Diagnostic Accuracy of Perfusion Computed Tomography in Cerebral Glioma Grading
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ABSTRACT
Objective: To determine the diagnostic accuracy of perfusion computed tomography (PCT) in the grading of cerebral glioma.
Study Design: Cross-sectional analytical study.
Place and Duration of Study: Department of Radiology, Allied Hospital, Faisalabad, from January to June 2014.
Methodology: All the patients with untreated glioma had an initial non-contrast head CT and then PCT using 128 multidetector CT scanner. Perfusion maps of permeability surface (PS) and cerebral blood volume (CBV) were generated and measured. As control, a second volume of interest was placed in the contralateral healthy cortex. PCT parameters were compared with World Health Organization (WHO) glioma grades.
Results: Fifty patients of 30 - 70 years of age of both genders (mean 45.13 ±5.54), 31 (62%) males and 19 (38%) females were studied. These patients were classified as low-grade glioma group (22 patients) and high-grade glioma group (28 patients). PS showed the sensitivity of 95.45%, specificity of 92.86% and diagnostic accuracy of 94% in differentiating the low-grade and high-grade glioma by using a cut-off value of 3.6 ml/100 g/minute. By using a cut-off value of CBV of 2.08 (ml/100 g) among low-grade and high-grade glioma group, CBV showed the sensitivity of 77.3%, specificity of 89.3%, and diagnostic accuracy of 84%.
Conclusion: The derived parameters (PS and CBV) correlate well with tumor histopathology, differentiating low-grade from high-grade gliomas. PS showed better accuracy for glioma grading.


INTRODUCTION
Among intra axial brain tumor, gliomas are the most frequent cerebral tumors in adults that exhibit varying degrees of cellular and nuclear pleomorphism, mitotic activity, vascular proliferation, and necrosis.1,2 Tumor grade differentiation is often difficult using routine neuroimaging alone. The recent technical developments have enabled a fast relatively simple, practical and available approach to assess essential parameters of vascular physiology namely regional cerebral blood volume (rCBV), regional cerebral blood flow (rCBF) and permeability surface area product (PS). Perfusion CT imaging provides qualitative information on tumor vasculature that closely parallels the degree of tumor malignancy.3,4 Perfusion CT technique has been previously used in the evaluation of cerebral ischemia and infarctions but recent studies have investigated the role of perfusion maps for evaluating brain neoplasms.5 PCT renders important physiological and hemodynamic information in patients with intra-axial brain tumors, allowing differentiation between low-grade and high-grade gliomas by quantifying regional CBV, CBF and permeability of the blood-brain barrier in a single acquisition.6 As tumor neoangiogenesis and neovascularisation play an important role in tumor growth and spread; therefore, measurement of perfusion parameters enables us to access the tumor grade, the determination of treatment options, and the assessment of treatment response and prognosis.7 Perfusion CT imaging has the advantage of being easily repeated, unlike invasive procedures such as surgical excision or biopsy.

In vivo measurement of tumor-vessel permeability is important for grading of tumors because increased permeability is associated with neoangiogenesis seen in brain tumors and to study the response of tumors to various therapeutic agents, especially antiangiogenic agents.8 Studying the permeability scan helps in better understanding the mechanism of entry of therapeutic agents into the central nervous system, and for development of methods to enhance chemotherapeutic agent delivery by selectively altering the blood brain barrier.9

The rationale of this study was to assess that glioma grade would be correlated with various perfusion CT parameters; permeability surface (PS) and cerebral blood volume (CBV) and to study that high-grade glioma would show different parameter levels as compared with low-grade glioma, which may help in better characterizing glioma so that some of the limitations of invasive procedure of histologic grading and conventional morphologic imaging can be overcome.
The objective of this study was to determine the diagnostic accuracy of perfusion computed tomography (PCT) in the grading of cerebral glioma.

METHODOLOGY
The study was undertaken in Department of Radiology, Allied Hospital, Faisalabad, over a period of six months from January to June 2014. Consecutive patients were recruited from outpatient department of Allied Hospital, Faisalabad. Informed written consent was taken from all the patients. All patients with diagnosed intra-axial brain tumor on imaging studies were included, who had not received any kind of biopsy or treatment at the time of examination and were planned to undergo biopsy. Exclusion criteria were patients who had estimated glomerular filtration rate (eGFR) < 50 ml/minute, known kidney disease and those showing uncommonly movements / irritability. The study protocol was approved by the Hospital Ethical Committee.

All selected patients were examined by 128-slice GE CT scanner that included a NCCT, PCT. PCT was then followed by biopsy in order to assess the histopathological grade of the examined tumor.

A low dose unenhanced brain CT was performed before obtaining perfusion scan in order to locate the lesion and to plan the slice positions of PCT and to target the centre of the tumor. The acquisition parameters were 80 kVp and 120 mAs. Dynamic perfusion CT was performed with 4 cm (8 slices of 5mm thickness) plane coverage. PCT image was acquired as a cine series 50 seconds, beginning 5 seconds after 40 to 50 mL of non-ionic iodine contrast injection through a peripheral intra-venous catheter by using an automatic power injector.

Commercially available software (CT perfusion; GE Optima 660) was used to calculate parametric maps of CB and PS by using baseline perfusion CT data. Arterial input and venous output time-attenuation curves were created, with regions of interest manually drawn by the experienced CT technologist, mostly in the artery with the greatest peak and slope on time-attenuation curves, and the superior sagittal sinus, respectively.

After tumor localization on NCCT by a radiologist, PCT was assessed for permeability surface (PS), cerebral blood volume (CBV), and the values were obtained from the lesion as well as from the normal cortex. Cut-off value of CBV parameter for discrimination between high- and low-grade glioma was taken as 2.08 ml/100 g (i.e. higher values high grade glioma and lower values suggesting low grade glioma). PS value was taken 3.6 ml/100 g/minute (i.e. > 3.6 ml/100 g/minute suggesting high grade glioma and lower suggesting low grade glioma) for calculating the diagnostic accuracy of CBV and PS.

Data was analyzed on SPSS version 17. Independent sample t-test was used for measurement of quantitative parameters and was expressed as mean ±SD. In each patient, histopathological grading results were considered the standard criteria for the calculation of the sensitivity, specificity, PPV, NPV and accuracy for the grading of glioma with dynamic PCT. P value < 0.05 was taken as significant.

RESULTS
A total of 50 patients were included in this study. All the patients were between 30 - 70 years of age (mean 45.13 ±5.54 years) of both genders (31=62% males and 19=38% females).

These patients with glioma underwent PCT before any line of treatment. Then all the patients had histopathological examination. The biopsy specimens were examined and graded as per World Health Organization [WHO] guidelines. Six patients of the low-grade group had grade I astrocytoma and 16 were having grade II astrocytoma on histopathological result. In the high-grade group, 10 patients had grade III anaplastic astrocytoma, and 18 patients had diagnosis of glioblastoma multiforme.

Patients were divided into two low-grade (22 patients) and high-grade (28 patients) glioma group with mean and standard deviation of PCT parameters for these two groups (Table I).

<table>
<thead>
<tr>
<th>PCT parameter</th>
<th>Low-grade glioma (22 patients)</th>
<th>High-grade glioma (28 patients)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>PS ml/100 g/min</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Range</td>
<td>0.28 - 3.58</td>
<td>4.08 - 18.30</td>
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<tr>
<td>Mean ± SD</td>
<td>1.66 ±0.86</td>
<td>11.70 ±4.3</td>
<td></td>
</tr>
<tr>
<td>CBV ml/100 g</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Range</td>
<td>0.57 - 2.07</td>
<td>2.10 - 7.19</td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>1.57 ±0.38</td>
<td>5.31 ±1.44</td>
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Table II: Sensitivity, Specificity, PPV, NPV and diagnostic accuracy of CBV and PS.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CBV</th>
<th>PS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>17/ (17+5)*100 =77.3%</td>
<td>21/ (21+1)*100 =95.45%</td>
</tr>
<tr>
<td>Specificity</td>
<td>25/ (25+5)*100 =99.3%</td>
<td>26/ (26+2)*100 =92.86%</td>
</tr>
<tr>
<td>Diagnostic Accuracy</td>
<td>17+25/ (17+3+5+25)*100 =84%</td>
<td>21+26/ (21+2+1+26)*100 =84%</td>
</tr>
<tr>
<td>Positive Predictive value (PPV)</td>
<td>17/ (17+3)*100 =85.0%</td>
<td>21/ (21+2)*100 =91.3%</td>
</tr>
<tr>
<td>Negative Predictive value (NPV)</td>
<td>25/ (25+5)*100 =83.3%</td>
<td>26/ (26+1)*100 =96.3%</td>
</tr>
</tbody>
</table>

Figure 2 (a,b): Glioma in right parietal region showing (a) CBV value of 2.03 ml/100 g and (b) PS value of 1.3 ml/100 g/minute, suggesting low-grade glioma.
Out of 20 cases of low-grade glioma at CBV cut-off value of 2.08 ml/100 g, 17 were low-grade and 3 were high-grade on histopathology. Out of the 23 cases diagnosed as low-grade at PS cut-off value of 3.6 ml/100 g/min, two were high-grade and 21 were low-grade on histopathology.

Calculations for sensitivity, specificity, PPV, NPV and diagnostic accuracy of CBV and PS for glioma grading (Table II). The accuracy was greater for PS than CBV.

**DISCUSSION**

The histopathological assessment of tissue for tumor grading is currently a standard and reliable method but with inherent limitations, such as invasiveness, sampling error, inter observer variation and tumor heterogeneity.

Another important limitation of the histologic grading system is that gliomas having similar grades respond differently to similar treatment regimens, suggesting that there is a need for other non-invasive imaging techniques to characterize and grade brain tumor such as perfusion parameters in predicting patients prognosis and outcome, apart from histologic grading.

The degree of vascular proliferation is one of the most important elements in the determination of tumor grade and prognosis so the preoperative non-invasive assessment and quantification of glioma neovascularity apart from morphologic characteristics is helpful to determine the prognosis of the tumor, to select an appropriate biopsy site, to evaluate transition from low-grade to a high-grade glioma.

The perfusion parameters are primarily based on estimation of microvascular proliferation and tumor neoangiogenesis. Increased vascular permeability has also been correlated with malignancy and is a surrogate marker of tumor angiogenesis and, therefore, for tumor grade. Higher permeability has been associated with higher tumor grade.

PCT, apart from giving hemodynamic information, also shows numerous advantages over PWI; the most important of which is the linear relationship between density changes and the tissue concentration of the contrast agent. Moreover, susceptibility artefacts generated by PWI can create diagnostic concerns in post-treatment tumor patients.

Most of the literatures regarding the use of perfusion imaging for glioma grading is based on various MR perfusion techniques. Recently, PCT has been used to grade gliomas on the basis of perfusion parameters. Ellika et al. differentiated low- and high-grade gliomas with high sensitivity (85.7%) and specificity (100%) by using PCT and a CBV normalized relative to a normal-appearing contralateral white matter threshold of 1.92. They also found that the mean value of CBV of the low and high-grade glioma group was 1.44 and 3.06 respectively.

Jain et al. found that both PS and CBV showed strong association with glioma grading. High-grade glioma showed higher PS and CBV values as compared with low-grade glioma according to Ahmad et al. Mean values of PS, CBV in high-grade gliomas were significantly higher compared with low-grade. PS demonstrated the highest diagnostic (97% sensitivity), positive (100%) and negative (94%).

In this study, the authors found diagnostic accuracy of 94% of PS in differentiating the low- and high-grade glioma by using the cut-off value of 3.6. These findings are in agreement with the study of Ahmad et al. By using a cut-off value of 2.08 of CBV among low-grade and high-grade glioma group, we found the sensitivity of 77.3%, specificity of 89.3%, positive predictive value of 85%, and negative predictive value of 83.33%, and diagnostic accuracy of 84%. These results are near to that of Ellika et al. and Ahmad et al.

Maarouf’s results revealed that CBV was the most accurate diagnostic marker which is in contrary to the present results which showed the PS as the more sensitive parameter in grading of glioma. However, the sensitivity and specificity of PS are near to our results.

This study also proved that CBV and PS are the two most important diagnostic parameters in the grading of brain gliomas, which is consistent with previously published data.

Potential limitation of our study could be the surgical sampling error, particularly in cases where the histologic specimen was obtained with biopsy only.

**CONCLUSION**

PCT parameters (PS and CBV) had good correlation with glioma grading and correlate well with tumor histopathology. PS had higher accuracy than CBV.

**REFERENCES**


