

**Table 3 Three on-going randomized phase 3 studies for newly diagnosed glioblastoma**

Regimen	Organized by	Number of patients
Stupp's regimen with/without bevacizumab	Roche (AVAglio)	920
Stupp's regimen with/without bevacizumab	RTOG 0825	720
Stupp's regimen with/without cilengitide for patients with methylated MGMT promoter status	Merck Serono (CENTRIC)	504
Stupp's regimen vs. adjuvant dose-dense (3-1) temozolomide	RTOG 0525	834

MGMT: O<sup>6</sup>-methylguanine-deoxyribonucleic acid-methyltransferase.

bitor, for MGMT promoter methylated GBM (CENTRIC) are to be tested for newly diagnosed patients. In conclusion, the survival of patients with GBM continues to improve, albeit more slowly than we would like. Various new agents are currently under study, singly and in combination. Improved understanding of the complex biology of GBM may allow for more rational and effective therapy selection for patients, further extending survival in the years to come.

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## Prediction of malignancy grading using computed tomography perfusion imaging in nonenhancing supratentorial gliomas

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**Abstract** Tumor grade differentiation is often difficult using routine neuroimaging alone. Computed tomography perfusion imaging (CTP) provides quantitative information on tumor vasculature that closely parallels the degree of tumor malignancy. This study examined whether CTP is useful for preoperatively predicting the grade of malignancy in glioma showing no enhancement on contrast-enhanced magnetic resonance imaging (MRI). Subjects comprised 17 patients with supratentorial glioma without enhancement on MRI. CTP was performed preoperatively, and absolute values and normalized ratios of parameters were calculated. Postoperatively, subjects were classified into two groups according to histological diagnosis of grade 3 (G3) glioma or grade 2 (G2) glioma. Absolute values and normalized ratios for each parameter were compared between G3 and G2. Accuracies of normalized ratios for cerebral blood flow ( $nCBF$ ) and cerebral blood volume ( $nCBV$ ) in predicting a diagnosis of G3 were assessed. In addition,  $nCBV$  was compared between diffuse astrocytoma, G2 oligodendroglial tumor (OT), and G3 OT. Values for  $nCBF$  and  $nCBV$  differed significantly between G3 and G2. Using  $nCBV$  of 1.6 as a cutoff, specificity and sensitivity for distinguishing G3 were 83.3% and 90.9%,

respectively. No significant difference in  $nCBV$  was seen between diffuse astrocytoma and G2 OT, whereas differences were noted between G2 and G3 OTs, and between diffuse astrocytoma and G3 OT. CTP offers a useful method for differentiating between G3 and G2 in nonenhancing gliomas.

**Keywords** Computed tomography perfusion imaging · Diffuse astrocytoma · Glioma · Nonenhancement · Oligodendrogloma · Preoperative diagnosis

### Introduction

Glioma is graded according to World Health Organization (WHO) classification, with grade 1 or 2 graded as low-grade glioma (LGG) and grade 3 or 4 commonly defined as high-grade glioma (HGG) [1]. As treatment and prognosis differ substantially between LGG and HGG, the ability to differentiate between grade 2 (G2) glioma and grade 3 (G3) glioma, as the border between LGG and HGG, is very important. On contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI), G2 gliomas are nonenhanced due to preservation of blood–brain barrier (BBB), whereas G3 gliomas are commonly enhanced due to increased vascular permeability caused by disruption of the BBB within the tumor [2–4]. However, the relationship between histological grading and contrast enhancement on CT and MRI is not always clear. Preoperatively differentiating between G3 and G2 gliomas that are nonenhanced on conventional neuroimaging is often difficult. When patients with nonenhancing glioma are encountered, neurooncologists may perform various examinations to differentiate between G3 and G2 gliomas, such as positron emission tomography (PET) for direct assessment of tumor

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metabolism, magnetic resonance spectroscopy to detect magnetic resonance signals of metabolites, and diffusion-weighted MRI to clarify structures within and surrounding the tumor. Assessment of intratumoral vasculature is one approach that may help to clarify the intratumoral biological characteristics and malignancy of a tumor, as intratumoral angiogenesis and high vascularity, which are regulated by hypoxia and various vascular endothelial growth factors, are essential for tumor growth and progression [5–7].

Angiography enables direct observation of intratumoral vessels, but is hazardous and remains limited for depiction of intratumoral microvasculature. Magnetic resonance perfusion imaging (MRP) and CT perfusion imaging (CTP) provide reliable information on the intratumoral microvasculature [8–12]. Numerous studies of perfusion imaging have shown that increasing malignancy of the glioma is associated with increased intratumoral blood volume and vascular permeability [10, 13–15]. Quantitative evaluation from perfusion imaging thus depends on both the microvasculature (vascular density and diameter), and vascular permeability due to disruption or absence of the BBB within the tumor. Previous reports have shown good correlations between findings on perfusion imaging and malignancy grading in enhancing glioma. In contrast, the BBB of vessels is preserved in nonenhancing glioma, since extravasation of contrast medium through the BBB in tumor vessels is considered to represent the main cause of tumor contrast enhancement [4]. As MRI remains the preferred technique for assessing brain tumors, studies using MRP to thoroughly evaluate gliomas greatly outnumber those using CTP, and MRP has also been applied to neurooncological applications for nonenhancing gliomas, such as determining biopsy targets and predicting malignant progression [16–18]. In recent years, CTP has gained acceptance as a valuable imaging technique for assessing hemodynamics in brain tumors [13, 14, 19–22]. However, whether CTP is useful for grading malignancy of nonenhancing gliomas remains unclear. CTP retains the advantage of a linear relationship between attenuation changes on CT and tissue concentration of contrast medium, unlike MRP [8, 20]. We therefore hypothesized that CTP should accurately provide quantitative information on only the microvasculature within the tumor, excluding extravasation due to permeability, when limited to patients with nonenhancing glioma. In the present study, we performed CTP on patients with nonenhancing glioma, and compared cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT), as quantitative values provided from CTP, with postoperative histological diagnosis. The present study aims to determine whether CTP is useful for prediction of preoperative malignancy

grading (WHO G2 or G3) in nonenhancing glioma on contrast-enhanced MRI.

## Patients and methods

### Patients

The study protocol was approved by the Ethics Committee of Iwate Medical University, Morioka, Japan. Consecutive patients admitted to the Department of Neurosurgery at Iwate Medical University between September 2006 and January 2010 and meeting the entry criteria were recruited to this study. Entry criteria for this study comprised: diagnosis of supratentorial glioma; tumor bulk not clearly enhanced on gadolinium-enhanced T1-weighted MRI (Gd-T1WI); tumor bulk sited in the supratentorial cerebrum; no past history relating to the brain, including surgical operation, irradiation, administration of anticancer agents or steroids, stroke, infection, or other disorders such as demyelinating disease; and provision of written informed consent to participate. Subjects comprised 17 patients (7 men, 10 women) with mean age of 47.8 years. Patient data including age, tumor site, operation method, postoperative histological diagnosis, and malignancy grade are summarized in Table 1.

**Table 1** Patient summary

No.	Age (years)	Tumor site	Surgery	Histology	WHO grade
1	76	Temporal lobe	Biopsy	AA	3
2	58	Frontal lobe	Resection	AO	3
3	45	Frontal lobe	Resection	AO	3
4	34	Frontal lobe	Resection	AO	3
5	29	Frontal lobe	Resection	AO	3
6	21	Frontal lobe	Resection	AOA	3
7	78	Frontal lobe	Biopsy	DA	2
8	68	Frontal lobe	Biopsy	DA	2
9	68	Parietal lobe	Biopsy	DA	2
10	65	Frontal lobe	Resection	DA	2
11	58	Frontal lobe	Resection	DA	2
12	52	Frontal lobe	Resection	Oli	2
13	46	Temporal lobe	Resection	Oli	2
14	42	Frontal lobe	Resection	OA	2
15	30	Frontal lobe	Resection	OA	2
16	27	Frontal lobe	Resection	DA	2
17	16	Temporal lobe	Resection	OA	2

AA anaplastic astrocytoma, AO anaplastic oligodendroglioma, AOA anaplastic oligoastrocytoma, DA diffuse astrocytoma, Oli oligodendroglioma, OA oligoastrocytoma

## Conventional MRI and CTP

Conventional MRI was performed for all subjects within 7 days before surgery. Spin-echo Gd-T1WI was performed approximately 2 min after intravenous injection of gadolinium (0.2 ml/kg, Magnevist; Bayer Schering Pharma, Berlin, Germany), using a 3.0-T whole-body scanner (GE Yokogawa Medical Systems, Tokyo, Japan) with a standard head coil. We confirmed that the tumor in each patient did not show clear enhancement with gadolinium on Gd-T1WI.

CTP was also performed within 7 days before surgery using a 16-row multidetector CT system (Aquilion 16; Toshiba Medical Systems, Tokyo, Japan), in accordance with the methods described by Sasaki et al. [23]. After performing noncontrast CT to determine the location of the tumor bulk, a multislice scan targeting the tumor bulk was performed (80 kV<sub>p</sub>; 40 mA; 1.5 s/rotation, 30 rotations field of view, 240 × 240 mm<sup>2</sup>; four contiguous 8-mm-thick sections; total scan time, 45 s). Five seconds after intravenously injecting 40 ml (4 ml/s) nonionic iodine contrast medium (Iopamiron 300; Bayer Schering Pharma) using a power injector, dynamic scanning was started and tissue attenuation of contrast medium was monitored on a slice. Radiation doses for the scanning protocol were as follows: volume CT dose index, 150 mGy; dose-length product, 480 mGy cm; and effective dose, 1.34 mSv. Data were transferred to a commercial workstation (M900 Quadra; Ziosoft, Tokyo, Japan), and scaled color maps for CBF, CBV, and MTT were automatically created. All mathematical analyses were performed by the deconvolution method [19, 24], using CTP analysis software supplied with the workstation described above. Among the three types of deconvolution algorithms implemented in this software, we used the block-circulant singular value decomposition method. Regions of interest (ROI) for venous output and arterial input functions were manually placed at the superior sagittal sinus and a single branch of the insular segment of the middle cerebral artery on either the pathological or nonpathological side, or A2 segment of the anterior cerebral artery, respectively. ROI were also placed over the entire tumor bulk and apparently normal white matter (ANWM) on the nonpathological side, on color maps for each parameter. Size of the ROI for ANWM was established as 1.0 cm<sup>2</sup>. In the measurement of absolute values, the vascular-pixel elimination (VPE) method was used to exclude pixels from large vessels at the cerebral surface, sulci, and cisterns [23, 25]. In the present study, we established the VPE threshold as 6.0 ml/100 g for CBV, since high-CBV areas suggesting large cortical vessels on color map disappeared satisfactorily at 6.0 ml/100 g when the threshold was varied between 5.0 and 8.0 ml/100 g using our analysis software. Large vascular pixels were

thus defined as pixels with CBV values >6.0 ml/100 g and were automatically eliminated. Regional absolute values (*r*CBF, *r*CBV, and *r*MTT) were then calculated automatically for all ROI. The measurements described above were performed twice for each patient by two investigators (M.S. and K.K.) who were blinded to all clinical data, including individual patient information and histological diagnosis. Absolute values of all parameters for each patient were determined as the mean of four measured values, as determined twice by each investigator. The second test was performed 1 week after the first test, with a different randomized order of measurements from the first test. We also calculated normalized ratios (*n*CBF, *n*CBV, and *n*MTT) as the absolute value for the tumor divided by the absolute value for the ANWM for each parameter in all patients. All patients underwent surgery, with tumor resection for 13 patients and CT-guided stereotactic needle biopsy for 4 patients (Table 1). The region targeted in stereotactic biopsy was based on findings from the CBV color map. If the color map showed heterogeneous perfusion within the tumor, the targeted region corresponded to the region with the highest perfusion area for CBV. In cases with tumor resection, histological diagnosis was determined by observation at the lesion showing the most malignant histological features in all preparations. Post-operatively, histological diagnosis using specimens obtained from surgery was made by one of the investigators (A.K.) with no prior knowledge of CTP data.

## Statistical analyses

All data were analyzed using PASW Statistics version 18 software (SPSS Japan, Tokyo, Japan). Inter- and intrarater reliabilities for all absolute values were evaluated according to classification of the intraclass correlation coefficient (ICC) [26]. For ICC<sub>(1,1)</sub> and ICC<sub>(1,k)</sub> as interrater reliability, agreement of all absolute values (CBF, CBV, and MTT) between first and second tests was analyzed for tumor and ANWM for each investigator, using one-factor analysis of variance (ANOVA). For ICC<sub>(2,1)</sub> and ICC<sub>(2,k)</sub> as intrarater reliability, agreement of all absolute values between the two investigators was analyzed for tumor and ANWM for each test, using two-factor ANOVA. Patients were assigned to one of two histological grading groups according to histological classification: WHO G2 or WHO G3. Frequency of biopsy was compared between G2 and G3 groups using Fisher's exact probability test. We compared absolute values for the tumor lesion for each parameter between G2 and G3 using the Mann-Whitney *U* test. Furthermore, the normalized ratio for each parameter was compared between these groups again using the Mann-Whitney *U* test. The accuracy of *r*CBF and *n*CBV in predicting a diagnosis of G3 was assessed using receiver

operating characteristic (ROC) curves. ROC curves were calculated in increments of 0.1. Absolute values and normalized ratios for CBV were compared between diffuse astrocytoma, G2 oligodendroglial tumor (OT), and G3 OT, using the Mann–Whitney *U* test. G2 OTs comprised oligodendroglioma or oligoastrocytoma, whereas G3 OTs comprised anaplastic oligodendroglioma or anaplastic oligoastrocytoma. Statistical significance was established at the *P* < 0.05 level in all analyses.

**Results**

Based on histological diagnosis after surgery, 6 patients were assigned to the G3 group and 11 patients were assigned to the G2 group (Table 1). Of these 17 patients, 4 patients underwent stereotactic biopsy. Frequency of biopsy did not differ significantly between G3 and G2 groups (*P* = 0.25).

Interrater reliability was classified as “almost perfect” for both tumor and ANWM for each investigator: ICC<sub>(1,1)</sub> and ICC<sub>(1,k)</sub> for M.S. were 0.943 and 0.971 for tumor, and 0.961 and 0.980 for ANWM, respectively, and those for K.K. were 0.966 and 0.983 for tumor, and 0.942 and 0.970 for ANWM, respectively. Intrarater reliability was also classified as “almost perfect” for both tumor and ANWM in each test: ICC<sub>(2,1)</sub> and ICC<sub>(2,k)</sub> in the first test were 0.987 and 0.993 for tumor, and 0.973 and 0.987 for ANWM, respectively, and those in the second test were 0.971 and 0.985 for tumor, and 0.973 and 0.986 for ANWM, respectively. Absolute values of tumor lesions for each parameter in G3 and G2 groups are summarized in Table 2. Absolute values for all parameters varied widely, with no significant differences in any parameters identified between G3 and G2 groups. Normalized ratios for each parameter are summarized in Table 3. Significant differences between G3 and G2 groups were identified for *n*CBF and *n*CBV, with no significant differences in *n*MTT.

The cutoff for accuracy was defined as the point lying closest to the upper-left corner of the ROC curve.

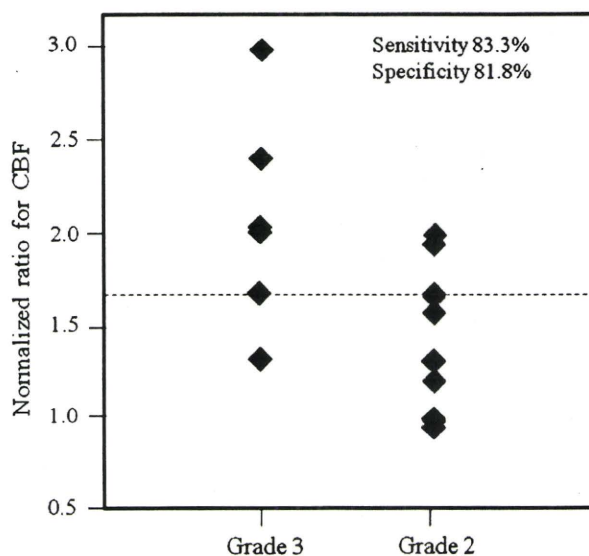
**Table 2** Absolute values for each parameter

	<i>r</i> CBF (ml/100 g/min)	<i>r</i> CBV (ml/100 g)	<i>r</i> MTT (s)
G3 ( <i>n</i> = 6)			
Range	10.8–27.0	1.9–3.2	6.8–10.8
Mean ± SD	18.3 ± 5.3	2.5 ± 0.5	8.5 ± 1.5
G2 ( <i>n</i> = 11)			
Range	8.8–23.3	1.3–2.6	7.0–12.2
Mean ± SD	15.5 ± 4.2	2.1 ± 0.4	8.8 ± 1.5
<i>P</i>	0.27	0.25	0.76

*SD* standard deviation

**Table 3** Normalized ratios for each parameter

	<i>n</i> CBF	<i>n</i> CBV	<i>n</i> MTT
G3 ( <i>n</i> = 6)			
Range	1.34–3.00	1.54–2.39	0.76–1.06
Mean ± SD	2.10 ± 0.57	1.92 ± 0.37	0.90 ± 0.12
G2 ( <i>n</i> = 11)			
Range	0.92–2.00	0.91–1.75	0.79–1.07
Mean ± SD	1.41 ± 0.38	1.26 ± 0.28	0.91 ± 0.09
<i>P</i>	0.01	0.004	0.76



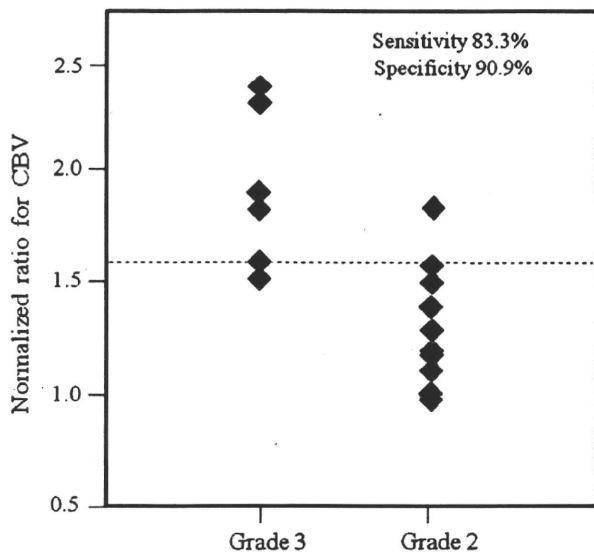
**Fig. 1** Relationship between *n*CBF value and WHO grading. Using a cutoff of 1.7 (dashed line), *n*CBV was ≥1.7 for 5 (83.3%) of 6 patients with G3, compared with <1.7 for 9 (81.8%) of 11 patients with G2

Sensitivity and specificity in predicting a diagnosis of G3 were 83.3% and 81.8% for *n*CBF (cutoff 1.7), and 83.3% and 90.9% for *n*CBV (cutoff 1.6) (Figs. 1, 2). Accuracy for predicting a diagnosis of G3 was higher with *n*CBV than with *n*CBF.

A comparison of *n*CBV was made between G3 OT, G2 OT, and diffuse astrocytoma (Table 4). Significant differences in *n*CBV were identified between G3 and G2 OTs (*P* = 0.009), and between G3 OT and diffuse astrocytoma (*P* = 0.02), whereas no significant difference was seen between G2 OT and diffuse astrocytoma (*P* = 0.36).

**Illustrative cases**

We now describe the cases of two patients for whom CTP provided useful information for predicting tumor grading. Gd-T1WI for case 6 showed glioma with no clear enhancement in the right frontal lobe (Fig. 3a). Using the



**Fig. 2** Relationship between *n*CBV value and WHO grading. Using a cutoff point of 1.6 (dashed line), *n*CBV was  $\geq 1.6$  for 5 (83.3%) of 6 patients with G3 and  $< 1.6$  for 10 (90.9%) of 11 patients with G2

**Table 4** Normalized ratio (mean  $\pm$  SD) for CBV in G3 OT, G2 OT, and diffuse astrocytoma

	<i>n</i> CBV
G3 OT ( <i>n</i> = 5)	1.99 $\pm$ 0.36
G2 OT ( <i>n</i> = 5)	1.16 $\pm$ 0.24
Diffuse astrocytoma ( <i>n</i> = 6)	1.35 $\pm$ 0.31

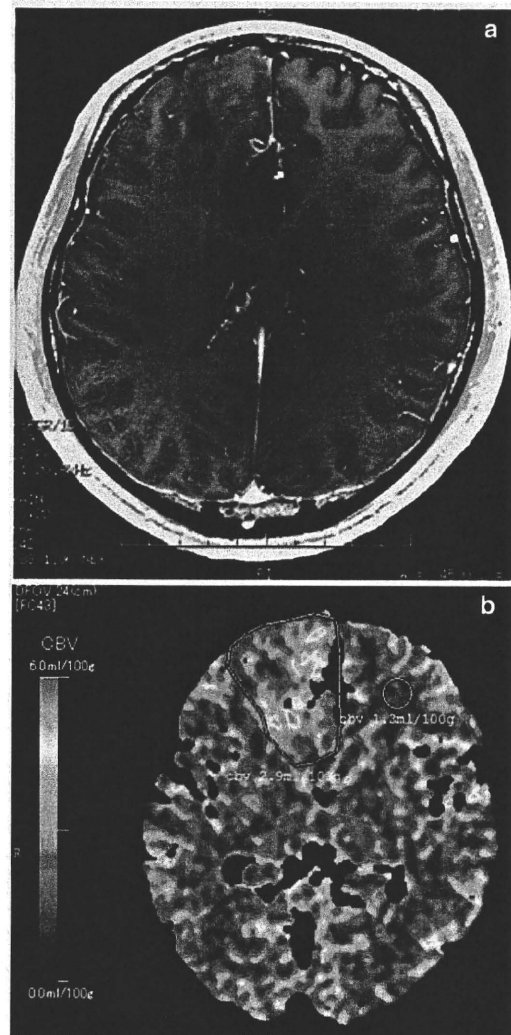
OT oligodendroglial tumors

VPE method, color mapping of CBV demonstrated large vessels of the cerebral surface to be successfully excluded (Fig. 3b). Color mapping of CBV depicted areas of hyperperfusion within the tumor. The *n*CBV for this case (*n*CBV = 2.3) was higher than the cutoff point. Tissue specimens obtained from gross total resection showed typical histological features of G3 anaplastic oligoastrocytoma.

Gd-T1WI for case 14 showed nonenhancing glioma of the right frontal lobe (Fig. 4a). The VPE method satisfactorily eliminated large vessels of the cerebral surface (Fig. 4b). On color mapping, areas of hyperperfusion seemed to be minor compared with those in case 6. The *n*CBV in this case (*n*CBV = 1.2) was lower than the cutoff point. After tumor resection, histological diagnosis was G2 oligoastrocytoma.

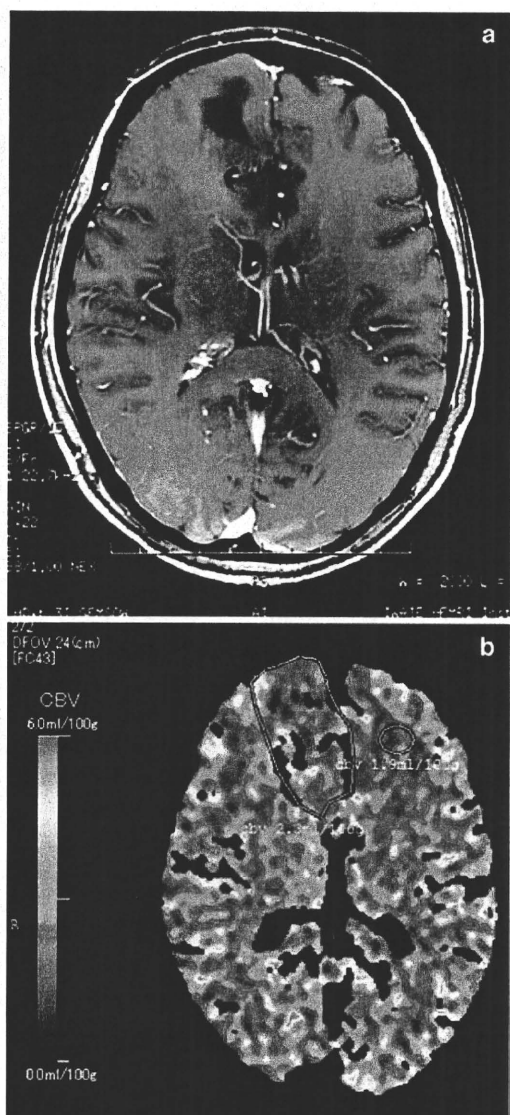
**Discussion**

Previous reports have documented that G3 gliomas make up 40–46% of nonenhancing gliomas on conventional MRI [3, 4]. Our finding of G3 tumors in 6 (35.2%) of 17 patients



**Fig. 3** Gd-T1WI (a) and color map of CBV (b) for case 6. Circle ROI covering the entire tumor bulk and ANWM localized on the nonpathological side

was close to this level. Thus, preoperative differentiation between G3 and G2 using MRI is often difficult. Biopsy or resection allowing histological diagnosis currently remain the basis for differentiation between G3 and G2 gliomas. However, neuroimaging can provide useful information on pathological diagnosis, particularly for patients who do not undergo biopsy or resection allowing histological diagnosis. Novel neuroimaging procedures other than routine MRI are thus desired. CTP and MRP provide reliable information on tumor vasculature, which can help to determine the extent of malignancy in glioma [8, 10, 22]. Although limitations of CTP include radiation dose and limited area of coverage compared with MRP, the linear relationship between attenuation changes on CT and tissue concentration of contrast medium and the lack of confounding sensitivity to flow artifacts allow CTP to



**Fig. 4** Gd-T1WI (a) and color map of CBV (b) for case 14. Circle ROI covering the entire tumor bulk and ANWM localized on the nonpathological side

potentially offer a more accurate representation of tissue microvasculature than similar MRP studies [8, 20]. Furthermore, CTP offers advantages such as measurement of quantitative absolute values, greater availability, fast scanning time, high spatial resolution, low cost, and the ability to use this technique for patients who cannot undergo MRI due to the presence of metallic materials in the body [14, 22, 27].

CBF derived from CTP has been suggested to show a tendency toward overestimation, compared with that derived from PET [28]. Since overestimation of CBF in CTP was attributable to the presence of large vessels on the cerebral surface, as contrast materials act as a nondiffusible

intravascular tracer in CTP unlike in PET, the VPE method has been proposed to eliminate flow in large vessels [25]. Accurate measurement of CBV contributes to accurate CBF and MTT, as these parameters are closely associated in the central volume principle as  $CBF = CBV/MTT$  [29]. We therefore used the VPE method in the present study. We think that optimal threshold differs according to the specific analysis software used for CTP. While VPE threshold was 8.0 ml/100 g in the report by Kudo et al. [25], we established a threshold of 6.0 ml/100 g, since high-CBV areas from cortical large vessels disappeared satisfactorily at this threshold for the analysis software used in our study. Another reason for using the VPE method is that OTs are commonly seen as superficially located tumors in the brain [30, 31]. Elimination of superficial large vessels at the cerebral surface, sulci, and cisterns thus seems warranted when CTP is performed for OTs.

In previous reports of CTP,  $rCBV$  values ranged from 2.3 to 8.87 ml/100 g for HGG and from 0.95 to 3.28 ml/100 g for LGG, differing significantly between HGG and LGG [13, 14, 20]. The present mean  $rCBV$  values in G3 and G2 (Table 2) agreed with previous findings. In addition, mean  $rCBV$  values in both G3 and G2 were less than half of 6.0 ml/100 g as VPE threshold. These findings suggest that the VPE method used in this study did not exclude tumor vessels along with other large vessels from CBV maps. While  $rCBV$  for G3 tended to be on the low side compared with previous reports, this could have resulted from the exclusion of patients with enhancing glioma as subjects in this study. Extravasation of contrast medium through the BBB in enhanced glioma may directly lead to increased CBV, due to the linear relationship between attenuation changes on CT and tissue concentration of contrast medium. Jain et al. [20] documented that  $rCBF$  and  $rCBV$  in nonenhancing G3 glioma do not differ significantly from those in nonenhancing G2 glioma, although sample size in that report was small. The present study with more subjects suggested that even nonenhancing G3 glioma retains more vascular density than G2, although the difference in  $rCBV$  between the two groups was minor (Table 2). However, this result might have been influenced by the disproportionate number of OTs in the G2 (42%) and G3 (83%) groups. If vascular density is significantly higher in G3 OT than in anaplastic astrocytoma, the large number of G3 OTs may have result in a high mean CBV for the G3 group in this study. This issue represents a definite limitation to the present study.

Concentration of contrast medium within the tumor might be subtly influenced by individual parameters such as body size and cardiac output volume, and differences in analytical software among institutes. We must emphasize the importance of estimation using normalized ratios, as



this allows us to ignore these differences. Ellika et al. [22] reported findings for *n*CBV using CTP in 19 patients with glioma, composed of a mixture of enhancing and nonenhancing WHO G1–G4 gliomas, and the utility of *n*CBF and *n*CBV for distinguishing HGG from LGG. They also documented *n*CBF and *n*CBV ranges of 0.78–3.75 and 1.5–3.7 in two patients with nonenhancing G3 glioma, and ranges of 1.26–1.48 and 0.94–1.72 in three patients with nonenhancing G2 glioma, respectively. Mean values of *n*CBF and *n*CBV in G3 and G2 in this study (Table 3) seemed close to the values reported by Ellika et al.

Radiographic grading of gliomas with conventional MRI is not always accurate, with 85.7% sensitivity for predicting HGG, even when including subjects with enhancing glioma [22]. When subjects are limited to those with nonenhancing gliomas, radiographic grading using conventional MRI should be more difficult. A previous report documented 85.7% sensitivity and 100% specificity for identifying HGG using *n*CBV [22]. In the present study, CTP could distinguish nonenhancing G3 glioma from nonenhancing G2 glioma with 83.3% sensitivity and 90.9% specificity using *n*CBV (Fig. 2). This was superior to the results for *n*CBF. Accuracy for distinguishing G3 using *n*CBV in the present study was by no means inferior to that reported by Ellika et al. [22], but subjects in this study were limited to those with nonenhancing glioma. These results suggest that *n*CBV in CTP is useful as an auxiliary examination in addition to routine neuroimaging for predicting the grade of malignancy in nonenhancing gliomas.

Previous studies using MRP have documented higher relative CBV in OT than in other gliomas [32–34]. Lev et al. [33] suggested that OTs tend to appear as high blood volume lesion on MRP, without respect to tumor grade. Two reports using MRP documented that G2 OTs show higher relative CBV than diffuse astrocytoma [32, 34]. Also in a report using CTP by Narang et al. [15], G2 OTs showed a trend towards higher CBV than G2 astrocytic tumors, although no significant difference was found, and no significant difference in CBV between G3 OTs and G2 OTs was identified. Those reports explained the high relative CBV of OT by a hypothesis based on the specific histological features of fine capillary networks [33]. Furthermore, those reports suggested that grading malignancy may be difficult when patients with OT are included, due to a high relative CBV. In the present study, no significant difference in *n*CBV was seen between diffuse astrocytoma and G2 OT, whereas significant differences were found between G3 OT and G2 OT. The difference between the reports described above and the present investigation might be explained by differences between MRP and CTP, and by the use of the VPE method in this study. Signal changes in dynamic susceptibility contrast (DSC) MRI for MRP do not depend on only the concentration of contrast material,

but also on T2\* or T2 relaxation rates, which are affected by calcified foci and hemorrhage within tumor tissue. These histological features are commonly seen in OTs. DSC signals might thus be higher in OTs than in diffuse astrocytoma, even when the microvascular densities are comparable. The VPE method may have eliminated pixels of high-CBV vessels in OTs, if vascular density in OTs is significantly higher than that in diffuse astrocytoma. However, exclusion of large vessels at the cerebral surface and sulci from CTP maps is important, as OTs grow superficially in the brain. Cha et al. [32] explained for reason of high relative CBV for OTs in MRP by the predominant cortical location in addition to distinct vascular pattern in OTs. We think that CTP with the VPE method is useful for simple malignancy grading in subjects with OTs. Conversely, MRP offers potential advantages for the diagnosis of OTs. However, CTP should not be performed additionally to MRP if the purpose in examination is achieved by MRP, as CTP retains drawbacks such as radiation dose and iodine contrast medium.

The present study possesses some limitations regarding the interpretation of study results. First, the number of patients in this study was small, with remarkably fewer cases of anaplastic astrocytoma compared with OT in G3, as mentioned above. Further investigation including a larger number of cases of anaplastic astrocytoma is needed. A second limitation is the possible discrepancy between histological diagnosis and the region of highest CBV within the tumor. The region targeted for stereotactic biopsy was not rigorously transferred from the region of highest *n*CBV (“hot spots”). However, risk of histological misdiagnosis caused by sampling error during biopsy might be negligible, since the number of patients who underwent biopsy was small in both G3 and G2, and no significant difference in frequency of biopsy was seen between groups. In patients who underwent tumor resection, histological diagnosis was not made using tissue specimens rigorously corresponding to “hot spots.” However, histological diagnosis based on the most malignant histological features should be closely associated with high CBV, as increased malignancy is associated with higher vascular density. CTP with a 16-row multidetector CT scanner, covering only four contiguous 8-mm-thick sections, did not cover the entire tumor bulk in some patients. For those patients, histological diagnosis was made using tumor tissues corresponding to the area depicted in CTP. A third limitation was that data calculated from CTP in this study were not the highest CBV values for a small ROI placed in “hot spots” on a color map, but rather were mean values for a large ROI covering the entire tumor bulk. This issue also influences the second limitation. We thought that the simple protocol in this study, combining absolute values as a mean in a large ROI with histological diagnosis from the

area of the most malignant features, is suitable for application in clinical practice, as tissue sampling error of regions corresponding to a small ROI can be avoided. High ICC in inter- and intrarater reliabilities showed that the protocol used in this study offers high reproducibility.

## Conclusions

We performed CTP combined with the VPE method for 17 patients, to clarify whether CTP can accurately differentiate between G3 and G2 nonenhancing glioma. Our results showed that *n*CBV from CTP was highly accurate in differentiating G3 from G2 nonenhancing gliomas. The most important result was that CTP enabled differentiation between G3 and G2 nonenhancing OTs. CTP combined with the VPE method offers a useful technique for differentiating between G3 and G2 in nonenhancing gliomas.

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