

The Role of CT Perfusion Parameters in Grading of Brain Gliomas in Correlation with Histopathology

Satheesh Kumar E¹, D. Ramesh², N. Kailasanathan³

ABSTRACT

Introduction: Glioma is a primary brain tumor that arises from the supportive cells of the brain. Grading of gliomas is essential in planning therapeutic approach, assess response to therapy and to prognosticate the tumor. The aim of this study was to find the most sensitive and specific CT perfusion parameters and their cut offs that can be used to differentiate low and high grade brain gliomas and to compare CT perfusion parameters with histopathological grading of the glioma.

Methods and Materials: We performed CT perfusion (CTP) in 50 patients, with age ranging from 20 to 70 years, having brain glioma diagnosed by conventional and contrast enhanced MRI and Time-attenuation curves were obtained and quantitative perfusion parameters were calculated by applying neuro perfusion software which include Cerebral Blood Volume (CBV), Cerebral Blood Flow (CBF) and Permeability Surface area product (PMB).

Results: Comparing the CT perfusion parameters between high grade and low grade gliomas showed that there is a highly significant increase of CBF, CBV and PMB among high grade tumor group versus low grade group.

Conclusion: Significant differences in perfusion parameters between low and high grade gliomas were apparent in this study. CT perfusion may be of great clinical use in differentiation between low and high grade gliomas. In our study we found that the tumor blood flow (CBF) and tumor permeability (PMB) are the most sensitive CT perfusion parameters rather than tumor blood volume (CBV) in glioma grading.

Keywords: Cerebral blood flow, Cerebral blood volume, CT Perfusion, Glioma grading, Permeability.

INTRODUCTION

Glioma is a primary brain tumor that arises from the supportive cells of the brain. The glial cells play an important role in the protection of neurons, maintenance of homeostasis and formation of myelin. Among intra axial brain tumors, gliomas are the most frequent cerebral tumors in adults. They are very heterogenous tumors that show extensive cellular and nuclear pleomorphism, microvascular proliferation, mitotic activity and necrosis.^{1,2}

Grading of gliomas is essential in planning therapeutic approach, assess response to therapy and to prognosticate the tumor.² High-grade gliomas (WHO grades III & IV) are invasive and highly vascular tumors and because of their intrinsic tendency to undergo progressive genetic alterations and malignant transformation, patients with high grade glioma have poor survival period, whereas low grade gliomas (WHO grades I&II) have low proliferative potential, and patients have relatively prolonged survival.³

The only way to grade gliomas at present is histopathological examination through stereotactic biopsy and cytoreductive surgery which is invasive and has technical difficulties such as

non target biopsies.

Neoangiogenesis with proliferative angiogenic activity, characterized by greater proportion of immature and leaky vessels are features of malignant brain tumors. Advanced imaging techniques which provide information about the hemodynamics of the tumor can help in accurately characterizing the tumor, as vascular proliferation is one of the marker of higher tumor grade. Such a technique may overcome the shortcomings of errors of histopathological sampling and conventional imaging techniques.⁴

Conventional MRI is the initial imaging modality of choice for imaging gliomas because of its superior soft tissue contrast resolution. It has a minimal role in identifying the glioma grades because the contrast enhancement pattern does not indicate microvascular density or neoangiogenesis of the tumor. It just reveals disturbed or absent blood brain barrier.⁵

Perfusion imaging has been useful in grading cerebral neoplasms and may provide reliable information on tumor physiology such as microvasculature, angiogenesis, necrosis, and cellularity.⁶⁻¹² The aim of this study was to find the most sensitive and specific CT perfusion parameters and their cut offs that can be used to differentiate low and high grade brain gliomas and to compare CT perfusion parameters with histopathological grading of the glioma.

MATERIAL AND METHODS

This prospective study was performed after obtaining clearance from our institutional ethical committee and institutional informed consent guidelines were observed.

Patients referred from neurosurgery department with suspected glioma on MRI, who are willing for CT perfusion are included in this study during the period from January 2016 to June 2016. Pregnant women, and very old patients with compromised renal functions were not included in this study. Relevant entries in the proforma for each patient were made after reviewing his/her case sheet & previous medical records.

The population enrolled in this study was composed of 50 patients diagnosed as having brain glioma by conventional and contrast enhanced MRI. All patients were required to provide written informed consent before study participation.

All CT perfusion studies were done using 16 SLICE CT scanner (Somatom Emotion, Siemens Healthineers) with syngo®

¹Resident, ²Professor, ³Director and Professor, Barnard Institute of Radiology, Madras Medical College, Chennai - 600003, India.

Corresponding author: Dr. Satheesh Kumar, No. 11, Kuppu Kounder Street, Panruti-607106, India.

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Volume Perfusion CT Neuro (VPCT Neuro) software. The technique is based on a cine mode continuous acquisition of dynamic flow of contrast. The imaging parameters were 80 kV and 100 mAs, 24 spiral images were obtained.

A bolus of 50 ml of the non-ionic contrast material Iohexol 350 (Omnipaque 350) was injected through a 18-gauge cannula placed in the volar aspect in the cubital vein at a flow rate of 5 ml/s. CT scanning was initiated with 5 seconds delay.

Bone, cerebrospinal fluid and blood vessels which are non parenchymal pixels were excluded by applying automatic segmentation. Venous reference was selected from superior sagittal sinus for the perfusion CT process so as to obtain peak vascular enhancement since accurate absolute density of arteries can be restricted by partial volume effects in 10 mm thick axial sections.

Time-attenuation curves were obtained and quantitative perfusion parameters were calculated by applying neuro perfusion software. Four types of parameter maps were generated for each patient. They are,

- Temporal maximum intensity projection - (MIP) in Hounsfield units (HU),
- Cerebral Blood Volume - CBV (ml/100 ml),
- Cerebral Blood Flow - CBF (ml/100 ml/min) and,
- Permeability Surface area product - PMB (ml/100 ml/min)

The shape of the arterial input function necessary for the Patlak analysis was automatically determined from branches of the Middle cerebral artery or Anterior cerebral artery, the peak of the input function was normalized to the peak of the superior sagittal sinus. Regions of interest were independently determined and manually drawn on the maps.

Initially, ROIs were drawn on the MIP images, on the solid part of tumor, trying to exclude areas with necrosis or vessels. The ROIs were then automatically copied onto the perfusion maps and corresponding CBV, CBF and PMB values were acquired. For every patient, reference ROIs were also drawn on the healthy contralateral hemisphere and perfusion parameters were obtained as control values. All the patients were followed up and histopathological reports were collected from the pathologist.

STATISTICAL ANALYSIS

The collected data were analyzed with IBM.SPSS statistics software 23.0 version. To describe about the data - descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables.

The Shapiro Wilk's test for normality showed the data was normally distributed, hence to find the significant difference between the bivariate samples in Independent groups the Unpaired sample t-test was used. Receiver Operator Characteristic (ROC) curve analysis was used to find the Sensitivity, Specificity, PPV and NPV on comparison with Histopathological grading.

To assess the relationship between the variables Pearson's Correlation was used. To find the significance in categorical data Fisher's Exact test was used. In all the above statistical tools the probability value 0.05 is considered as significant level.

RESULTS

Among 50 patients in the study group 28 patients had high

grade gliomas and 22 patients had low grade gliomas on histopathology. The most common tumors were glioblastoma multiforme and low grade astrocytoma.

CT perfusion maps of a 45 year old female (Fig 1) shows intensely enhancing lesion with central necrotic areas in right frontal lobe invading corpus callosum. CBF,CBV and Permeability maps show increased values in the solid areas of the tumor. Post operative tissue diagnosis was Glioblastoma multiforme.

CT perfusion study of another 28 year old male patient (Fig 2) shows poorly enhancing lesion in the right insular region. CBF,CBV and Permeability maps show no significant increase in perfusion parameters. Post operative tissue diagnosis was Grade II Astrocytoma.

The CT perfusion parameters were analysed and the mean values CBF,CBV,PMB were calculated for high grade and low grade gliomas (shown in Fig 3)

Comparing the CT perfusion parameters between high grade and low grade gliomas using the Unpaired sample t-test showed that there is a highly significant increase of CBF, CBV and PMB among high grade tumor group versus low grade group ($P < 0.012$).

The Receiver Operator Characteristic (ROC) curve analysis of the CT perfusion parameters showed the following cut off values in discriminating high grade and low grade gliomas.

- 52.38 ml/min./100 g for CBF with sensitivity of 96.4%, specificity of 95.5%, PPV of 96.4%, NPV of 95.4%
- 3.78 ml/100 g for CBV with sensitivity of 78.6%, specificity of 77.3%, PPV of 81.5% and NPV of 71.9%
- 3.44 ml/min./100 g for PMB with sensitivity of 85.7%, specificity of 86.4%, PPV of 88.9% and NPV of 82.6%

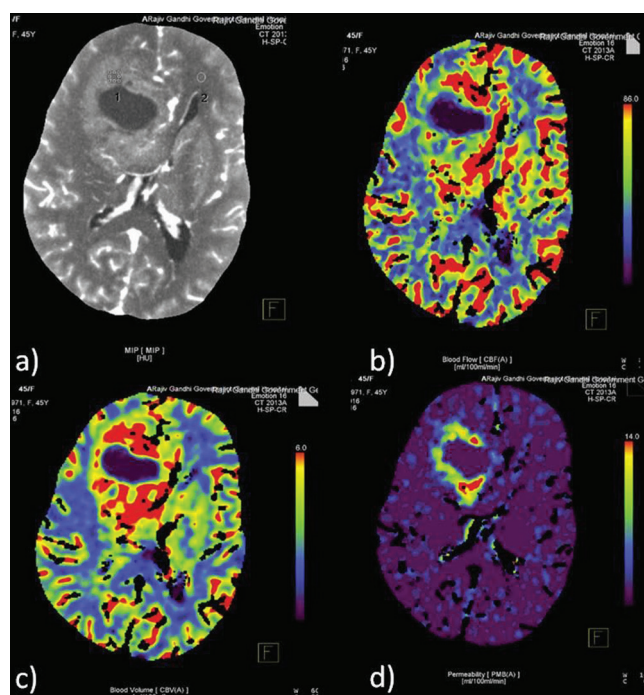


Figure-1: 45 year old female (a) MIP image shows intensely enhancing lesion with central necrotic areas in right frontal lobe invading corpus callosum. CBF (b), CBV (c) and Permeability (d) maps show increased values in the solid areas of the tumor. HPE was Glioblastoma multiforme.

Comparison of the CT perfusion parameters of high grade tumor group versus contralateral normal brain (Fig 4) showed that there is a significant increase of intratumoral CBF, CBV and PMB among high grade gliomas with P value of less than 0.05. Comparison of the CT perfusion parameters of low grade tumor group versus contralateral normal brain (Fig 4) showed that there is a nonsignificant difference of CBF, CBV and PMB among low grade tumor group versus contralateral normal brain parenchyma with P value of more than 0.05.

DISCUSSION

Malignant gliomas are heterogeneous group of tumors according to their histologic features, angiogenesis, prognosis and imaging features. The abnormal tumoral vessels formed by neoangiogenesis can be used as an indicator of tumor grade and response to therapy due to their defective wall leading to leakage of contrast material (increased permeability).

CT perfusion is a new imaging technique which measures blood perfusion, blood volume and permeability which were found to correlate with tumoral neoangiogenesis. The disadvantages of CT perfusion include use of iodinated contrast agents and radiation exposure.

The aim of this study was to find the most sensitive and specific parameters to each group and the most useful parameters and cut offs that can be used to differentiate the two groups.

In this study, we studied 50 patients diagnosed as glioma by conventional and contrast enhanced MRI with proposed inclusion and exclusion criteria, of which 28 patients were found to have high grade glioma and 22 patients were found to have low grade glioma on histopathology. Patients in the study were diagnosed based on biopsy and/or surgical excision. Multi-parametric assessment of the high grade and low grade gliomas was done including assessment of CBF, CBV and PMB.

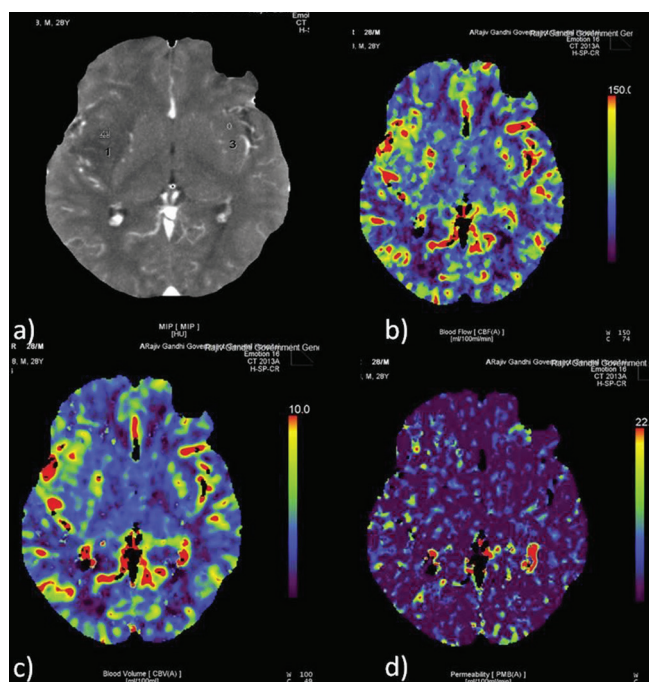


Figure-2: 28 year old male (a) MIP image shows poorly enhancing lesion in the right insular region. CBF (b), CBV (c) and Permeability (d) maps show no significant increase in perfusion parameters. HPE was Grade II Astrocytoma.

On comparing high grade and low grade gliomas regarding the CT perfusion parameters according to the results, it was clear that CBF, CBV and PMB parameters were relatively above the cut off values in patients with high grade glioma and were relatively below the cut off values in patients with low grade glioma.

Nevertheless, both CBF and PMB proved to be the two most important diagnostic parameters in the grading of brain gliomas.

CONCLUSION

In conclusion, perfusion CT can be readily incorporated into the existing CT protocols to provide an in vivo marker of tumor angiogenesis. Because there may be an error in classifying these tumors on the basis of morphologic MR imaging features alone, perfusion CT can provide complementary information about tumor vascularity of gliomas, which can be useful in predicting prognosis and tumor response to various antiangiogenic therapies.

By capturing physiological information reflecting the tumor vasculature, perfusion CT can be useful in diagnosis and grading of brain gliomas. Significant differences in perfusion parameters between low and high grade gliomas were apparent in this study. This parametric differentiation was demonstrated with great sensitivity and specificity, and accordingly CT perfusion may be of great clinical use in differentiation between low and high grade gliomas. In our study we found that the

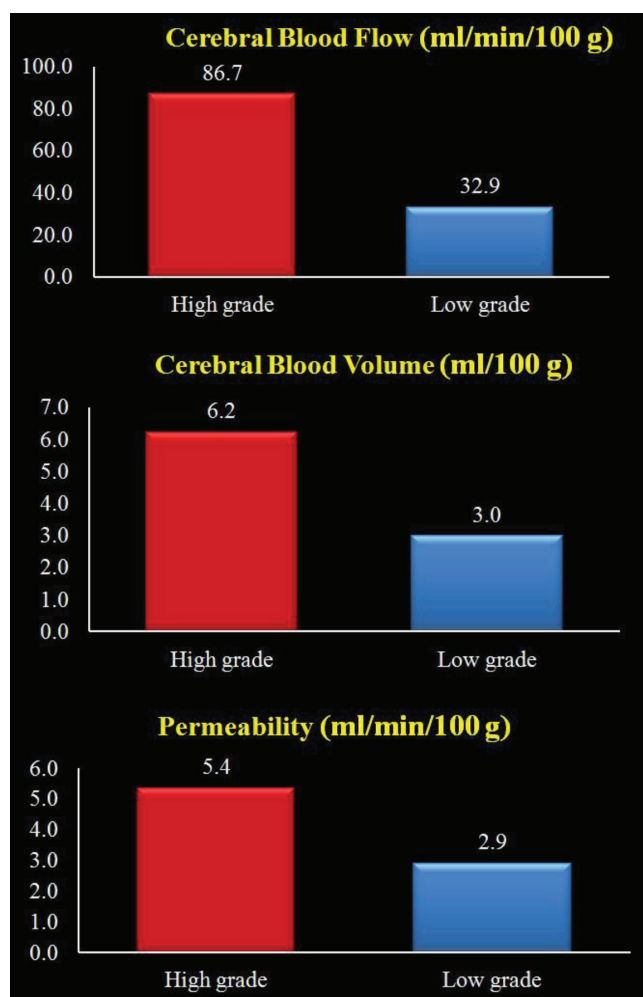


Figure-3: Mean values of CT perfusion parameters in high grade and low grade gliomas in this study

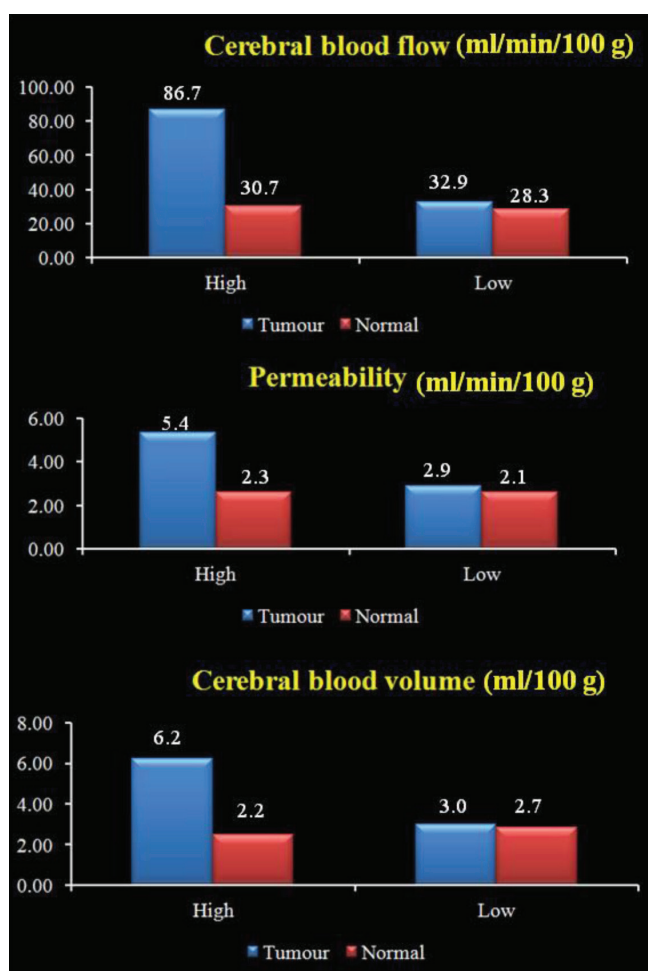


Figure-4: Comparison of the CT perfusion parameters of high and low grade tumor groups versus contralateral normal brain

tumor blood flow (CBF) and tumor permeability (PMB) are the most sensitive CT perfusion parameters rather than tumor blood volume (CBV) in glioma grading.

Perfusion CT maps can also be very useful for surgical biopsy of very small or indeterminate lesions and/or radiosurgery guidance to target the areas of increased CBV, with a better histologic yield and better response to treatment.

The sensitivity and specificity of Perfusion CT in tumor grading are not currently matched by any other imaging technique. These data may justify the more routine use of this technique in the assessment and follow-up of patients with gliomas.

Hence, perfusion CT is a useful diagnostic tool in brain tumor assessment and differentiation between high and low grade gliomas with high diagnostic accuracy.

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