10.21761/jms.v8i02.13

ORIGINAL RESEARCH ARTICLE

Correlation of Perfusion MRI of Brain Tumors with their Histopathological Grade

Vishal R Rana[1], Neeraj Prajapati[2*], Vinod K Mogha[3], Shashank Sah[3$], Namrata Singh[3]

ABSTRACT

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 neoadjuvant radiation or chemotherapy, whereas low-grade gliomas are not. The study aims to differentiate glioma grades by using perfusion MRI and to correlate findings of brain tumors on perfusion MRI with histopathological grading.

Materials and Methods: We investigated 50 consecutive patients with brain tumors who had undergone both conventional and perfusion MR imaging during a period of one and half year period. 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. Lymphomas have less vascularity than other tumors, with a mean rCBV of 1.85 ± 0.77. Metastasis is a relatively high vascular tumor with a mean rCBV of 4.57 ± 0.67, which is near to grade 3 gliomas. High-grade gliomas can be differentiated from low-grade gliomas with cut-off value of mean rCBV of 2.86 with a sensitivity of 93%.

Conclusion: Perfusion MRI is a useful and dependable means of noninvasively preoperative diagnosis and assessing the histologic grade of brain tumors, especially gliomas and determining the appropriate treatment according to the vascularity of the tumor and respective grade of glioma.

Keywords: MRI brain, Perfusion scan, Histological grade.

Submission: 06-10-2023; **Acceptance:** 29-11-2023; **Published:** 31-12-2023

[1]Junior Resident, [2]Professor, [3]Assistant Professor

Department of Radiodiagnosis, [$]Department of Neurosurgery Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India.

Corresponding Author: Neeraj Prajapati, Professor, Department of Radiodiagnosis, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India, e-mail: drneerajprajapati@rediffmail.com

How to cite this article: Rana VR, Prajapati N, Mogha VK, Sah S, Singh N. Correlation of Perfusion MRI of Brain Tumors with their Histopathological Grade. SRMS J Med Sci. 2023;8(2):115-121.

Source of support: Nil

Conflict of interest: None

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 neoadjuvant 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 tumors cannot be done.[3] Gadolinium-based MR imaging is a useful and established tool for the characterization of cerebral tumors, but contrast enhancement alone is a poor differentiator between different grades of gliomas; therefore, additional markers are required.[4,5] The degree of vascular proliferation is an important marker in determining gliomas' aggressiveness and histopathological grading.[6]

Presently, an invasive biopsy is required for appropriate management of a newly identified brain tumor suspected to be of glial origin. Perfusion MR imaging may provide a non-invasive diagnostic tool for grading of lesions, as well as in identifying the most malignant region within the tumor for guiding stereotactic biopsy and monitoring response to treatment that precedes conventionally assessed changes in morphology and enhancement pattern of the tumor. Relative cerebral blood volume (rCBV) derived from dynamic susceptibility contrast (DSC) perfusion MR imaging has been the most widely used parameter in predicting the grade of the tumor.[7]

The purpose of this study was to determine the relationship between rCBV and the histopathologic grade of brain tumors, especially gliomas and to determine the corrected rCBV ratio cut-off value, which can discriminate

between different grades of gliomas, and the sensitivity and specificity of these values. The sim of the study is to differentiate grades of gliomas by using perfusion MRI and to correlate findings of brain tumors on perfusion MRI with histopathological grading

MATERIALS AND METHODS

In the prospective observational study, 50 consecutive patients with brain tumors who had undergone both conventional and perfusion MR imaging were investigated during a period of one and half year period. All patients who underwent rCBV mapping gave informed written consent under guidelines approved by the Ethical Committee at Shri Ram Murti Smarak Institute of Medical Science, Bareilly. Before imaging, we inserted an 18- or 20-gauge IV catheter in the ante cubital vein for contrast agent administration. The presence of brain tumors was confirmed by surgical resection followed by biopsy in all patients.

MR Imaging Studies

Cerebral perfusion studies were performed on a Siemens MRI Magnetom Skyra – 3.0 Tesla 48 channel (Berlin, Germany) using intravenous 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 nonenhanced axial T1-weighted (2000/9 [repetition time msec/echo time msec]) and T2-weighted (5520/81) images of the brain. The size, location, and 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 sequence was 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 x 1.7 x 4.0 mm. Five to seven sections were obtained to cover the entire tumor volume identified on the T2-weighted images. A section gap of 0 to 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. Ten acquisitions were performed before contrast injection to establish a precontrast baseline. At the 10^{th} 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 bolus injection of normal 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.[8,9] The rCBV of each pixel was then calculated by numerical integration of area under the concentration-time curve (i.e. rCBV = $\int C_{(t)}$ dt). Thus, increased signal intensity on the rCBV map indicated increased rCBV, and *vice-versa*.

Qualitative and Quantitative Analysis

Normal white matter within the contralateral hemisphere was used as the internal standard reference for quantitative analysis.[10] To determine maximum rCBV ratios, a region of interest (ROI), including at least 20 pixels, was meticulously established in the tumor region, which according to rCBV map, showed maximum intensity and 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 intra-tumoral area with a high signal intensity, we assigned the tumor to the high rCBV group.

Statistical Analysis

All the analyses were performed using SPSS version 20. Mean and standard deviation were calculated for quantitative data and frequency & percentages were calculated for qualitative data. We used the independent T-test, ANOVA, and POST HOC tests to compare the mean. The level of significance was considered as *p-value* < 0.05 or 5%.

RESULTS

The mean age of the study group was 44.5 ± 17.75 years, with incidence increasing with the age as maximum

Table 1: Comparison of findings between MRI and histopathology

Diagnosis	*MRI*	*Histopathology*
Lymphoma	2	2
Meningioma	5	4
Metastasis	6	7
Schwannoma	4	4
Glioma	33	33
Total	50	50

Table 2: Comparison between score of rCBV and glioma grade groups on MRI

	Glioma grade	*N*	*Mean ± Std. deviation*	*p-value*
Mean rCBV	Low	5	1.56 ± 0.64	0.001
	High	28	5.74 ± 1.68	

patients are in old age group, i.e., more than 50 years and male predominance is present with male:female ratio of 2.5:1.

Headaches and weakness are common complaints among patients. Maximum of the patients, around 78% were present with single lesions and heterogenous signal intensity and post-contrast enhancement.

Out of 50 patients, 49 patients have similar findings on both MRI and histopathology; however, 1 case that was given as intraosseous meningioma on MRI came out to be metastatic on histopathology. So, the true positive rate is 98% (Figures 1-6).

Glioma came out to be the most common tumor followed by meningioma and metastasis. Among gliomas, grade 4 tumors are most common with 51.5% followed by grade 3 with 24.2% (Table 1).

The mean rCBV in low grade was found to be 1.56 ± 0.64 and in high grade was found to be 5.74 ± 1.68 and the *p-value* was found to be 0.001 (using independent t-test) (Table 2).

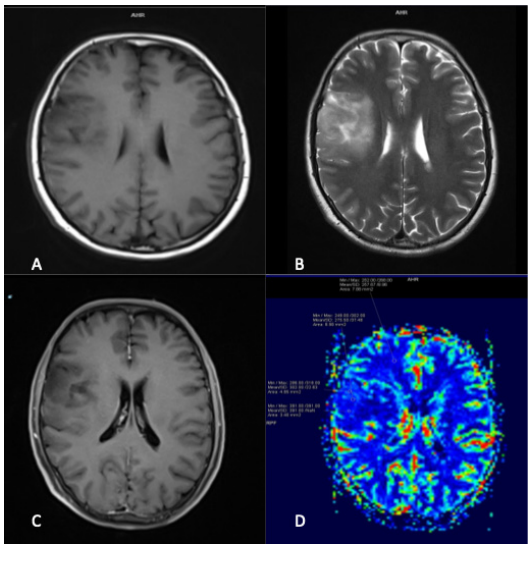

Figure 1: Astrocytoma grade 1 in a 45 year old male. (A,B) T1 and T2-weighted image show area of altered signal intensity in the right fronto-parietal region. (C) contrast-enhanced T1-weighted image shows no enhancement in the above lesion. (D) rCBV map shows the placement of ROIs for measurement of rCBV in the above lesion and shows minimally raised rCBV (mean rCBV 0.75) value as compared to normal white matter. On histopathology, the above lesion proves to be astrocytoma grade 1

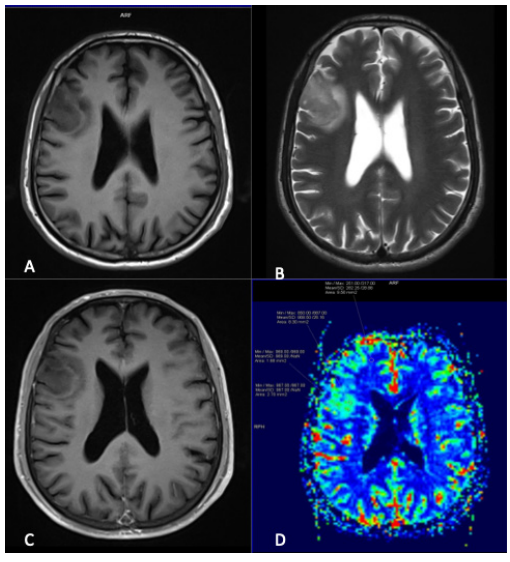

Figure 2: Astrocytoma grade 2 in a 35 year old male. (A,B) T1 and T2- weighted image shows heterogeneous area of altered signal intensity in the right frontoparietal region with mild perilesional edema (C) Contrast-enhanced T1- weighted image shows subtle enhancement in the above lesion. (D) rCBV map shows the placement of ROIs for measurement of rCBV in the above lesion and shows mild raised rCBV (mean rCBV 2.3) value as compared to normal white matter. On histopathology, the above lesion proves to be astrocytoma grade 2

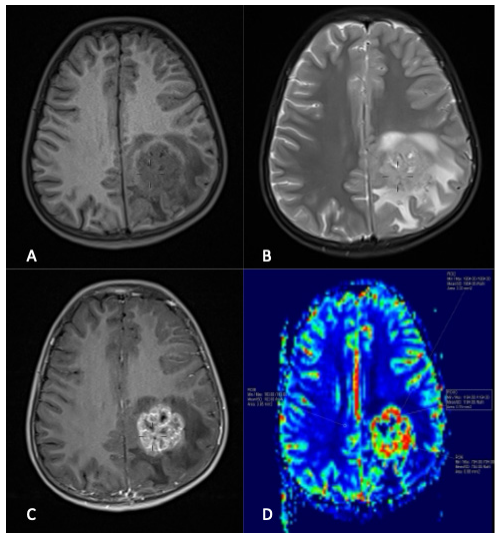

Figure 3: Ependymoma grade 3 in 17-year-old male. (A,B) T1 and T2- weighted images shows a multilobulated heterogeneous lesion appearing hypointense on T1 and isointense in T2 (compared to cerebral cortex) with marked perilesional edema and areas of necrosis within. (C) Contrast-enhanced T1- T1-weighted image showing heterogeneous post-contrast enhancement with central non-enhancing areas. (D) rCBF maps show perfusion MR findings of the tumoral lesions and shows moderately raised rCBV values (mean rCBV 4.6) within the lesion. On histopathology, the lesion was found to be Ependymoma grade 3

Table 3: Comparison of mean score of rCBV between histopathological and grade groups using ANOVA test

		Mean rCBV						p-value
		N	*mean*	*SD*	*Medium*	*Min*	*Max*	
Histopathological	Lymphoma	2	1.85	0.77	1.85	1.3	2.4	0.002
	Metastasis	7	4.57	0.67	4.5	3.9	5.85	
	Meningioma	4	3.19	1.88	2.4	1.9	5.99	
	Schwannoma	4	2.6	0.43	2.8	2.1	2.9	
	Grade-I	2	1	0.35	1	0.75	1.25	0.001
	Grade-II	6	2.6	1.16	2.2	1.40	4.20	
	Grade-III	8	4.98	0.76	4.8	3.90	6.40	
	Grade-IV	17	6.53	1.47	6.9	1.98	8.37	

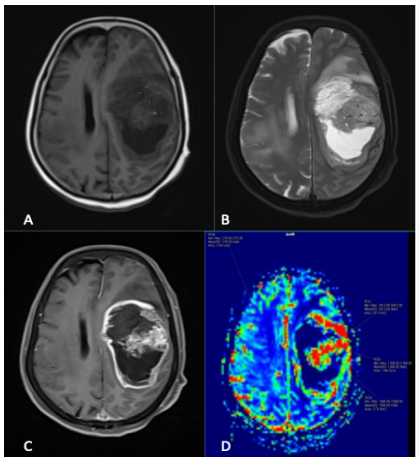

Figure 4: Glioblastoma (grade 4) in a 65 year-old female. (A,B) T1 and T2-weighted image shows a large heterogeneous signal intensity mass in the left frontoparietal cortical, subcortical region with perifocal edema and necrotic area at its posterior aspect.c (C) Contrast-enhanced T1-weighted image shows heterogeneous contrast enhancement in the centre solid part and in the 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 (mean rCBV 6.15) in the solid portion of the tumor and some areas in the periphery consistent with high-grade glioma. Histopathological it came out to be Glioblastoma grade 4

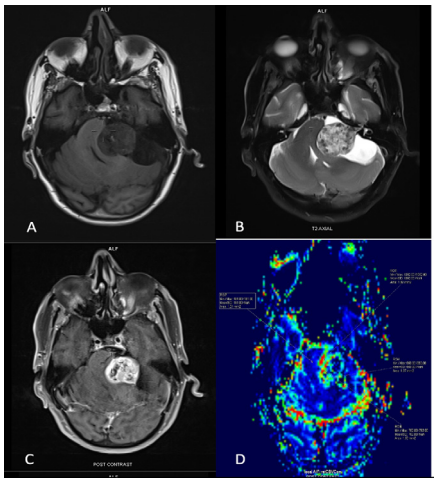

Figure 5: Schwannoma in a 62 year old male. (A,B) T1 and T2-weighted image shows a heterogeneous extra-axial lesion in the left CP angle cistern showing intra canalicular extension with the widening of left auditory canal. (C) Contrast-enhanced T1-weighted image shows intense heterogeneous contrast enhancement. (D) rCBV map shows mild to moderate raised rCBV (mean rCBV 2.9) inthe tumor. Schwannoma was confirmed on histopathology

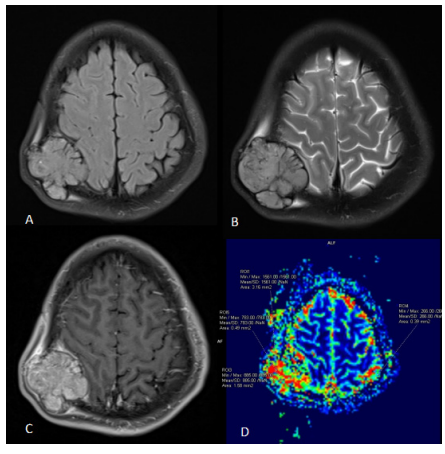

Figure 6: Intraosseous meningioma/metastasis in 44 year old male. (A,B) FLAIR and T2-weighted image shows a lobulated extra-axial lesion in the right posterior high parietal region causing erosion and destruction of underlying bone and extending to the scalp. (C) Contrast-enhanced T1-weighted image shows intense heterogeneous contrast enhancement. (D) rCBV map shows moderate raised rCBV (mean rCBV 4.04) in the portion of the tumor. On MRI it was given as intraosseous meningioma. But on histopathology, it turned out to be metastasis

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.

Lymphomas have less vascularity than other tumors with a mean rCBV of 1.85 ± 0.77.

Metastasis is a relatively high vascular tumor with mean rCBVof 4.57 ± 0.67, which is near to grade 3 gliomas.

High-grade gliomas can be differentiated from low-grade gliomas with a cut-off value of mean rCBV of 2.86 with a sensitivity of 93% (Table 3).

DISCUSSION

Gliomas are the most common central nervous system neoplasm 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.[11,12]

In our study, a maximum number of patients was in the age group of > 60 years (24%), followed by the age group 50 to 60 years (20%), and 9 cases were in the 31 to 40 years (18%). The maximum number of cases (22 cases, 44%) was more than 50 years. The mean age in our study was found to be 44.5 years, correlated with the study done by Hakyemez B,[13] where he found the mean age to be 49.7 ± 17.5 years**,** Bisdas S[14] *et al.* also found the mean age to be 44.2 ± 15.3 years.

Gliomas

In our study, we calculated the rCBV of high and low-grade gliomas and we found that rCBV in low grade was 2.36 ± 0.94 and in high grade was 7.31 ± 2.32 with a *p-value* of 0.001, which are well correlated with the studies done by Aronen *et al.*[15] where they demonstrated statistically significant differences in rCBV measurements between low and high- grade gliomas. They found that the mean rCBV values of grade 1, 2, 3 and 4 gliomas were 0.75 to 1.25 (mean, 1.00 ± 0.35), 1.40 to 4.20 (mean, 2.60 ± 1.17), 3.90 to 6.40 (mean, 4.98 ± 0.76) and 1.98–8.37 (mean 6.54 ± 1.47), respectively; Sugahara *et al.*[16] also found that the rCBV ratios of glioblastomas, anaplastic astrocytomas and low-grade gliomas were 4.00 to 16.20 (mean, 7.32), 0.98 to 7.93 (mean, 4.61) and 0.64 to 2.01 (mean, 1.26), respectively; Knopp *et al.*,[17] found these ratios to be 1.73 to 13.70 (mean, 5.07) in high-grade gliomas and 0.92 to 2.19 (mean, 1.44) in low-grade; Hakyemez B *et al.*[13] 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). 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.*[18]

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 glioma had low rCBV, which reflects a low level of neovascularity or contrast leakage through the altered blood-brain barrier. Sugahara *et al.*[16] reported two cases of anaplastic glioma with no raised vascularity, suggesting that a lack of neovascularity within a tumor does 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 signal-lowering effects of gadolinium, resulting in falsely low rCBV values.

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 who have undergone malignant transformation. This was supported by the previous study conducted by Caseiras G *et al.*[19]

Lymphoma

Lymphomas of the primary central system account for about 6% of all intracranial masses. It is hard to differentiate these lesions from high-grade gliomas and metastases with conventional MRI. Accurate diagnosis is very crucial for management as, unlike other high-grade intracranial neoplasms, lymphoma is treated with combined radiation and chemotherapy therapy without surgery. In our study, there were two lymphoma cases; the mean rCBV was found to be 1.3 ± 0.77 and the max rCBV was 2.4 ± 0.77 with *p-value* of 0.002. These findings are well correlated with the study done by Mansour A *et al.*,[20] where they found that PWI shows a marked reduction in rCBV (relative to the contralateral normal-appearing white matter) and the average rCBV was 0.67 (range of 0.03 -2.0); Goyal P *et al.*[21] also performed perfusion study on brain lymphoma and found mean rCBV to be 1.22 ± 0.32 and maximum rCBV to be 3.09 ± 1.04. Lee H I *et al.*[22] also found out the same findings. The maximum relative CBV ratio ranged from 0.67 to 2.67 (mean: 1.68 ± 0.71). The maximum relative CBV ratios of primary and secondary cerebral lymphomas ranged from 0.67 to 2.67 (mean: 1.65 ± 0.76) and from 1.66 to 2.06 (mean: 1.86 ± 0.28), respectively. Kickingereder P *et al.*[23] also found that the ratios for both $rCBV_{max}$ and $rCBV_{mean}$ were significantly lower in patients with PCNSL than in those with glioblastoma ($rCBV_{max}$ and $rCBV_{mean}$ ratios were 4.16 ± 1.65 and 2.04 ± 0.72 for PCNSL. A study done by Cho S *et al.*[18] also showed similar results and found the mean rCBV of 1.80 ± 0.23 in lymphoma.

Metastasis

Intracranial metastases are the most frequently encountered tumors with high-grade gliomas, and the most frequently metastasized tumor to the brain is lung cancer. It is important to discriminate these tumors from other types, especially high-grade gliomas, in order to establish the treatment protocol and evaluate the prognosis. In our study we found the rCBV in metastasis

(5.32–8.11) higher than lymphoma, schwannoma and low-grade gliomas but lower than meningioma and high grade gliomas. Our findings correlate well with the study done by Server A *et al.*,[24] where metastasis showed raised rCBV of approx. 4.3 ± 1.6 and concluded that rCBV was useful in differentiating between GBMs and metastases and supports the hypothesis that perfusion MR imaging can detect infiltration of tumor cells in the peri-enhancing region; Li X *et al.*[25] also concluded same findings and their study showed raised mean tumoral rCBV of approx. 3.88 ± 1.66 and concluded that inflow-based vascular space occupancy has the potential to discriminate glioblastoma from solitary brain metastasis, especially in the intratumoral region. Law M *et al.*[26] also found raised rCBV of approx. 3.0 ± 1.7 concluded that perfusion-weighted MR imaging distinguishes between metastasis and primary gliomas.

Meningioma

Meningiomas are extraaxial localized, generally benign lesions. It is useful to distinguish between benign, malignant, and atypical meningiomas before resection since it would help in both surgical and treatment planning. In our study we concluded that rCBV ratio of meningioma was higher than gliomas and metastasis in the range of 1.9 to 5.99. These findings are well correlated with the study done by Cha *et al.* where they demonstrate increased rCBV (p > 05) in typical meningiomas; Kremer *et al.*[27] obtained similar rCBV ratios in typical meningiomas with very high rCBV of (9.1 ± 4.4) ($p < 0.001$). Hakyemez B *et al.*[13] also, similar rCBV ratios of 8.02 ± 3.89) were higher than those of high-grade gliomas and metastases. Yang *et al.*[28] also reported the same findings: the mean rCBV ratio was 8.02 ± 4.74 for typical meningiomas.

Schwannoma

Schwannomas account for about 6% of all intracranial neoplasms. Suppose once they reach a large size, the intracanalicular part is not obvious. In that case, it may be difficult to discriminate them from meningiomas and metastases localized at the cerebellopontin angle system. In our study we found the rCBV value of schwannoma to be higher than lymphoma, grade 1 and 2 glioma in the range of (2.1–2.9). In their study, Hakyemez B[13] *et al.* also found similar rCBV values of (3.23 ± 0.81). Ota Y *et al.*[29] found similar rCBV values for schwannoma 3.74 (2.86 ± 4.84).

CONCLUSION

In conclusion, dynamic contrast-enhanced T2*-weighted perfusion MR imaging performed in these 50 cases provided valuable information about the vascularity of brain tumors and led to the correct diagnosis and assessment of histologic tumor grade. The modality is thus a useful and dependable means of noninvasively preoperative diagnosis and assessing the histologic grade of brain tumors especially gliomas and determining the appropriate treatment according to the vascularity of the tumor and respective grade of glioma.

REFERENCES

1. Lee, S. J., Kim, J. H.Perfusion MR imaging in gliomas: comparison with histologic tumor grade. Korean journal of radiology, 2(1), 1–7.
2. Law M, Yang S, Babb JS, Knopp EA. Comparison of cerebral blood volume and vascular permeability from dynamic susceptibility contrast-enhanced perfusion MR imaging with glioma grade. AJNR Am J Neuroradiol. 2004 May;25(5):746-55
3. Hakyemez B, Erdogan C, Ercan I. High-grade and low-grade gliomas: differentiation by using perfusion MR imaging. Clin Radiol. 2005 Apr;60(4):493-502.
4. Arvinda HR, Kesavadas C, Sarma PS. Glioma grading: sensitivity, specificity, positive and negative predictive values of diffusion and perfusion imaging. J Neurooncol. 2009 Aug;94(1):87-96.
5. Danchaivijitr N, Waldman AD, Tozer DJ. Low-grade gliomas: do changes in rCBV measurements at longitudinal perfusion-weighted MR imaging predict malignant transformation? Radiology. 2008 Apr;247(1):170-8.
6. Knopp EA, Cha S, Johnson G, Mazumdar A. Glial neoplasms: dynamic contrast-enhanced T2*-weighted MR imaging. Radiology. 1999 Jun;211(3):791-8.
7. Boxerman JL, Schmainda KM, Weisskoff RM. Relative cerebral blood volume maps corrected for contrast agent extravasation significantly correlate with glioma tumor grade, whereas uncorrected maps do not. AJNR Am J Neuroradiol. 2006 Apr;27(4):859-67
8. Kleihues P, Cavenee WK. World Health Organization Classification of Tumours of the Nervous System. Lyon: WHO/IARC; 2000.
9. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. World Health Organization Histological Classification of Tumours of the Central Nervous System. 4th ed. Lyon: International Agency for Research on Cancer; 2007.
10. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK.World Health Organization Classification of Tumours of the Central Nervous System. 4th ed., updated ed. Lyon: International Agency for Research on Cancer; 2016.
11. Kleihues P, Burger PC, Scheithauer BW. Histological Typing of Tumours of the Central Nervous System. Berlin: Springer-Verlag; 1993.
12. Brem S, Cotran R. Tumor Angiogenesis: A Quantitative Method for Histologic Grading, JNCI: Journal of the National Cancer Institute, Volume 48, Issue 2, February 1972, Pages 347–356
13. Hakyemez B, Erdogan C, Bolca N, Yildirim N, Gokalp G, Parlak M. Evaluation of different cerebral mass lesions by perfusion-weighted MR imaging. J MagnReson Imaging. 2006 Oct;24(4):817-24.
14. Bisdas S, Kirkpatrick M, Giglio P, Welsh C, Spampinato MV, Rumboldt Z. Cerebral blood volume measurements by perfusion-weighted MR imaging in gliomas: ready for prime time in predicting short-term outcome and recurrent disease?

AJNR Am J Neuroradiol. 2009 Apr;30(4):681-8.
15. Aronen HJ, Gazit IE, Louis DN, Buchbinder BR, Pardo FS, Weisskoff RM, Harsh GR, Cosgrove GR, Halpern EF, Hochberg FH.. Cerebral blood volume maps of gliomas: comparison with tumor grade and histologic findings. Radiology. 1994 Apr;191(1):41-51.
16. Sugahara T, Korogi Y, Kochi M, Ikushima I, Hirai T, Okuda T, Shigematsu Y, Liang L, Ge Y, Ushio Y, Takahashi M. Correlation of MR imaging-determined cerebral blood volume maps with histologic and angiographic determination of vascularity of gliomas. AJR Am J Roentgenol. 1998 Dec;171(6):1479-86.
17. Knopp EA, Cha S, Johnson G, Mazumdar A, Golfinos JG, Zagzag D, Miller DC, Kelly PJ, Kricheff II. Glial neoplasms: dynamic contrast-enhanced T2*-weighted MR imaging. Radiology. 1999 Jun;211(3):791-8.
18. Cho SK, Na DG, Ryoo JW, Roh HG, Moon CH, Byun HS, Kim JH. Perfusion MR imaging: clinical utility for the differential diagnosis of various brain tumors. Korean J Radiol. 2002 Jul-Sep;3(3):171-9.
19. Caseiras GB, Chheang S, Babb J, Rees JH, Pecerrelli N, Tozer DJ, Benton C, Zagzag D, Johnson G, Waldman AD, Jäger HR, Law M. Relative cerebral blood volume measurements of low-grade gliomas predict patient outcome in a multi-institution setting. Eur J Radiol. 2010 Feb;73(2):215-20.
20. Mansour A, Qandeel M, Abdel-Razeq H, Abu Ali HA. MR imaging features of intracranial primary CNS lymphoma in immune competent patients. Cancer Imaging. 2014 May 7;14(1):22.
21. Goyal P, Kumar Y, Gupta N, Malhotra A, Gupta S, Gupta S, Mangla M, Mangla R. Usefulness of enhancement-perfusion mismatch in differentiation of CNS lymphomas from other enhancing malignant tumors of the brain. Quant Imaging Med Surg. 2017 Oct;7(5):511-519.
22. Lee IH, Kim ST, Kim HJ, Kim KH, Jeon P, Byun HS. Analysis of perfusion weighted image of CNS lymphoma. Eur J Radiol. 2010 Oct;76(1):48-51. doi: 10.1016/j.ejrad.2009.05.013. Epub 2009 Jun 4
23. Kickingereder P, Sahm F, Wiestler B, Roethke M, Heiland S, Schlemmer HP, Wick W, von Deimling A, Bendszus M, Radbruch A. Evaluation of microvascular permeability with dynamic contrast-enhanced MRI for the differentiation of primary CNS lymphoma and glioblastoma: radiologic-pathologic correlation. AJNR Am J Neuroradiol. 2014 Aug;35(8):1503-8.
24. Server, A., Orheim, T.E.D., Graff, B.A. Diagnostic examination performance by using microvascular leakage, cerebral blood volume, and blood flow derived from 3-T dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging in the differentiation of glioblastoma multiforme and brain metastasis. Neuroradiology 53, 319–330 (2011).
25. Li X, Wang D, Liao S, Guo L, Xiao X, Liu X, Xu Y, Hua J, Pillai JJ, Wu Y. Discrimination between Glioblastoma and Solitary Brain Metastasis: Comparison of Inflow-Based Vascular-Space-Occupancy and Dynamic Susceptibility Contrast MR Imaging. AJNR Am J Neuroradiol. 2020 Apr;41(4):583-590.
26. Law M, Yang S, Wang H, Babb JS, Johnson G, Cha S, Knopp EA, Zagzag D. bis: sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopic imaging compared with conventional MR imaging. AJNR Am J Neuroradiol. 2003 Nov-Dec;24(10):1989-98.
27. Kremer S, Grand S, Rémy C, Pasquier B, Benabid AL, Bracard S, Le Bas JF. Contribution of dynamic contrast MR imaging to the differentiation between dural metastasis and meningioma. Neuroradiology. 2004 Aug;46(8):642-8.
28. Yang S, Law M, Zagzag D. Dynamic contrast-enhanced perfusion MR imaging measurements of endothelial permeability: differentiation between atypical and typical meningiomas. AJNR Am J Neuroradiol. 2003;24(8):1554-1559.
29. Ota Y, Liao E, Capizzano AA, Kurokawa R, Bapuraj JR, Syed F, Baba A, Moritani T, Srinivasan A. Diagnostic Role of Diffusion-Weighted and Dynamic Contrast-Enhanced Perfusion MR Imaging in Paragangliomas and Schwannomas in the Head and Neck. AJNR Am J Neuroradiol. 2021 Oct;42(10):1839-1846.