Utility of Tissue Similarity Maps Based on Relative Cerebral Blood Volume for Grading Gliomas as Validated by Histological Results

Su Hu, Xi-Ming Wang, Yi-Xing Yu, Ling Yang, Mo Zhu, Guang-Yu Hao, Jing Zhang, Chun-Hong Hu
Department of Radiology, First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006, China

Key words: Blood Volume; Glioma; Perfusion Imaging; Neoplasm Grading

INTRODUCTION
Gliomas are the most common primary brain tumors. Grading gliomas is of significant clinical importance because treatment plans vary between high- and low-grade gliomas. Histopathologic grades of gliomas are closely related to microvasculature. Magnetic resonance (MR) perfusion-weighted imaging (PWI) is a technique to quantitatively evaluate tumor microenvironments by measuring cerebral blood volume (CBV). Tissue similarity maps (TSM) based on relative cerebral blood volume (rCBV) are generated from a novel algorithm depending solely on the signal intensity time course without the need for a concentration-time curve, which is required when using the conventional rCBV algorithm; therefore, TSM-based rCBV (rCBV\textsubscript{TSM}) measurements are not influenced by certain factors, such as contrast-to-noise ratio and arterial input function (AIF). However, applying TSM-based rCBV measurement to grading gliomas has rarely been discussed. The main purpose of this study was to investigate the value of using TSM-based rCBV measurement for grading gliomas.

METHODS
Clinical data
A total of 27 patients (14 males, 13 females; mean age, 51.8 ± 12.5 years; range, 20–67 years) who each had been diagnosed with an intraaxial tumor between October 2011 and February 2013 were included in this study. All patients had undergone preoperative MR imaging (MRI) with PWI before their tumor resections. All tumors had been pathologically confirmed as gliomas (10, Grades 2; 10, Grades 3; and 7 Grades 4, according to the 2007 WHO criteria) after tumor resection. The time interval between preoperative MRI and surgery for each patient was <15 days.

Imaging acquisition
Images were obtained using a 3 Tesla magnet (Signal HDx 3.0, General Electric, Waukesha, Wisconsin, USA) and an 8-channel head coil. Routine MRI and PWI data for preoperative evaluation were acquired. For PWI, 10 precontrast time points and 40 postcontrast time points were obtained with a temporal resolution of 2 s. PWI data were obtained using an echo planar imaging pulse sequence with following parameters: TR/TE, 1600 ms/22.8 ms; slice thickness, 5 mm; matrix, 128 × 128; and flip angle of 90°. The contrast agent gadopentetic acid (Gd-DTPA) was used with a dose of 0.1 mmol/kg body weight and a flow rate of 2 ml/s.

Data analysis
Perfusion-weighted imaging data were calculated using TSM and CBV algorithms with MATLAB 7.6 (Math Works, Natick, MA, USA); TSM and CBV diagrams were then both generated. For each patient, two regions of interest (ROI) each were drawn in areas with visible blood supply to the parenchyma of the glioma and in areas with normal white matter (WM). The following parameters were then obtained: The CBV\textsubscript{PWI} value of the tumor (CBV\textsubscript{PWI-tumor}), the CBV\textsubscript{PWI} value of WM (CBV\textsubscript{PWI-WM}), the CBV\textsubscript{TSM} value of the tumor (CBV\textsubscript{TSM-tumor}), and the CBV\textsubscript{TSM} value of WM (CBV\textsubscript{TSM-WM}). The rCBV\textsubscript{PWI} and rCBV\textsubscript{TSM} value of each glioma were then calculated (rCBV\textsubscript{PWI-tumor} = CBV\textsubscript{PWI-tumor}/CBV\textsubscript{PWI-WM}; rCBV\textsubscript{TSM-tumor} = CBV\textsubscript{TSM-tumor}/CBV\textsubscript{TSM-WM}).

Statistical analysis
Statistical analyses were performed with SPSS 17.0 software (IBM, Armonk, New York, USA). First, the homogeneity of the variance of both the gliomas’
rCBV\textsubscript{PWI-tumor} and the rCBV\textsubscript{TSM-tumor} was tested. Second, the correlations between partial manifestations (necrosis or cystic, peritumoral edema and enhanced performance) in conventional MRI findings and pathological grading of gliomas were calculated with a Mann–Whitney Test. Lastly, either the Kruskal–Wallis H-test was used to compare both the rCBV\textsubscript{PWI-tumor} and rCBV\textsubscript{TSM-tumor} between gliomas of grades 2, 3 and 4, and the least significance difference (homogeneity of variance) or the Tamhane’s T2 (heterogeneity of variance) tests were applied to compare those of any two groups. A \( P < 0.05 \) was considered to be statistically significant.

**RESULTS**

The gliomas were most often located in the frontal lobe (\( n = 12 \)), followed by the temporal lobe (\( n = 5 \)), the lateral ventricle trigone (\( n = 3 \)), the parietal lobe (\( n = 2 \)) and the parieto-occipital regions (\( n = 2 \)). A few lesions also occurred in the occipital lobe (\( n = 1 \)), thalamus (\( n = 1 \)) and the body of the corpus callosum (\( n = 1 \)).

The lesions presented as round or oval masses (\( n = 18 \)) [Figure 1] and as irregular shapes (\( n = 9 \)) with the largest diameters ranging from 1.2 to 8.4 cm with an average of about 4.16 ± 1.61 cm.

The MRI signals of the tumor were hypo- (\( n = 20 \)), iso- (\( n = 2 \)), or hyper-intense (\( n = 5 \)) on T1-weighted images and were hyperintense (\( n = 27 \)) on T2-weighted images. Most of the lesions generated heterogeneous signals (\( n = 21 \), 77.78%), which indicated intratumoral necrosis or cystic areas in 20 cases and hemorrhages in five cases. Twenty-four cases (88.89%) showed intense enhancement with Gd-DTPA [Figure 1]. Peritumoral edema was found in most cases (\( n = 25 \), 92.59%).

**Discussion**

Magnetic resonance perfusion imaging is a functional imaging technique that can offer hemodynamic parameters and can indicate the degree of vascularization by detecting signal changes when a contrast agent passes through the cerebrovascular system. PWI is one of the best ways to preoperatively grade glioma, as the CBV value can be used to reflect angiogenesis at the tumor capillary level.

As seen in Table 1, the extent of peritumoral edema and the degree of enhanced performance in high-grade gliomas were both larger than that of low-grade gliomas (\( P < 0.01 \)). There was no statistical difference in necrosis or cystic areas between high- and low-grade gliomas (\( P = 0.166 \)).

Postprocessed images could be obtained with two algorithms. The parenchyma of the glioma was shown to have substantial blood supply while the blood supply of the cystic necrotic areas was limited [Figure 1].

The differences of rCBV\textsubscript{PWI-tumor} values among grades 2, 3, and 4 gliomas were statistically significant (\( P = 0.001 \)). The rCBV\textsubscript{PWI-tumor} of grades 2 gliomas (1.80 ± 0.45, 1.01–2.37) was significantly lower than that of grades 3 (6.06 ± 2.28, 2.08–9.92) (\( P = 0.001 \)) and grades 4 (6.47 ± 2.30, 4.39–10.43) (\( P = 0.004 \)). There was no statistical difference between grades 3 and 4 (\( P = 0.978 \)). Similarly, the differences of rCBV\textsubscript{TSM-tumor} value among grades 2, 3, and 4 were statistically significant (\( P = 0.002 \)). The rCBV\textsubscript{TSM-tumor} of grades 2 gliomas (2.25 ± 0.40, 1.70–2.72) were significantly lower than that of grades 3 (6.04 ± 2.49, 2.50–10.06) (\( P = 0.003 \)) and grades 4 gliomas (6.27 ± 2.76, 2.97–10.35) (\( P = 0.024 \)). There was no statistical difference when grades 3 and grades 4 gliomas were compared (\( P = 0.997 \)).

**Table 1: Correlations between partial manifestations in conventional MRI findings and pathological grading gliomas**

| MRI manifestations | High-grade | Low-grade | \( P \) |
|--------------------|------------|-----------|--------|
| Necrosis or cystic (\( n \)) | None | 5 | 2 | 0.166 |
| | Mild | 3 | 5 | 0.978 |
| | Moderate | 4 | 2 | 0.003 |
| | Severe | 5 | 1 | 0.001 |
| Peritumoral edema (\( n \)) | None | 1 | 1 | 0.005 |
| | Mild | 1 | 5 | 0.978 |
| | Moderate | 5 | 4 | 0.003 |
| | Severe | 10 | 0 | 0.978 |
| Enhanced performance (\( n \)) | None | 0 | 3 | 0.002 |
| | Mild | 1 | 4 | 0.978 |
| | Moderate | 3 | 1 | 0.003 |
| | Severe | 13 | 2 | 0.978 |

*Gliomas of grade 1 and grade 2 were grouped as low-grade gliomas and gliomas of grade 3 and grade 4 were grouped as high-grade gliomas for the purposes of analysis. MRI: Magnetic resonance imaging. A \( P \) value was derived from Mann-Whitney test.**
so as to accurately reflect the histological conditions of tumor. There are apparent correlations between rCBV and histopathological grading of gliomas.\textsuperscript{[4]}

However, the values obtained from conventional PWI can be affected by a number of factors, including AIF and r2 relaxivity. They also can be influenced by the volume or rate of the contrast agent, the paramagnetic nature of the contrast agent, and the variability of hemodynamic parameters from person to person.\textsuperscript{[2,5]}

We utilized the novel postprocessing method TSM with MATLAB software. It can provide information about the tumoral and peri-tumoral tissues by comparing the mean square errors of signal in each pixel. Compared with the conventional rCBV algorithm, TSM algorithm can provide more precise information about tissue hemodynamics.\textsuperscript{[3]}

In this preliminary study, the data from MR perfusion imaging of 27 patients with pathologically proven gliomas were computed by both TSM and conventional rCBV algorithms. The results showed that there are no differences in grading gliomas between these two algorithms: The higher the grade, the larger the value of \( \text{rCBV}_{\text{TSM}} \) or \( \text{rCBV}_{\text{PWI}} \). Therefore, TSM-based rCBV can be used for preoperative evaluation of gliomas.

This study has several limitations. First, the sample size is small. Second, the data may have been affected by subjective factors, such as the selection of the location of ROI. Therefore, further prospective studies with larger population and a uniform protocol is necessary to determine whether the TSM algorithm can provide more preoperative information about gliomas.

\textbf{References}

1. Law M, Yang S, Babb JS, Knopp EA, Golfinos JG, Zagzag D, \textit{et al.} Comparison of cerebral blood volume and vascular permeability from dynamic susceptibility contrast-enhanced perfusion MR imaging with glioma grade. AJNR Am J Neuroradiol 2004;25:746-55.
2. Jahng GH, Li KL, Ostergaard L, Calamante F. Perfusion magnetic resonance imaging: A comprehensive update on principles and techniques. Korean J Radiol 2014;15:554-77.
3. Haacke EM, Li M, Juvvigunta F. Tissue similarity maps (TSMs): A new means of mapping vascular behavior and calculating relative blood volume in perfusion weighted imaging. Magn Reson Imaging 2013;31:481-9.
4. Cha S, Knopp EA, Johnson G, Wetzel SG, Litt AW, Zagzag D. Intracranial mass lesions: Dynamic contrast-enhanced susceptibility-weighted echo-planar perfusion MR imaging. Radiology 2002;223:11-29.
5. Calamante F, Connelly A, van Osch MJ. Nonlinear DeltaR*2 effects in perfusion quantification using bolus-tracking MRI. Magn Reson Med 2009;61:486-92.