Original Research Article

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Correlation of Perfusion MR image Grading and Histopathological Grading of Primary Intra Axial Gliomas: A Prospective Study

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Abstract

Objective: To determine the diagnostic accuracy of pre operative Perfusion Magnetic Resonance Image Grading and its correlation with post operative Histopathological Grading of Primary Intra Axial Gliomas. *Materials and Methods:* In order to determine relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), 30 patients with glioma underwent dynamic contrast enhanced T2 weighted and conventional T1 and T2 weighted imaging. rCBV and rCBF maps were obtained by fitting a gamma –variate function to the contrast material versus time curve. rCBV, rCBF ratios between tumor and corresponding area of normal side (maximum rCBV/ rCBF of tumor and rCBV/rCBF of contralateral white matter) were calculated and compared between glioblastomas (grade IV), anaplastic gliomas (grade III) and low grade gliomas (grade I & II). The grading obtained by the perfusion MR images was compared with the post operative histopathological grading. *Results:* Mean rCBV & rCBF ratios were 10.53±2.73 & 9.30±1.10 for glioblastomas (grade IV), 7.55±1.35 & 6.96±0.88 for anaplastic gliomas (grade III), 4.72±0.92 & 4.54±0.54 for diffuse astrocytomas and oligodendrogliomas (grade II), 1.84±0.94 & 1.59±0.79 for low grade gliomas (grade I), and were thus significantly different; $p< 0.03$ between glioblastomas and anaplastic gliomas, $p< 0.02$ between anaplastic gliomas and diffsuse astrocytomas, oligodendrogliomas, $p< 0.003$ between grade II and low grade gliomas, $p<0.01$ between glioblastomas and lowgrade gliomas. Stastistically significant correlation was seen by applying Chi- square test ($p <0.0001$). Further the correlation of perfusion MR grading and Histopathological grading was proven by applying Speraman's correlation value ($p <0.0001$). *Conclusion:* Perfusion MR imaging is a useful and reliable technique for estimating the histological grading of primary intra axial gliomas.

Keywords: Perfusion Magnetic Resonance Imaging; Relative Cerebral Blood Volume; Primary Intra Axial Glioma.

Introduction

Glioma is the most commonest type of Central Nervous Tumor according to World Health Organization (WHO). Gliomas are classified into four grades. Grade I & II are low grade, grade III & IV are high grade. For planning the treatment and assessing the prognosis, definite histopathological grading is needed, and for this, important crieteria is vascular proliferation in the tumor. Newer development of Perfusion MR imaging have permitted the creation of relative cerebral blood volume (rCBV) maps and relative cerebral blood flow (rCBF) maps, which leading to the quantitative and qualitative assessment of tumor vascularity [1,2].

Cerebral Blood Flow(CBF) is defined as the volume of blood passing through a given amount of brain tissue per unit of time, most commonly ml/min/100g of brain tissue, CBF is difficult to measure, and relative CBF (rCBF) is being calculated instead of CBF; which relative to normal white matter.

Cerebral Blood Volume is defined as the volume of blood in a given amount of brain tissue (ml/100 g of brain). rCBV and rCBF ratio calculated by obtained value from the side of lesion divided by the value of side of normal corresponding white matter.

Tumor grade and in targeting the site of biopsy is done using these maps. Very few studies have reported good correlation between rCBV and histological grade of gliomas, no study to has

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assessed the sensitivity and specificity of rCBV & rCBF measurement for discriminating between high grade and low grade gliomas. Dynamic susceptibility contrast (DSC) was the first perfusion imaging technique using perfusion to show a significant correlation between the rCBV, rCBF, tumor grade and increased tumor vascularity in patients with gliomas [3,4,5]. The purpose of this study is to assess the correlation of pre operative perfusion MR image grading with post operative histopathological grading in gliomas, relationship between rCBV & rCBF and histological grading of gliomas [6].

Materials and Methods

All patients were from the Institue of neurosurgery, MMC & RGGGH, Chennai. The present study was performed between July 2016 and December 2017 after getting approval from Institutional Ethics Committee, Madras Medical College, Chennai-3. Patients with CT or MRI confirmed tumor were selected for this study. Prior to this MRI perfusion study none of the patients were treated with chemotherapy, surgery or XRT. MRI perfusion study was conducted within 10 days before surgery. A total of 30 cases of brain tumors, suspected to be gliomas were enrolled; 19 were males and 11 were females, and their ages ranged from 18 to 65 years (mean 46 years). The presence of glioma was confirmed by surgical resection (n=29) or by stereotactic biopsy (n=1). All tumors were graded according to the WHO grading system. There were grade I & II is 15 and grade III & IV is 15. MRI diagnosed as gliomas with post op HPE results like metastases, lymphomas and demyelinations were excluded from this study.

MR Imaging Studies

All these 30 patients were imaged (from the base to the top of the head) using 3.0 T MRI scanner (MR750 w3.0T; GE). MRI scans consisted of conventional MRI (T1-weighted imaging, T2-weighted imaging, T2 fluid -attenuated inversion recovery (FLAIR), diffusion – weighted imaging (DWI), DSC-PWI and contrast enhanced T1WI (transverse, coronal and axial plane) [7]. DSC-PWI was performed using a gradient recalled echo-echo planar imaging sequence during IV administration of 0.2 mol/kg of gadopentetic acid dimeglumine salt injection (magnevist) at a rate of 3 ml/second, followed by a bolus of injection of saline about 20ml . The DSC-PWI was performed as those for conventional MRI [8,9].

Generation of rCBV & rCBF Maps and Image Analysis

Image data was delivered to an AW4. 6 work station and analysed using analysis software (functool V.9.4.05). The pure axial T2WI or pure axial enhanced T1WI MRI images and DSC-PWI were fused together. The region of interest (ROI) of the largest solid area of tumor perfusion was selected according to DSC-PWI perfusion colour gradation (avoiding the sac, hemorrhage and artefact) [10,11,12]. The contralateral normal ROI was selected by using the tumor mirror image. DSC-CBV and DSC-CBF data of each ROI were measured 3 times and calculated the average value [13,14].

Table 1: Summarizes the mean value of rCBV and rCBF ratios of all four grades of gliomas

Mean value	Grade 1	Grade 2	Grade 3	Grade 4
rCBV ratio	1.84±0.94	4.72±0.92	7.55±1.35	10.53±2.73
rCBF ratio	1.59±0.79	4.54±0.54	6.96±0.88	9.30±1.10

Examples of Types of Gliomas in our Study

1. A 41 years old female (Case No 25) with a low-grade glioma located at the left side of the frontal lobe. (A) T1WI - the focal lesion showed a low signal. (B) Contrast T1WI - the focal lesion had no obvious contrast enhancement. (C) DSC-CBV imaging. Low perfusion with a rCBV ratio value of 3.27. (D) DSC-CBF imaging. Low perfusion with rCBF ratio value of 2.08 [Figure 1].

2. A 45-year-old female (Case No 5) with glioblastoma (WHO grade IV). (A) Axial T2 WI imaging reveals a left temporal lobe with mass effect, a moderate amount of edema, and

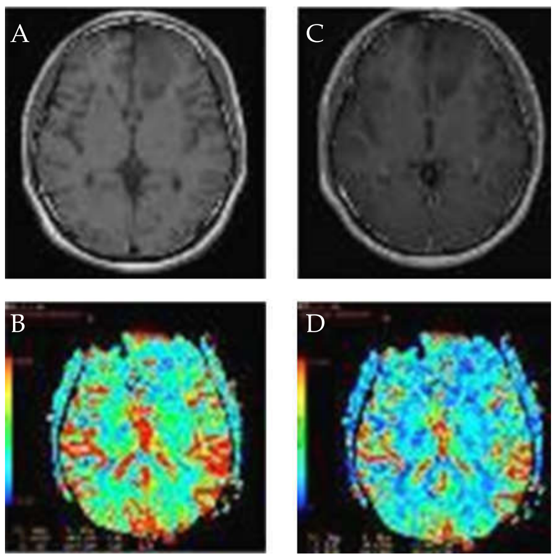


Fig. 1:

homogeneous signal. (B) T1-weighted contrast imaging reveals marked enhancement. (C) CBV map reveals the elevated perfusion [Figure 2].

A 55-year-old male (Case No 19) with an oligodendroglioma (WHO grade II). (A) Axial T2 WIdemonstrates a right frontal and temporal lobe lesion with mass effect, a small amount of edema,

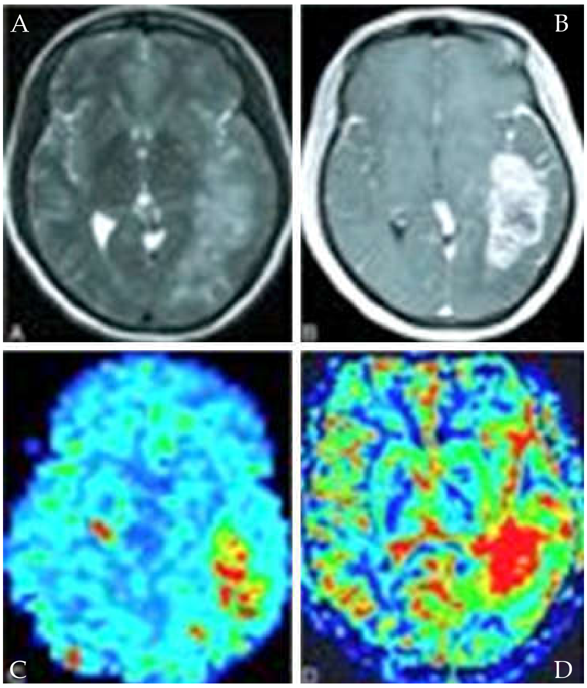


Fig. 2:

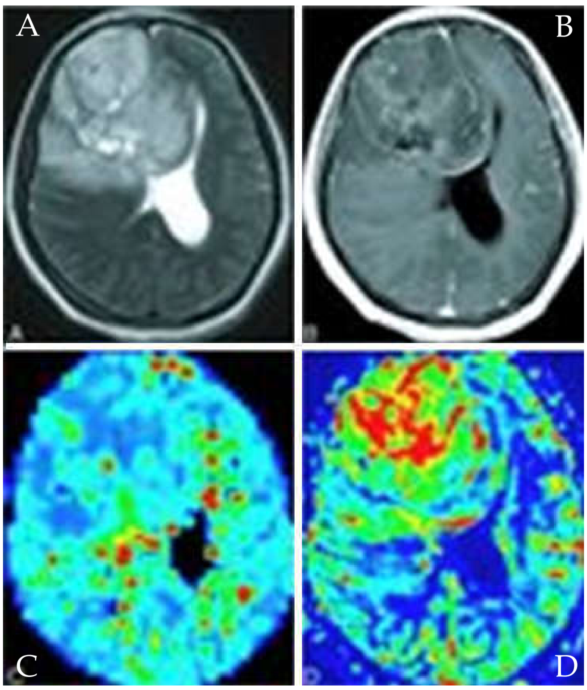


Fig. 3:

and heterointense signal. (B) Contrast-enhanced T1-weighted imaging shows mild enhancement.(C) CBV map shows elevated perfusion in the tumor parenchyma [Figure 3].

A 60 years old male (Case No 13) with anaplastic astrocytoma (WHO grade III) located at the right side of the temporal lobe. (A) T1WI - low signal mixed with high signal small patch sample bleeding. (B) Contrast T1WI - uneven enhancement and the center area with low signal without enhancement. (C) DSC-CBV imaging. The mass showed uneven high perfusion, with a DSC-rCBV ratio value of 8.40. (F) DSC-CBF imaging. The mass showed uneven high perfusion, with a DSC-rCBF value of 8.2 [Figure 4].

Pathological Specimen Analysis

After surgery specimen were collected and embedded in a paraffin block and cut into 3micro

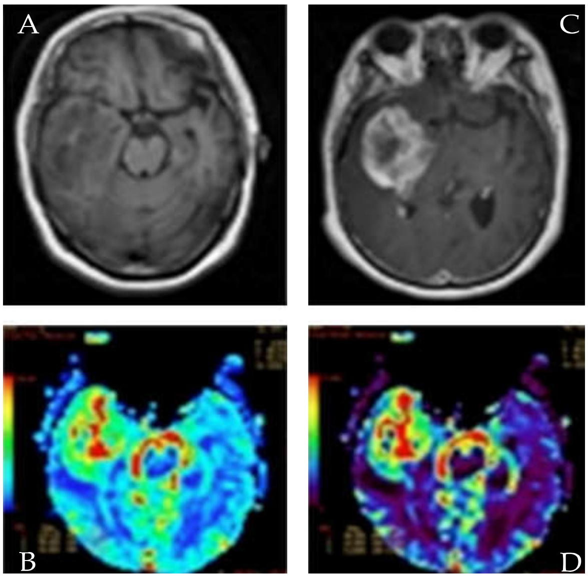


Fig. 4:

meter thick serial slice and examined by using Eosin and Hemotoxylin staining, IDH, Ki67 and Immunohistochemical staing for glial fibrillary acidic protein (GFAP). After analysing by Neuropathologists analyses, based on tumor cells histological types (Nuclear atypia, cellular pleomorphism, mitoses, tissue necrosis) and the results of IHC for Ki67, tumors were classified into Gliomas of low grade (LGG; grade I& grade II) and high grade (HGG; grade III & grade IV) according to the WHO criteria [15,16].

Histology of a low-grade glioma (grade I) - Tumor cells was large volume with abundant cytoplasm [Figure 5].

Histology of Diffuse astrocytoma (grade II). Low grade cellularity, no atypia or mitoses, with a large eosinophilic cytoplasm [Figure 6].

Histology of Oligodendroglioma (grade II). Cells with clear cytoplasm, uniform and round central nuclei with fine chromatin surrounded by a clear halo [Figure 7].

Histology of anaplastic astrocytoma (grade III). Nuclear atypia and pleomorphism with highly variable cytoplasm [Figure 8].

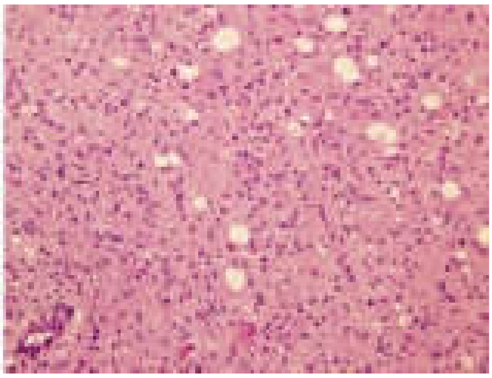


Fig. 5:

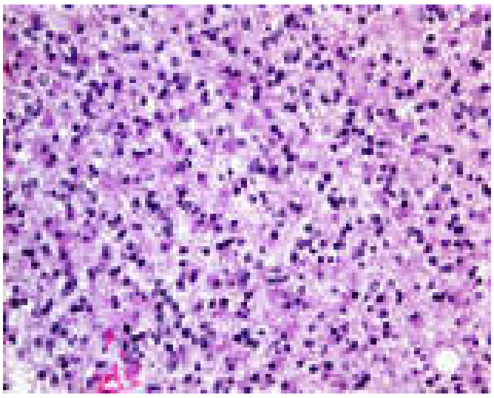


Fig. 6:

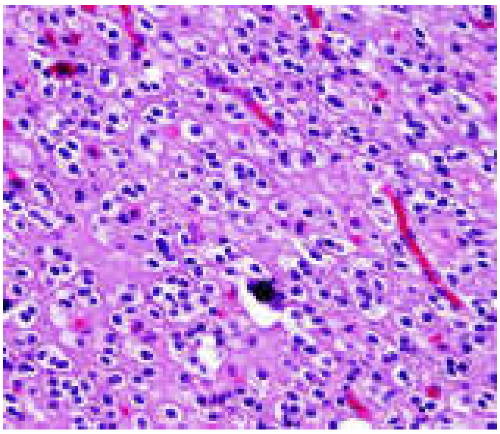
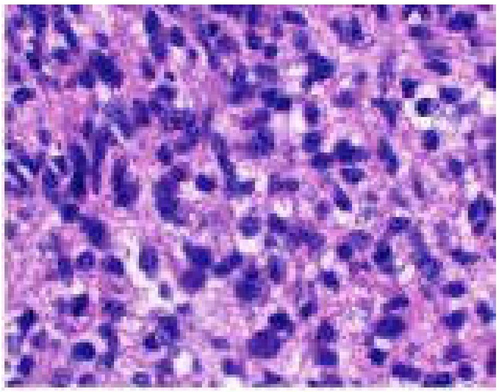


Fig. 7:

Histology of a glioblastoma (grade IV). Capillary hyperplasia and vascular endothelial cell enlargement and an increase number of vascular endothelial cells [Figure 9].



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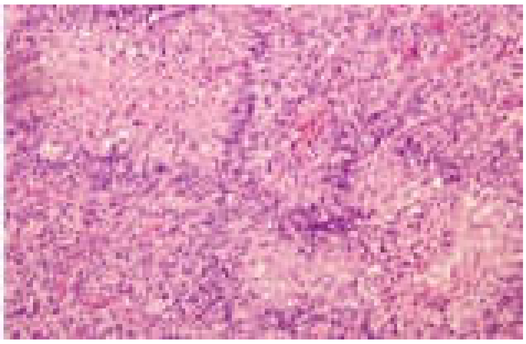

Fig. 9:

Data Analysis

Data analysis was done using SPSS software. The Data result were divided into 4 groups i.e grade I, II, III and IV gliomas. On an rCBV & rCBF map, a region of interest (ROI), was placed in the tumor with solid portion for measurement of rCBV and rCBF. This was measured three times and its maximum value was chosen. The relative Cerebral Blood Volume(rCBV) and relative Cerebral Blood Flow(rCBF) of white matter was obtained by placing the ROI, (atleast 20 pixels) and in contralateral frontal and occipital (parietal) white matter. The average of those rCBV & rCBF values was taken to assess the relationship between rCBV ratio, rCBF ratio and tumor histological grade [Table 2]. We compared rCBV, rCBF ratios between glioblastomas, anaplastic gliomas, diffuse astrocytomas, oligodendrogliomas and low grade gliomas using Kruskal-Wallis and Mann-Whitney U tests. For statistical computation, an SPSS statistical software package was employed, with the level of significance defined as $p < 0.5$.

Mean rCBV & rCBF ratios were 10.53 ± 2.73 & 9.30 ± 1.10 for glioblastomas (grade IV), 7.55 ± 1.35

& 6.96±0.88 for anaplastic gliomas (grade III), 4.72±0.92 & 4.54±0.54 for diffuse astrocytomas and oligodendrogliomas (grade II), 1.84±0.94 & 1.59±0.79 for low grade gliomas (grade I), [Table 1] and were thus significantly different; p< 0.03 between glioblastomas and anaplastic gliomas, p< 0.02 between anaplastic gliomas and diffsuse astrocytomas, oligodendrogliomas, p< 0.003 between grade II and low grade gliomas, p< 0.01 between glioblastomas and lowgrade gliomas, using the Mann-whitney U test.

The overall group difference in rCBV and rCBF ratios between these four groups was statistically significant (p <01, using Kruskals-Wallis test). Stastistical significant correlation was seen by applying Chi- square test (p <0.0001). Further the correlation of perfusion MR grading and Histopathological grading was proven by applying Speraman's correlation value (p <0.0001) [Table 3].

Table 2: Summarizes the rCBV, rCBF ratios, pathological grade and radiological grades of gliomas.

S. No	Age	Sex	Location	HPE Grading	MRI grading	RCBV Ratio	RCBF Ratio
1	40	M	Corpus callosum	Glioblastoma IV	IV	10.4	9.01
2	58	F	Left parietal	Anaplastic astrocytoma III	IV	7.80	8.20
3	40	M	Left frontal	Glioblastoma IV	IV	9.40	8.50
4	45	M	Right frontal	Glioblastoma IV	IV	12.8	10.1
5	45	F	Left temporal	Glioblastoma IV	IV	11.6	9.80
6	48	M	Right frontal	Glioblastoma IV	IV	11.2	10.2
7	30	F	Right temporal	Oligodendroglioma II	III	7.40	6.20
8	18	M	Left parietal	Anaplastic oligodendroglioma III	III	6.20	6.40
9	63	M	Left parietal	Anaplastic astrocytoma III	III	7.12	6.42
10	65	M	Left frontal	Anaplastic astrocytoma III	III	7.40	6.08
11	60	M	Right temporal	Glioblastoma IV	III	8.40	8.02
12	35	F	Left frontal	Anaplastic astrocytoma III	III	7.90	8.10
13	60	M	Right temporal	Anaplastic astrocytoma III	III	8.40	8.20
14	42	F	Left frontal	Anaplastic oligodendroglioma III	III	7.40	7.01
15	45	M	Right frontal	Anaplastic astrocytoma III	III	7.80	6.30
16	42	M	Left temporal	Diffuse astrocytoma II	II	5.82	5.71
17	25	F	Right temporal	Diffuse astrocytoma II	II	3.80	4.30
18	43	M	Corpus callosum	Oligodendroglioma II	II	3.80	4.10
19	55	M	Right frontal	Oligodendroglioma II	II	5.30	4.02
20	38	M	Right frontal	Diffuse astrocytoma II	II	3.70	4.10
21	62	M	Left thalamus	Diffuse astrocytoma II	II	5.40	5.71
22	55	M	Left parietal	Diffuse astrocytoma II	II	5.10	4.20
23	42	M	Left parietal	Diffuse astrocytoma II	II	3.80	4.20
24	60	F	Left frontal	Diffuse astrocytoma II	II	5.80	4.60
25	41	F	Left frontal	Low grade glioma I	I	3.27	2.08
26	51	F	Left temporal	Low grade glioma I	I	0.90	0.80
27	53	F	Corpus callosum	Low grade glioma I	I	3.01	2.20
28	42	M	Left frontal	Low grade glioma I	I	1.20	1.10
29	32	M	Left temporal	Low grade glioma I	I	0.90	1.30
30	37	F	Left temporal	Low grade glioma I	I	1.80	2.10

Table 3: Summarizes statistical correlation of perfusion MR grading and Histopathological grading by Chi-square test and Speraman's test

HPE grading	MRI grading				Total	Chi-square value	Speraman's correlation value
	I	II	III	IV			
Grade I	6 100.0%	0 0%	0 0%	0 0%	6 20.0%	69.764 P <0.0001	0.957 P<0.0001
Grade II	0 0%	9 100.0%	1 11.1%	0 0%	10 33.3%		
Grade III	0 0%	0 0%	7 77.8%	1 16.7%	8 26.7%		
Grade IV	0 0%	0 0%	1 11.1%	5 83.3%	6 20.0%		
Total	6 (100%)	9(100%)	9(100%)	6(100%)	30(100%)		

Discussion

The most common neoplasm of the brain are Gliomas from low grade astrocytoma to high grade glioblastoma based on histologic spectrum. The prognosis of patients with gliomas, particularly those with high grade glioblastoma remains poor inspite of all kinds of available treatment. So in optimal treatment strategy, the tumor grade determination should be accurate. Vascular proliferation of glioma is an important diagnostic crieterion for malignancy. Gliomas shows immature blood vessels, incomplete basement membrane and lack of smooth muscle layers which leads to higher permeability . The main indicator for Glioma malignancy is level of angiogenesis, so higher degree of vascular proliferation is found in high grade glioma.

MR perfusion imaging can quantitatively reflect density of tumor vessel, nature of the vessel and distribution. MR perfusion assess the angiogenesis in tumor and also assess the tumor invasion into the surrounding tissues. Increased perfusion parameter values in perfusion MRI denotes high angiogenesis with increased blood flow to the tumor. To extract this hemodynamic information, a diffusible tracer is injected and this tracer travel with in the vessels. Exogenous contrast agent requires injection of paramagnetic contrast agents such as gadolinium-diethylene-triamine penta acetic acid is used in perfusion imaging. DSC-PWI starts by rapid iv bolus injection of paramagnetic contrast agents. DSC-PWI has 2 methods including SE-EPI and GRE-EPI [17,18]. Magnetic susceptibility difference between surrounding tissue while these contrast agents travelling through nearby blood vessels can cause an uneven local magnetic field and accelerate protons to phase, this is the main principle of DSC-PWI [17,18]. Therefore T2 or T2* shortens, which resulting in the signal of corresponding T2WI or T2*WI decreasing transiently.

DSC-CBV is the most commonly used for brain tumors than DSC-CBF. In this study DSC-CBV and DSC-CBF parameters and their relative value are determined [17,18]. Both rCBV, rCBF increases with glioma grade demonstrated in this study. The relative classification value were significantly correlated ($p<0.01$) with pathological grade, this illustrates that rCBV and rCBF can be good indication of the hemodynamic response in glioma and can be used to assess the pathological grading of glioma prior to surgery.

The present study had a number of limitations, firstly, the small sample size and measurement somewhat biased. The potential for bias existed as if the head was titled in the scan and it may result in the marks on either side of the head not being at the same anatomic level and resulting in difference between the two sides would be inaccurate. Secondly the reliability of the data that obtained by the dynamic contrast T2 WI, because it was evaluated by a single section not by the complete tumor . In the future the sample size will be increased and classification of the grading of glioma further refined in order to meet WHO grading standards.

In conclusion, the present study demonstrated that pre op perfusion MR image grading well correlated with post op histopathological grading of primary intra axial Glioma. Perfusion MR imaging may be used to research the flow of blood to the brain glioma, help with pre operative classification of Glioma and help to formulate the correct surgical procedure and further management to monitor response and to detect recurrence.

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