A potential role of CT perfusion parameters in grading of brain gliomas

Rania Maarouf, Hossam Sakr *

Radiology Department, Ain Shams University, Cairo, Egypt

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KEYWORDS
CT perfusion; Glioma grading; Tumoral angiogenesis

Abstract  Background and purpose: Gliomas are very heterogeneous tumors, glioma grading is currently based on the histologic assessment. With noninvasive measurement of vascular permeability by CT Perfusion (CTP) multiple perfusion parameters which can be obtained with a single acquisition the aim of this study was to find the most sensitive and specific CTP parameters and their cutoffs that can be used to differentiate between low and high grade brain gliomas.

Material and methods: Twenty-five patients were included in this study divided into two groups: group A includes 15 patients with high grade glioma, group B includes 10 patients with low grade glioma; CTP was done for all patients, perfusion values of tumors were then calculated, and statistical analysis was done using IBM SPSS.

Results: A statistically highly significant difference was found between the two groups regarding the BF, BV and PS with $P$ values of 0.0003, 0.00026 and 0.0009 respectively. The two groups were found to be self-discriminated by BV and PS with sensitivity of 95% and 86% respectively.

Conclusion: CTP shows high sensitivity in terms of differentiation between high and low grade adult gliomas.

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1. Introduction

The most common primary brain neoplasms in adults are gliomas which are very heterogeneous tumors (1). Highly vascular ones are called high-grade gliomas, so, histopathological analysis is used in glioma grading (2), and stereotactic brain biopsy or cytoreductive surgery is the only way to obtain material for histopathological assessment (3); yet they have inherent limitations in their techniques and interpretation (4). Treatment strategies, prognosis and response to therapy depend on accurate grading, so it is important to choose the most representative part of the tumor to be biopsied, and the two most important factors in determining the malignancy of gliomas are infiltration of the nearby brain parenchyma and neangiogenesis (5).

Areas of postcontrast enhancement in the conventional MRI indicate disrupted or absent blood brain barrier and not necessarily neovascularity of the tumoral lesion (6).

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Various techniques used to measure tumor perfusion parameters in vivo resulting in more accurate grading of gliomas, assess their prognosis and response to therapy avoiding some of the limitations of both histologic grading and conventional morphologic imaging (7).

Various MR perfusion techniques have been used to assess brain gliomas to estimate tumor blood volume, blood flow and permeability; however, tissue attenuation measured by CT Perfusion (CTP) has a linear correlation with tissue concentration of a contrast agent, unlike perfusion MR imaging, so it probably provides a more accurate assessment of hemodynamic (tumor blood volume) and physiologic (tumor vascular leakiness) parameters. Other advantages of CTP include wide availability, short scan time, and relatively low cost as compared to MR perfusion, and CTP is likely well-suited to study brain gliomas and may be used as a widely available, easy and accurate imaging technique for assessment of perfusion parameters and their use as imaging biomarkers (3,5).

Thus the purpose of this study was to assess the role of CTP in the grading of adult brain gliomas.

2. Materials and methods

2.1. Study population

This study was carried out between September 2012 and December 2014, the institutional ethics committee approved this study and waived informed consent. All data were reviewed prospectively.

Inclusion criteria were (a) age between 20 and 70 years. (b) Both sexes were included. (c) The presence of brain glioma diagnosed by conventional and contrast enhanced MRI.

Exclusion criteria were (a) lactating and pregnant females whatever the gestational age (serum pregnancy test was done for all premenopausal female patients) and (b) Patients with impaired renal function (serum creatinine level higher than 1.3 mg/100 ml).

Table 1 Comparison between the two groups regarding the median CT perfusion parameters.

<table>
<thead>
<tr>
<th>Group</th>
<th>I (high grade)</th>
<th>II (low grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF</td>
<td>92.5 (90.5–94.5)</td>
<td>19.8 (17.8–21.8)</td>
</tr>
<tr>
<td>BV</td>
<td>6.4 (4.4–8.4)</td>
<td>2.9 (0.9–4.9)</td>
</tr>
<tr>
<td>PS</td>
<td>6.8 (4.8–8.8)</td>
<td>3.2 (1.2–5.2)</td>
</tr>
</tbody>
</table>

The population enrolled in this study was composed of 25 patients diagnosed as having brain glioma by conventional and contrast enhanced MRI, and they were further categorized into 2 groups as follows:

Group A (patients with high grade tumor by histopathology) includes 15 patients (10 males and 5 females), aged between 43 and 67 years, median age of 54 years.

Group B (patients with low grade tumor by histopathology) includes 10 patients (5 males and 5 females), aged between 28 and 60 years, median age of 44 years.

Thus, the total number of males in the study was 15, and total number of females was 10.

2.2. Acquisition of CTP images

All patients were required to provide written informed consent before study participation.

A second-generation 128-slice dual-source CT in dual-energy mode (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany) was used; pre-contrast axial cuts were taken during a breath hold at the end of inspiration. The coverage area starts from the level of the top of the skull vault till skull base. After tumor localization, a 2 cm lesion region was selected based on the pre-contrast series for the dynamic study in the maximal diameter of the tumor. A dynamic study of the selected area was performed in a single

Table 2 The results of Wilcoxon Rank Sum test for groups A and B (HS = highly significant, NS = non significant).

<table>
<thead>
<tr>
<th>BF</th>
<th>BV</th>
<th>PS</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>0.0003</td>
<td>0.00026</td>
</tr>
<tr>
<td>Sig.</td>
<td>HS</td>
<td>HS</td>
</tr>
</tbody>
</table>

Table 3 The results of Wilcoxon Rank Sum test for groups I and contralateral normal brain (HS = highly significant, S = significant, NS = non significant):

<table>
<thead>
<tr>
<th>BF</th>
<th>BV</th>
<th>PS</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>0.010515</td>
<td>0.007428</td>
</tr>
<tr>
<td>Sig.</td>
<td>S</td>
<td>HS</td>
</tr>
</tbody>
</table>

Fig. 1 Comparison between the two groups regarding the median BV and PS.
breath hold at the end of inspiration at a static table position. A total of 50 ml of nonionic iodinated contrast medium, iopromide (Ultravist 300 mg of iodine/ml; Bayer Health Care) was injected at a rate of 5 ml/s.

The CT parameters used to acquire dynamic data were 1 s gantry rotation time, 100 kVp, 240 mA, acquisition in 4i transverse mode (four sections per gantry rotation) and 5 mm reconstructed section thickness.

Scanning was initiated after a 5 s delay from the start of injection, and images were acquired for a total duration of 30 s.

### 2.3. Analysis of the data

Data were processed at Syngo.via advantage Windows 4.0 workstation (Siemens AG, Munchen, Germany) with CTP software.

Functional data were calculated by the following steps:

- Displaying images at an appropriate window.
- Selecting sections between the beginning and end of contrast enhancement in the aorta.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>The results of Wilcoxon Rank Sum test for groups I and normal contralateral brain (HS = highly significant, S = significant, NS = non significant).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BF</td>
</tr>
<tr>
<td>$P$</td>
<td>0.3010</td>
</tr>
<tr>
<td>Sig.</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5</th>
<th>The different parameter of diagnostic validity test regarding the CBV and PS.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CBV</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>95</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>90</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>93</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>90</td>
</tr>
</tbody>
</table>
Obtaining a reference arterial input curve by placing a region of interest (ROI) in the aorta manually ensuring that the ROI did not include any mural calcification.

Obtaining a reference venous input curve by placing a region of interest (ROI) in the main superior sagittal sinus.

ROIs for tumor were hand drawn. In the presence of multiple tumors, ROIs were drawn for all tumors in the scanning range.

ROI was drawn in background brain parenchyma.

Perfusion values of tumor(s) and background brain including blood flow (BF), blood volume (BV) and Capillary permeability surface area product (PS) were then calculated averaging the functional parameters across all four sections and displayed as:

Tables of BF, BV, MTT, PS and HAF values.

Functional maps of BF, BV, MTT, and PS. These functional maps were displayed in colors ranging from blue to red, blue being the lower range of display for BF, BV, and PS and red being the upper range of display.

The following are used CTP parameters:

(1) Blood flow (BF): This is the volume flow rate of blood through the vasculature in a tumor. It is expressed in units of ml/min/100 g.

(2) Blood volume (BV): This is the volume of blood within the vasculature in a tumor that is actually ‘flowing’. Any stagnant pool of blood will not be included in the blood volume. It is measured in units of ml/100 g.

(3) Capillary permeability surface area product (PS): it is the unidirectional flux of contrast from blood plasma to interstitial space. It is measured in units of ml/min/100 g (8).

No adverse reactions to contrast media injection were observed among the 25 patients.

The tables and functional maps of the BF, BV, MTT, PS and HAF were all revised.

Fig. 4  Comparison between the positive predictive value (PPV) of the CBV and PS.

Fig. 5  Comparison between the negative predictive value (NPV) of the CBV and PS.
2.4. Collected data and statistical analysis

IBM SPSS statistics (V. 19.0, IBM Corp., USA, 2010) was used for data analysis. Data were expressed as Mean ± SD for quantitative parametric measures and as Median Percentiles for quantitative non-parametric measures.

Inter-observer agreement was assessed by calculation of the weighted kappa statistic (κ) and the prevalence-adjusted and bias-adjusted kappa (PABAK) (9).

Wilcoxon Rank Sum test was used for comparison between two independent groups for non-parametric data, while ranked Superman correlation test was used to study the possible association between each two variables among each group for non-parametric data.

The probability of error at 0.05 was considered significant while at 0.01 and 0.001 was highly significant.

The diagnostic validity test was also used.

3. Results

The results of the CT perfusion parameters of high grade brain tumors were as follows:

- The blood flow (BF) ranged from 42.4 to 238 ml/min./100 g with median BF of 92.5 ml/min./100 g (25th, 75th percentile: 90.5, 94.5 ml/min./100 g).
- The blood volume (BV) ranged from 3 to 10 ml/100 g with median BV = 6.4 ml/100 g (25th, 75th percentile: 4.4, 8.4 ml/100 g).
- The Capillary permeability surface area product (PS) ranged from 3 to 10 ml/min./100 g with median PS = 6.8 ml/min./100 g (25th, 75th percentile: 4.8, 8.8 ml/min./100 g).

while the results of the CT perfusion parameters of low grade brain tumor were as follows:

- The BF ranged from 13 to 14 ml/min./100 g with median BF of 19.8 ml/min./100 g (25th, 75th percentile: 17.8, 21.8 ml/min./100 g).
- The BV ranged from 2 to 7 ml/100 g with median BV of 2.9 ml/100 g (25th, 75th percentile: 0.9, 4.9 ml/100 g).
- The PS ranged from 1.5 to 7 ml/min./100 g with median PS of 3.2 ml/min./100 g (25th, 75th percentile: 1.2, 5.4 ml/min./100 g).

These results are summarized in Table 1 and Fig. 1.

Comparing the CT perfusion parameters between the two groups using the Wilcoxon Rank Sum test showed that there is a highly significant increase of BF and PS among high grade tumor group versus contralateral normal brain parenchyma with P value of less than 0.05 and a highly significant increase of BV among high grade tumor group versus contralateral normal brain parenchyma with P value of less than 0.01.

These results are summarized in Table 3.

4. Discussion

Malignant gliomas are heterogeneous group of tumors according to their histologic features, angiogenesis, prognosis and imaging features (10).

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) (7).

CT perfusion is a new imaging technique which measures blood perfusion, blood volume and permeability which were found to correlate with tumoral neoangiogenesis (11).

In this study we included 25 patients categorized into two groups, group I which includes patients diagnosed to have high grade glioma and group II which includes patients diagnosed to have low grade glioma.

Multi-parametric assessment of the two groups was done including assessment of BF, BV and PS.

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

Patients in the study were diagnosed based on biopsy and/or surgical excision.

On comparing the two groups regarding the CT perfusion parameters according to the results, it was clear that BV and PS parameters were relatively above the cutoff values in group I of high grade glioma and were relatively below the cutoff values in group II of low grade glioma.

Similar findings were found by Schramm et al. who reported higher BV in high grade tumor when compared to low grade brain tumor (12).

Ellika et al. (5), also were able to differentiate low and high grade gliomas with a high sensitivity (85.7%) which is slightly lower than the 95% sensitivity in the current study and 100% specificity compared to the 90% specificity in the current study (13).

Jain et al. (3), also were able to differentiate low and high grade gliomas by using PCT parameters and concluded that both PS and CBV have shown strong association with glioma grading, and this comes in concordance with our results showing that both PS and CBV parameters were found to be more effective than CBF in differentiation between the low and high grade gliomas (3).
The cutoff for BV in differentiation between the two groups = 4 ml/min./100 g (above these ranges lesion belongs to group I, and below the ranges the lesion belongs to group II). At which specificity = 95%, sensitivity = 90%.

PS was found to have less diagnostic performance in differentiating the two groups with best cutoff for discrimination = 3.5 ml/min./100 g (above these ranges lesion belongs to group I, and below the ranges the lesion belongs to group II). At which specificity = 86%, sensitivity = 90%, positive.

Schramm et al. (12), also implicated that high grade gliomas could be differentiated from low grade ones on the basis of all three PCT parameters studied, and they also reported that low grade gliomas exhibited no different perfusion parameters compared with the normal brain parenchyma (12); this also comes in agreement with our study which revealed that there was no statistically significant increase of BF (P value of 0.3), BV (P value of 0.2) and PS (P value of 0.4) among low grade gliomas when compared to normal brain parenchyma, whereas, there was a highly significant increase of BF, BV and PS (P value less than 0.01) among.

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**Fig. 6** 48 year old male presented with cystic astrocytoma. (A and B) early and late dynamic CECT. (C) CTP parameters. (D and E) functional maps for BF & BV respectively.
Fig. 7  34 year old male presented with oligodendroglioma. (A and B) Early and late dynamic CECT. (C) CTP parameters. (D and E) Functional maps for BF & BV respectively.
high grade gliomas when compared with the normal brain tissue.

Xyda et al. (14), also reported statistically significant increase in CBV, CBF and PS values in the high grade glioma group in comparison to healthy brain parenchyma and low grade gliomas (14).

In this study we confirmed the implication of the previously published data, that high grade gliomas can be differentiated from low grade gliomas on the basis of CBV, CBF and PS absolute values (12,14).

The clear increase in all three perfusion parameters in high grade gliomas in comparison with low grade glioma proves the studied perfusion parameters as valuable diagnostic markers for the grading and classification of gliomas before histopathological diagnosis.

Consistent with the previously published data our study shows that CBV and PS are the two most important parameters with similar prognostic values and higher than CBF (3,5); on the contrary, Xyda et al. (14) had shown that CBV and CBF values had comparable diagnostic accuracy with a sensitivity of 93% and 90% respectively and a specificity of 94% for both parameters. Moreover, they also reported that the most accurate diagnostic marker was the PS with the highest specificity of 100% and sensitivity of 97%; yet, our results revealed that CBV was the most accurate diagnostic marker with a sensitivity of 95% and specificity of 90%, whereas, PS showed 86% sensitivity and 90% specificity.

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

In conclusion, perfusion CT can be readily incorporated into the existing CT protocols to provide an in vivo marker of tumor angiogenesis. 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; at our study we found that the blood volume and permeability surface are the most sensitive CT perfusion parameters rather than blood flow in glioma grading.

Hence, PCT is a useful diagnostic tool in brain tumor assessment and differentiation between high and low grade gliomas with high diagnostic accuracy.
Conflict of interest

The authors declare that there are no conflict of interests.

References