Glioma Grading by Using Cerebral Blood Volume Measurements at Dynamic Susceptibility-Weighted Contrast Enhanced Perfusion MR Imaging

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Abstract

Introduction: MRI plays a critical role in the preoperative assessment of brain gliomas. Mass effect, cyst formation and necrosis on MRI studies do correlate significantly with malignant behaviour. Recent developments in MR imaging have allowed the assessment of CBV and perfusion abnormalities in brain tumours and this leads to the usefulness of MR perfusion imaging for preoperative grading of gliomas and have indicated that the technique significantly augments the sensitivity and specificity of conventional MR imaging in predicting histologic grade.

Aim of the Work: To determine the role of Cerebral Blood Volume Measurements at Dynamic Susceptibility-Weighted Contrast Enhanced Perfusion MR Imaging in diagnosis and grading of Gliomas.

Patients and Methods: Twenty one patients diagnosed as gliomas during the period from October 2009 and September 2010 were involved in this study; 13 were males and 8 were females with their age ranged from 32 to 73 years old with a mean age 54.84. Patients were referred from neurosurgery department, Assiut University; All patients were subjected to full history taking: Including onset of neurological manifestations and their progress, Clinical assessment: (By referring neurosurgeons); for neurological deficit and MRI brain including the following following protocol; Axial Diffusion weighted imaging, Axial T1W, Axial T2WI, Axial FLAIR, post contrast T 1 WI, and perfusion-weighted image. All patients underwent Perfusion MRI before surgery; the surgical procedures consisted respectively of seven burr hole biopsy, 10 subtotal and 4 total removals. Pathological diagnosis and grading of the glial tumors after resection were obtained then compared with PWI data.

Results: In this study; The rCBV correlates with the histological grade and is higher in high grade gliomas than in low-grade gliomas first two grades of gliomas (G1 and G2) were considered low-grade gliomas and (G3 and G4) were considered as high-grade gliomas.

Conclusion: Perfusion MR provides additional information to MRI in diagnosis of Gliomas. It detects the most malignant areas even when not enhancing. When added routinely to diagnostic MRI, rCBV maps offer meaningful functional parameter for assessing grade of cerebral gliomas.

Key Words: MRI – Brain glioma – Cerebral Blood Volume (CBV).

Introduction

MALIGNANT astrocytomas is characterized by their ability to recruit and synthesize vascular networks for further growth and proliferation. The degree of vascular proliferation is an important parameter in determining the biologic aggressiveness and histopathologic grading of astrocytomas [6,7].

Conventional magnetic resonance (MR) imaging with gadolinium-based contrast agents has been useful in the characterization of brain tumours prior to treatment. Although conventional contrast material-enhanced MR imaging may indicate the degree of tumor malignancy, studies have shown that the degree of contrast enhancement is not a reliable indicator of the tumor grade [8,9].

Consequently, authors have suggested that contrast enhanced dynamic perfusion imaging can improve the accuracy of MR-based glioma grading [10]. Perfusion MR imaging involves the use of first-pass bolus tracking analysis to derive relative Cerebral Blood Volume (CBV) maps, and studies have shown that the maximal relative CBV of gliomas correlates with the gloma grade [11].

Differentiation of high-grade gliomas (HGGs) and low-grade gliomas (LGGs) with MR-derived relative CBV maps is based on measurement of the ratio between the most elevated relative CBV area within the glioma [7,12].
Aim of the work: To determine the role of Cerebral Blood Volume Measurements at Dynamic Susceptibility-Weighted Contrast Enhanced Perfusion MR Imaging in diagnosis and grading of Gliomas.

Material and Methods

Twenty-one patients diagnosed as gliomas during the period from October 2009 and September 2010 were involved in this study; 13 were males and 8 were females with their age ranged from 32 to 73 years old with a mean age 54.84.

Methods:

All patients were subjected to:

- **Full history taking:** Including onset of neurological manifestations and their progress.
- **Clinical assessment:** (By referring neurosurgeons); for neurological deficit.

Radiological study:

Patients were referred from neurosurgery department, Assiut University Hospitals, Assiut University. Patients were subjected to brain MRI using MRI machine 1.5T at MRI unit; Assiut university Hospitals with the following protocol:

1. **Axial Diffusion weighted imaging (DWI)**: (TE): 112 msec, (TR): 6300msec, Matrix size 256X192, Section thickness: 5mm, FOV (field of view): 24X24, Interslice gap: 1mm, Scan time: 1.24min.
2. **Axial T1 W:** (TE): 9msec, (TR): 520msec, Matrix size 256x160, Section thickness: 5mm, FOV (field of view): 24X18, Interslice gap: 2mm, Scan time: 2.47min.
3. **Axial T2WI:** (TE): 120msec, (TR): 5565msec, Matrix size 256X192, Section thickness: 5mm, FOV (field of view): 24X18, Interslice gap: 2mm, Scan time: 38sec.
4. **Axial Fluid attenuation recovery (FLAIR WI):** (TE): 140msec, (TR): 8000 msec, Inversion time: 2000msec, Matrix size 256 x128, Section thickness: 5mm, FOV (field of view): 24x24, Interslice gap: 2mm, Scan time: 1.12 min.
5. **T1 postcontrast,** and
6. **perfusion-weighted image.**

Perfusion-weighted image (PWI):

Perfusion-weighted images were obtained following administration of a bolus of gadolinium diethylenetriamine penta-acetic acid (DTPA) in a dose of 0.1ml/kg body weight = (10ml); the injection was performed by manual injection in a speed of 3-5ml/s followed by 20ml of normal saline delivered via a large-bore cannula (18 or 20 gauge) in the antecubital vein. During manual injection the person doing the injection went into the scanning room with the patient before the scan, attached the injection system using a stopcock valve or bifurcated “Y” check valve system attached to two syringes one filled with saline, and one filled with contrast agent, and then watched the countdown clock for the proper time to inject (10 second after the beginning of the sequence).

By using as much force as possible, the contrast agent was injected at 3 to 5ml/second. An echo-planar imaging gradient-echo sequence at (TE = 80msec), (TR = 2000msec) and flip angle of 30 degrees was used. 25 sections were obtained, forming 1000 images; centered on the diffusion-weighted/T2WI imaging lesion. Section thickness was 6mm with no gap between slices (matrix, 256X128; field of view, 40X20cm). Images were obtained at 40 time points per section with average scanning time ranged from 40 seconds to 1 minute and 21 seconds.

Post processing of perfusion data:

PWI images were transferred to workstation by direct connection, Easy Vision release 4.2 in Assiut University Hospital.

Before start: Before attempting to make maps or do meaningful analysis on a perfusion MRI data set, we examined the raw data to ensure its freedom from major artifacts such as gross patient motion, scanner failure, lack of delivery of contrast agent, or any number of other technical flaws that can preclude useful analysis.

We quickly determine whether or not a given examination was of adequate quality by examining the signal versus time curve with a suitable ROI drawn. Exclusion of bad quality imaging is decided if there was extensive patient motion, or if the bolus never arrived, or if the scanner had technical problems. Then color maps (rCBV, TTP, MTT, T0) were generated automatically then the concentration time curve was obtained which represent the changes occurred.

First, ROI was put in the contralateral normal hemisphere as control normal region, then multiple ROIs was put in the different region of the lesion and surrounding it to see the extension of the lesion.

Dealing with PWI data:

- **RCBV map of all brain sections was liberated automatically.**
- **Relative rCBV ratio of the tumor was calculated by dividing the abnormal rCBV of the tumor by the rCBV of the normal contralateral hemisphere (white or gray) provided that the region of interest (ROIs) consists of more than 20 pixels.**
- **Multiple ROIs were located within both enhanced and unenhanced areas of the tumor in multiple**
slice sections and areas of highest rCBV ratio were identified and considered as the highest grade that the tumor reached.

After histopathological grading of the tumors, comparison was held between the maximum relative rCBV ratio of each tumor with its pathological grade.

Multiple ROIs were located in the peritumoral region to determine the extension of infiltration.

All the 21 patients underwent Perfusion MRI before surgery; the surgical procedures consisted respectively of seven burr hole biopsy, 10 subtotal and 4 total removals. Pathological diagnosis and grading of the glial tumors after resection were obtained then compared with PWI data.

Specimens were sent to the Department of Pathology, Assiut University Hospitals, immediately after surgical removal, fixed in formaline and processed for production of conventional haematoxyline and eosine-stained sections. Representative section(s) were examined microscopically and were diagnosed and graded according to the latest WHO classification of CNS tumours [13,14]. Tumours included 21 astrocytomas (5 WHO grade I, 4 WHO grade II, 9 WHO grade III, and 3 WHO grade IV). The same pathologist reviewed all the samples.

Results

This study included twenty one patients diagnosed radiologically as glial tumors using brain MRI with different pulse sequences including DWI (b0 and b1000), T1WI, T2WI, FLAIR and post-contrast T 1 WI.

Perfusion weighted image were done in all patients with post-processing of the PWI data to obtain rCBV map and liberate the intensity time curve, multiple ROIs put in different areas of the tumour at multiple sections to detect the area of maximum rCBV (area of maximum rCBV ratio in comparison with the contra lateral normal rCBV).

The glial tumours displayed postcontrast enhancement in postcontrast T1WI in the same area showed maximum relative rCBV ratio in only 9 patients out of the 21 patients (3 patients of low grade glioma, and 6 high grade glioma).

In this study: The rCBV correlates with the histological grade and was higher in high grade gliomas than in low-grade gliomas with the ranges of maximum rCBV ratios by PWI compared with histological grading were shown in Table (1). First two grades of gliomas (G1 “Fig. 1” and G2) were considered low-grade gliomas and (G3 “Fig. 2” and G4) were considered as high-grade gliomas; [this grading after Sugahara, et al.] [5].

For evaluation of infiltration of the tumor to surrounding area (peritumoural infiltration); The appearance of peritumoural area was studied in different pulse sequences DWI (b0 and b1000), T2WI, FLAIR and PWI; also measuring the rCBV ratio in the surrounding area of the tumor to compare the relative rCBV ratio between these areas with normal contralateral ones using the intensity time curve.

There was no contrast enhancement in the peritumoral area in the post contrast T1WI in all the patients, while in 16 out of the 21 patients, the peritumoural area show hyperintense signal in T2WI, FLAIR and DWI b0 and DWI b1000 images. This hyperintensity could be due to vasogenic edema or tumour cell infiltration.

The peritumoural area show high relative rCBV in 6 patients (two patients with G2, three patients with G3, two patients with G4) and low relative rCBV in the remaining studied cases. This high rCBV ratio suggesting that the high relative rCBV could be due the peritumoural infiltration and this indicating the superiority of the PWI in detection of the peritumoural infiltration.

![Image](image_url)

Fig. (1): Male patient aged 33 years; lt sided weakness 5 months duration; (A) FLAIR, (B) T2WI, (C) Post Gd T 1 WI show large Rt. Fronto-temporal lesion exhibiting bright signal in FALIR and T2WI with surrounding vasogenic edema and shows post Gd heterogenous enhancement, there is associated mass effect in terms of compression of the Rt. Lateral ventricle and midline shift to the left side. (D) Source Image. (E) Time intensity curve at the lesion showing increased rCBVr compared with normal brain at the left side; rCBV= 1.18. Diagnosed as Rt. frontal low grade glioma “Grade I”, that was confirmed by hispathological examination.
Fig. (2): Male patient 54 years complaining of right sided weakness 6 months ago; (A) T2WI showing: A hyperintense mass in the left tempoparietal region. (B) Postcontrast T1WI showing: Heterogenous enhancement of the mass. (C) RCBV map showing: Hyperperfusion of the mass. (D) Source image showing: Multiple ROIs; (1 and 4) in the contralateral white and gray matter respectively of right hemisphere, (2,3,5,6 and 7) on the mass and adjacent regions. (E) Signal intensity time curve showing: necrotic area 6, and hyperperfused area 2 and 3. The maximum rCBV ratio = 6.75. Histopathological examination confirmed the diagnosis of Grade 3 glioma.

Table (1): Range of maximum rCBV ratio in tumours.

<table>
<thead>
<tr>
<th>Grade of tumour</th>
<th>No of patients</th>
<th>Range of rCBV ratio</th>
</tr>
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<tbody>
<tr>
<td>Grade 1</td>
<td>5</td>
<td>1.14-1.29</td>
</tr>
<tr>
<td>Grade 2</td>
<td>4</td>
<td>1.42-2.16</td>
</tr>
<tr>
<td>Grade 3</td>
<td>9</td>
<td>2.69-6.78</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3</td>
<td>4.33-13.8</td>
</tr>
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</table>

Discussion

Angiogenesis (the formation of new blood vessels from preexisting capillary networks) is critical for the continued survival and growth of astrocytomas. The degree of vascular proliferation is one of the most important parameters in determining the histopathologic grade of astrocytomas [15].

It is not known whether angiogenesis plays a triggering or permissive role in tumour differentiation, but it is well recognized that the more malignant astrocytoma, the greater the degree of vascular hyperplasia [16-18].

MRI plays a critical role in the preoperative assessment of brain gliomas. Mass effect, cyst formation and necrosis on MRI studies do correlate significantly with malignant behaviour. Greater likelihood for gadolinium enhancement exists in high-grade tumours but 25% to 30% of low-grade gliomas do enhance with contrast. Lack of contrast enhancement on MRI studies does not equate with low tumour grade. In fact, a broad spectrum of histological types may present as non-enhancing lesions. Even after contrast administration, up to 25% of high-grade gliomas may show faint or no detectable enhancement. In addition, the risk of anaplasia in non-enhancing lesions on MRI increases significantly with the patient’s age [19,20].

In this current study; the glial tumours displayed postcontrast enhancement in postcontrast T1 WI in the same area showed maximum relative rCBV ratio in only 9 patients out of the 21 patients (3 patients with low grade glioma, and 6 patients with high grade glioma).

Paramagnetic contrast agents such as gadopentetate dimeglumine are routinely used as a part of MR imaging of intracranial neoplasms. The contrast enhancement seen on T1-weighted images is not related to the perfusion abnormality on T2*-weighted echo-planar images. Contrast enhancement in the conventional sense depicts the areas of contrast accumulation in the interstitial tissue caused by the disruption of the blood-brain barrier and not the underlying regional vascularity [18,21].

Recent developments in MR imaging have allowed the assessment of CBV and perfusion abnormalities in brain tumours [2,17]. A number of cross-sectional studies have revealed the usefulness of MR perfusion imaging for preoperative grading of gliomas [1-5] and have indicated that the technique significantly augments the sensitivity and specificity of conventional MR imaging in predicting histologic grade [1].

The rCBV maps are particularly sensitive in depicting the microvasculature and enable the detection of neovascularisation at the capillary level, as well as its quantification in relative terms. The rCBV correlates with the histological grade and is higher in anaplastic gliomas than in low-grade gliomas [22,23].

Histopathological examination was carried for all patients and classified into 4 grades and we considered the first two groups as low grade glioma and late two groups as high grade glioma [according to Sugahara, et al.] [5].

In this current study, the maximum relative rCBV ratio of pathologically proven grade 1 glioma was ranged from 1.14 to 1.29 and the maximum relative rCBV ratio of grade 2 glioma was ranged from 1.42 to 2.16. The maximum relative rCBV...
in grade 3 glioma was ranged from 2.69 to 6.78 and in grade 4 glioma was ranged from 4.3-13.8. These results are in accordance with the results of range of the maximum rCBV in different previous studies for the grades of the glial tumors [1-8].

From the above discussed ranges of maximum relative rCBV there were some overlapping ranges in glioma especially between (grade 3) and (grade 4) it could be concluded that, maximum relative rCBV can’t be used alone for diagnosis and grading of glial tumors and should be accompanied with other MRI pulse sequences.

In this current study; there was no contrast enhancement in the peritumoral area in the post contrast T 1 W1 in all the patients, while in 16 out of the 21 patients, the peritumoural area show hyperintesese signal in T2WI, FLAIR and DWI b0 and DWI b1000 images. This hyperintensity could be due to vasogenic edema or tumour cell infiltration. However PWI in 6 patients showed high relative rCBV ratio of the peritumoural region suggesting tumour infiltration and microvascularity rather than oedema, so we suggest that the PWI can differentiate between edema and peritumoural infiltration. Up to our knowledge we could not find any literatures discussing this point before.

Conclusion:
Perfusion MR provides additional information to MRI in diagnosis of Gliomas as it is associated with the changes in the microvascular structure and the alteration of the microscopic flow related to neoangiogenesis. It detects the most malignant areas even when not enhancing. When added routinely to diagnostic MRI, rCBV maps offer meaningful functional information. Perfusion MR is a noninvasive imaging method for characterising the functional properties of malignant processes, providing diagnostic information not available on conventional MRI and offering a functional parameter for assessing grade of cerebral gliomas.

References


