)	1 (4.0%)	
Pilocytic Astrocytoma	2 (13.3%)	0 (0.0%)	
Secondary GBM	0 (0.0%)	2 (8.0%)	
SEGA	1 (6.7%)	0 (0.0%)	
Histological Grade* **			<0.001[2]
I	3 (20.0%)	0 (0.0%)	
II	12 (80.0%)	0 (0.0%)	
III	0 (0.0%)	13 (52.0%)	
IV	0 (0.0%)	12 (48.0%)	
MRI vs HPE Grade			0.545[2]
Concordant	13 (86.7%)	24 (96.0%)	
Discordant	2 (13.3%)	1 (4.0%)	

Table 2: Association between Histological Tumour Grade and Parameters

Variable	Category(s) Suggesting Outcome Present	Category(s) Suggesting Outcome Absent	Total Positives	True Positives	True Negatives	False Positives	False Negatives
Histological Grade	III, IV	I, II	25 (62.5%)	-	-	-	-
Mean rCBV (Lesion) (Cutoff: 7 by ROC)	>=7	<7	25 (62.5%)	23 (57%)	13 (32%)	2 (5%)	2 (5%)
Mean rCBV (WM) (Cutoff: 2.4 by ROC)	>=2.4	<2.4	12 (30.0%)	11 (28%)	14 (35%)	1 (2%)	14 (35%)
rCBV Ratio (Cutoff: 5.6 by ROC)	>=5.6	<5.6	23 (57.5%)	21 (52%)	13 (32%)	2 (5%)	4 (10%)
Mean rCBF (Lesion) (Cutoff: 13.9 by ROC)	>=13.9	<13.9	27 (67.5%)	24 (60%)	12 (30%)	3 (8%)	1 (2%)
Mean rCBF (WM) (Cutoff: 2.1 by ROC)	>=2.1	<2.1	30 (75.0%)	23 (57%)	8 (20%)	7 (18%)	2 (5%)
rCBF Ratio (Cutoff: 2.9 by ROC)	>=2.9	<2.9	27 (67.5%)	24 (60%)	12 (30%)	3 (8%)	1 (2%)
MTT (Cutoff: 11.1 by ROC)	>=11.1	<11.1	22 (55.0%)	17 (42%)	10 (25%)	5 (12%)	8 (20%)
BAT (Cutoff: 21.4 by ROC)	<=21.4	>21.4	25 (62.5%)	19 (48%)	9 (22%)	6 (15%)	6 (15%)
Tmax (Cutoff: 1.6 by ROC)	<=1.6	>1.6	11 (27.5%)	9 (22%)	13 (32%)	2 (5%)	16 (40%)
TTP (Cutoff: 29 by ROC)	<=29	>29	17 (42.5%)	12 (30%)	10 (25%)	5 (12%)	13 (32%)

Table 3: Performance of Study Parameters for Predicting Histological Grade: III, IV vs I, II (high grade vs low grade)

Variable	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
Mean rCBV (Lesion) (Cutoff: 7 by ROC)	92.0% (74-99)	86.7% (60-98)	92.0% (74-99)	86.7% (60-98)	90.0% (76-97)
Mean rCBV (WM) (Cutoff: 2.4 by ROC)	44.0% (24-65)	93.3% (68-100)	91.7% (62-100)	50.0% (31-69)	62.5% (46-77)
rCBV Ratio (Cutoff: 5.6 by ROC)	84.0% (64-95)	86.7% (60-98)	91.3% (72-99)	76.5% (50-93)	85.0% (70-94)
Mean rCBF (Lesion) (Cutoff: 13.9 by ROC)	96.0% (80-100)	80.0% (52-96)	88.9% (71-98)	92.3% (64-100)	90.0% (76-97)
Mean rCBF (WM) (Cutoff: 2.1 by ROC)	92.0% (74-99)	53.3% (27-79)	76.7% (58-90)	80.0% (44-97)	77.5% (62-89)
rCBF Ratio (Cutoff: 2.9 by ROC)	96.0% (80-100)	80.0% (52-96)	88.9% (71-98)	92.3% (64-100)	90.0% (76-97)
MTT (Cutoff: 11.1 by ROC)	68.0% (46-85)	66.7% (38-88)	77.3% (55-92)	55.6% (31-78)	67.5% (51-81)
BAT (Cutoff: 21.4 by ROC)	76.0% (55-91)	60.0% (32-84)	76.0% (55-91)	60.0% (32-84)	70.0% (53-83)
Tmax (Cutoff: 1.6 by ROC)	36.0% (18-57)	86.7% (60-98)	81.8% (48-98)	44.8% (26-64)	55.0% (38-71)
TTP (Cutoff: 29 by ROC)	48.0% (28-69)	66.7% (38-88)	70.6% (44-90)	43.5% (23-66)	55.0% (38-71)

Table 4: Performance of Various Study Parameters

6. Discussion

Gliomas are the most common primary brain tumors. Perfusion MRI provides non-invasive measurement of vascularity of brain tumor. The presence of contrast enhancement on conventional MRI is caused by a pathological alteration in the blood-brain barrier (with or without concomitant angiogenesis); whereas the degree of neo-angiogenesis/micro-vascularity (with or without destruction of the blood-brain barrier) is reflected by the perfusion MRI.

On post-contrast T1 weighted images, most high grade gliomas have moderate to severe enhancement, whereas low grade gliomas have minimal or no enhancement. In our study, 3 out of 15 low grade gliomas showed moderate or strong enhancement on post-contrast scan; and 12 out of 15 low grade gliomas showed minimal or no enhancement on post-contrast scan. However, there was minimal enhancement on post-contrast scan in 4 out of 25 high grade glioma. As a result, standard MRI is unable to distinguish the grade of glioma.

There are two types of perfusion MRI: Arterial Spin Labelling (ASL) with endogenous contrast, and first-passage contrast technique with exogenous contrast. Whereas the ASL technique eliminates the need for contrast; it is limited in application due to it's extreme sensitivity to movement, and poor signal-to-noise ratio [13]. The other technique is based on drop-in-signal intensity caused by local field of inhomogeneity, inside the blood vessels, caused by first-passage of contrast material during the period, when the contrast material first passes through the brain. The concentration of contrast material is proportional to signal loss and rCBV values [14].

Spin echo and gradient-echo echo-planar sequences are used in first-pass perfusion MR. At the capillary level, the spin-echo technique is more sensitive than at the larger vessel level in detecting tumor vascularity. The gradient-echo technique, on the other hand is sensitive to the entire amount of blood in both capillaries and larger arteries [15,16].

Previous studies showed a correlation between the histopathological grade of cerebral glioma and rCBV, and have been evaluated many times. The results of previous perfusion MRI studies showed mean maximal rCBV ratio of high-grade glioma ranging between 3.64 and 7.32; and that of low-grade glioma ranging between 0.11 and 2.14. This is concordant with our study in which we found mean maximal rCBV ratio of 9.3 for high grade glioma, and mean maximal rCBV ratio of 3.69 for low grade glioma. In our study, mean maximal rCBF ratio was 7.8 for high grade gliomas, and mean maximal rCBF ratio was 2.05 for low grade glioma.

Lev M et al. achieved 100% sensitivity and 69% specificity using rCBV threshold value of 1.5, in differentiating between 32 consecutive cases of glioma [16]. Assuming a threshold value of 1.75, Law M et al. achieved sensitivity of 95.0% and specificity of 57.5 % [17]. Shin JH et al. calculated cut-off value of 2.93 for rCBV ratio (sensitivity 90.9%, and specificity 83.3%), and cut-off value of 3.57 for rCBF ratio (sensitivity 90.9%, and specificity 83.3%) [18]. The rCBV and rCBF ratios of high and low grade glioma were found to be significantly correlated using Pearson correlation coefficient.

In the high grade group, one of the subsequent studies distinguished between grade III and IV tumors. However, there was no statistically significant difference in rCBV and rCBF ratios between grade III and grade IV ($p > 0.05$). These findings in previous studies show that rCBV and rCBF ratios have limitations in differentiating low versus high grade brain tumor. A cut off value of 2.00 and 1.30 for rCBV and rCBF ratio respectively, was shown to be most effective in differentiating between high and low grade glioma in this study.

rCBV value of 2 grade IV lesions that showed modest enhancement was 2.59 and 2.39 respectively. These values were higher than cut off value. As a result, even though conventional MRI findings were doubtful for high grade glioma, perfusion MRI accurately characterised these lesions as high grade glioma.

On conventional MRI, 1 of grade II astrocytoma (which resembled high grade glioma with necrosis, oedema and significant enhancement) had low rCBV (1.55), and low rCBF (1.19), indicating that it was a low grade glioma.

Another case showed substantial enhancement in grade I lesion, which is rare for low grade glioma. Furthermore, because rCBV score was rather high (2.88), the tumor was mistaken as high grade glioma on perfusion MRI.

The two cut off values stated above, could be useful in predicting glioma grade. But these results show us that as the threshold level is lowered, the specificity is decreased, and some low grade glioma can then be misidentified as high grade glioma. However, when the rCBV cut off value is adjusted to 3.00, the sensitivity decreases.

Perfusion data's significance to tumor grading, over qualitative MRI is debatable, and it is rarely cited in relevant papers. In this study, we found 3 instances where conventional MRI was not able to correctly grade brain tumor. In these patients, we could correctly grade brain tumor based on findings on contrast perfusion weighted MRI. However, both conventional and perfusion MRI misread the glioma grade in 1 case. As a result, more research with larger number of cases is needed, to better assess the efficacy of perfusion data, in determining tumor grade in day to day clinical practice.
Our study had various limitations which include:
• The lack of one-to-one association between diseased specimen, and disordered region, on perfusion or conventional MRI.
• Larger multicentric studies are required to get a widely accepted cut off value.

7. Conclusion

We come to conclusion that high grade brain tumor display higher CBF, than do low grade brain tumor. Three parameters showed good diagnostic accuracy, which includes rCBF ratio, mean rCBF (lesion), and mean rCBV (lesion). These parameters can be used to predict the grade of the glioma, with good diagnostic accuracy. Using perfusion MRI, we can predict the grade of glioma, which can eliminate the need for biopsy or surgery, especially when the tumor is in the eloquent cortex or brainstem, which may increase the chance of postoperative neurological impairments [19,20]. For low-grade gliomas, close surveillance with local radiation therapy is a feasible therapeutic option in individuals. Perfusion imaging's complementary function in the management of low grade gliomas may be more crucial, especially given the inherent sampling error associated with a limited number of biopsy samples. If there is

a discrepancy between histopathological grade and conventional MRI findings, additional information provided by perfusion imaging may be useful.

Declarations

Ethics Approval: Institute Ethical Committee (IEC) approval taken for doing this study.
Consent to Participate: Consent taken from all study participants.
Consent for Publication: Consent taken from all study participants.
Availability of Data and Material: Yes
Competing Interests: There is no Competing Interest
Funding: No Funding taken for doing this study

Authors' Contributions:

a) Vikrant Bardhan: Data collection, Review of previous publications
b) Pankaj Sharma: Writing manuscript
c) Sanjeev Kishore: Statistical analysis of data
d) Rajnish Arora: Patient recruitment and follow up

Acknowledgement

None.

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