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Differentiating the histologic grades of gliomas preoperatively using amide proton transfer-weighted (APTW) and intravoxel incoherent motion MR imaging

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Abstract

The purpose of this work was to investigate the diagnostic performance of amide proton transfer-weighted (APTW) and intravoxel incoherent motion (IVIM) MRI in the preoperative grading of gliomas. Fifty-one patients with suspected gliomas were recruited and underwent a preoperative MRI exam that included APTW and IVIM sequences. All cases were confirmed by postsurgical histopathology. APTW signal intensity, true diffusion coefficient (D), perfusion fraction (f), and pseudo-diffusion coefficient (D*) were applied to assess the solid tumor component and contralateral normal-appearing white matter. Relative APTW signal intensity (rAPTW) was also used. Independent-samples and paired-samples *t*-tests were used to compare differences in MRI parameters between low-grade gliomas (LGGs) and high-grade gliomas (HGGs) groups. The diagnostic performance was assessed with receiver operating characteristic curve. 26 patients were pathologically diagnosed as LGG, and 25 diagnosed as HGG. APTW, rAPTW, and f values were significantly larger (all $p < 0.001$), while D was significantly lower ($p < 0.001$) in the HGG group than in the LGG group. There was no significant difference between D* values for the two groups. rAPTW had an area under the curve (AUC) of 0.957, with a sensitivity of 100% and a specificity of 84.6%, followed by APTW, f, D and D*. The combined use of APTW and IVIM had the best diagnostic performance, with an AUC of 0.986. In conclusion, APTW and IVIM, as two promising supplementary sequences for routine MR imaging, could be valuable in differentiating LGGs from HGGs.

Graphical Abstract

APTW imaging can generate image contrast mainly related to endogenous cellular proteins in tissue, and IVIM MR imaging can separate water molecular diffusion from microcirculation. 51 glioma patients were recruited to investigate the diagnostic performance of APT and IVIM MR

imaging. Our results show that these supplementary MRI methods are valuable in differentiating low- from high-grade gliomas.

Keywords

Amide proton transfer; intravoxel incoherent motion; glioma; preoperative grading

1 INTRODUCTION

Gliomas are the most common primary tumor in the central nervous system (CNS). According to a statistical report conducted by the Central Brain Tumor Registry of the United States¹, primary CNS tumors ranked first in children and adolescents (ages 0–19), and seventh in adult (ages 20+) in average annual incidence rates for all human cancers. An accurate preoperative grading of glioma is a very important issue in the treatment of gliomas, since the therapeutic strategy and prognosis depend greatly on the grade. Routine gadolinium (Gd)-enhanced MRI is a standard protocol for glioma imaging in the clinic. However, Gd exposure carries the risk of renal insufficiency². Moreover, glioma patients require frequent MRI scans. Recent research^{3, 4} has revealed that linear Gd-based contrast agents are prone to deposit in the dentate nucleus and the globus pallidus. Therefore, Gd-free MRI modalities have some advantages over Gd-enhanced MRI.

Amide proton transfer-weighted (APTW) imaging, a specific kind of chemical exchange-dependent saturation transfer (CEST) MRI, can be used to detect the amide protons of endogenous, low-concentration mobile proteins and peptides in tissue^{5, 6}. APTW imaging has been introduced into the clinic for imaging of brain tumors^{7–10}, breast cancer^{11, 12}, lung cancer^{10, 13} and prostate cancer¹⁴, as well as non-tumorous diseases such as stroke^{15–17}, Parkinson's disease¹⁸ and ventral hernia¹⁹. Previous studies^{7, 8} employing APTW imaging suggested that APTW imaging as an MRI biomarker of malignant gliomas could help identify the most actively proliferating components of tumors, distinguish the viable, actively growing tumor from radiation necrosis, and predict tumor response to therapy.

Several preliminary studies^{20–24} have shown that APTW signal intensity was a new promising imaging biomarker in differentiating glioma grade.

Diffusion-weighted MRI (DWI) can produce *in vivo* image contrasts of biologic tissues based on the Brownian motion of water molecules²⁵. The apparent diffusion coefficient (ADC) is the most important parameter calculated from DWI, and has been widely used to characterize glioma, both preoperatively and postoperatively. However, ADC generated by a conventional, mono-exponential DWI model includes the capillary blood microcirculation (perfusion); therefore, ADC is inherently overestimated and may not correctly reflect water molecular diffusion *in vivo*. To separate water molecular diffusion from microcirculation via a single acquisition scheme, Le Bihan *et al.* proposed intravoxel incoherent motion (IVIM) imaging to specifically visualize the microscopic motion of water²⁶. IVIM imaging, using multiple b values, has previously been used in stroke, white matter disease, brain tumors, pancreas, prostate, breast cancers, and other cancers²⁵. Specially, several studies^{27–31} have applied IVIM imaging to explore the correlation between IVIM parameters and histologic grade in gliomas.

In this study, 51 patients with glioma were enrolled and underwent a preoperative MRI exam. The hypothesis of this confirmatory study was that the two aforementioned non-invasive advanced MRI modalities, protein-based APTW and bi-exponential model-based IVIM imaging could be valuable in grading gliomas.

2 METHODS

Patients

This prospective study was approved by the local ethics committee, and written, informed consent was obtained from all patients. From July 2015 to June 2016, 51 patients, of whom 21 were female (mean age, 38.1 ± 13.4 ; age range, 18–63), and 30 were male (mean age, 42.9 ± 14.3 ; age range, 19–63), were admitted to the study. Patients who met the following criteria were recruited: (1) no younger than 18 years of age; (2) a suspected intracranial occupying lesion in the supratentorial region on routine MR imaging. The exclusion criteria were as follows: (1) contraindications for MR scanning; (2) severe motion artifacts. Glioma grade was determined based on the 2007 WHO classification of tumors of the CNS. The numbers of patients with grade-II, -III, and -IV gliomas were 26, 14, and 11, respectively, namely, 26 low-grade gliomas (LGGs) and 25 high-grade gliomas (HGGs). The histological types of gliomas were as follows: 13 oligodendrogliomas, 13 oligoastrocytomas, 5 anaplastic astrocytomas, 9 anaplastic oligoastrocytomas, and 11 glioblastoma multiforme (GBM).

MRI protocols

All cases were examined on a Philips 3.0T whole body scanner (Achieva, 3.0T; Philips Medical Systems, Best, The Netherlands) with bore size 94 cm, gradient strength 80 mT/m, and slew rate 200 T/m/s. A SENSE 16-multichannel receiver head coil was used for the head scanning. Our scanning protocols were performed to obtain axial imaging using the following sequences: T1-weighted imaging (T1W; TR/TE = 400/20 ms, matrix = 512×512 ,

field of view (FOV) = $230 \times 230 \text{ mm}^2$, slice thickness = 6 mm); T2-weighted imaging (T2W; TR/TE = 2800/105 ms, matrix = 512×512 , FOV = $230 \times 230 \text{ mm}^2$, slice thickness = 6 mm); fluid-attenuated inversion recovery imaging (FLAIR; TR/TE = 8000/204 ms, matrix = 512×512 , FOV = $230 \times 230 \text{ mm}^2$, slice thickness = 6 mm); APT; IVIM; and Gd-enhanced T1-weighted (Gd-T1W) imaging. Gadopentetate dimeglumine (0.2 ml/kg body weight; Magnevist; Bayer Schering, Guangzhou, China) was finally injected as a bolus via an antecubital vein at a speed of 2.0 ml/sec to acquire axial Gd-T1W images.

APTW and IVIM imaging parameters

Two-dimensional single slice APTW imaging was obtained using a fat-suppressed, turbo-spin-echo pulse sequence, with a pulse-train radiofrequency saturation scheme (duration = $200 \text{ ms} \times 4$; inter-pulse delay 10 ms; power $2 \mu\text{T}$). The detailed parameters were as follows: TR/TE = 3000/11 ms; FOV = $230 \times 230 \text{ mm}^2$; slice thickness = 6 mm; matrix = 128×128 (reconstructed to 400×400); voxel size = $1.80 \times 1.80 \times 6.00 \text{ mm}^3$ ($0.58 \times 0.58 \times 6.00 \text{ mm}^3$, reconstructed); and sensitivity-encoding factor = 2. A multi-offset, multi-acquisition APTW imaging acquisition protocol was used [31 offsets = 0, ± 0.25 , ± 0.5 , ± 0.75 , ± 1 , ± 1.5 , ± 2 , ± 2.5 , ± 3 (2), ± 3.25 (4), ± 3.5 (8), ± 3.75 (4), ± 4 (2), ± 4.5 , ± 5 , ± 6 ppm; the values in parentheses are the number of acquisitions, which was one, if not specified]. The higher number of acquisitions between ± 3 and ± 4 ppm was used to increase the signal-to-noise ratio of the APTW images. The total scan time was 3 min 12 sec.

IVIM imaging was based on a diffusion-weighted, single-shot EPI pulse sequence, with the following parameters: TR/TE = 1985/75 ms, FOV = $230 \times 230 \text{ mm}^2$; slice thickness = 6 mm; reconstruction matrix = 192×192 ; in-plane resolution = $1.52 \times 1.90 \text{ mm}^2$ (acquired) or $1.20 \times 1.20 \text{ mm}^2$ (reconstructed) and number of signal averages = 3. Ten b values (0, 10, 20, 40, 80, 130, 200, 400, 700 and 1000 sec/mm^2) in three orthogonal directions were chosen in order to cover both the initial pseudodiffusion decay ($b < 200 \text{ sec/mm}^2$) and the molecular diffusion decay ($b \geq 200 \text{ sec/mm}^2$). A local shim box covering the whole brain was applied to minimize susceptibility artifacts. The total scan time was 3 min 55 sec.

Imaging postprocessing and analyzing

APTW raw image data were processed using the Interactive Data Language (IDL; ITT Visual Information Solutions, Boulder, CO, USA) to obtain APTW pseudo-color images. APTW imaging was quantified through the magnetization transfer ratio asymmetry (MTR_{asym}) analysis with respect to the water resonance. The calculated MTR_{asym} (3.5 ppm) image, using the B_0 -corrected MT-spectrum data at the offset of ± 3.5 ppm, was usually called the APTW image²¹. Relative APTW ($\text{rAPTW} = \text{APTW}_{\text{tumor}} - \text{APTW}_{\text{CNAWM}}$) was also used in our analysis. The bi-exponential IVIM model was applied to measure the true diffusion coefficient (D), perfusion fraction (f), and pseudo-diffusion coefficient (D^*), using the software provided by Philips (PRIDE DWI Tool, version 1.5, Philips Healthcare).

Each case was analyzed by two experienced neuroradiologists independently. Similar to the previous studies^{7, 20, 32}, five small approximately circular regions of interest (ROIs; diameter, 10–20 pixels on APTW) were carefully placed manually on areas of T2W hyperintensity and gadolinium enhancement in the co-registered T2W and Gd-enhanced

T1W images³³, respectively, for each case. If the gadolinium enhancement is not available, the procedure was primarily based on the T2W hyperintensity). The maximum APTW and f , and minimum D and D^* from all ROIs for each patient were recorded (Fig. 1). Areas of hemorrhage, liquefactive necrosis, cystic changes, and cerebrospinal fluid-fill^{32, 34} were always avoided. The contralateral normal-appearing white matter (CNAWM) was also analyzed for comparison. r APTW was defined as the difference of the $APTW_{\text{tumor}}$ and $APTW_{\text{CNAWM}}$ ^{35–38}.

Statistical analysis

All measured values were expressed by the mean $\pm$ standard deviation. The objectivity reliability for all parameters between two observers was analyzed by the Cronbach alpha and the standardized Cronbach alpha. The Cronbach alpha and the standardized Cronbach alpha > 0.75 indicated an excellent reliability. APTW, r APTW, D , f , and D^* were compared between the LGG and HGG groups by independent-sample t -test. A paired-sample t -test was applied to compare the difference between the tumor and CNAWM parameters for the LGG and HGG groups respectively. The one-way analysis of variance (ANOVA) was used to compare grade-II, -III, and -IV gliomas. The Levene's test was applied to test homogeneity of variance. The LSD- t test was used when the equal variance were assumed, while Dunnett T3 test was used when the equal variance were not assumed. The diagnostic accuracy of each parameter was evaluated by the receiver operating curve (ROC), area under the curve (AUC), and corresponding cut-off value. AUC values < 0.7 , 0.7 – 0.9 , and > 0.9 indicated low, medium, and high diagnostic performance respectively. The logistic regression was applied to evaluate the diagnostic performance of the combination indices. Statistical analyses were performed on SPSS 20.0 (IBM SPSS Statistic version 20, Chicago, IL, USA) and MedCalc 15.2.2 (MedCalc Software bvba, Ostend, Belgium). Two-sided $p < 0.05$ were considered to be statistically significant.

3 RESULTS

All the parameters measured by two observers were highly consistent, with all Cronbach alphas and standardized Cronbach alphas larger than 0.9 (Table 1).

Descriptive statistics regarding demographic data obtained from two groups were summarized in Table 2. In these 51 patients, males had a higher morbidity than females (30:21, ratio 1:0.7) ($p = 0.023$). The mean age of HGG patients was higher than that of LGG patients ($p < 0.05$).

All measured values and the differences within and between the two groups were shown in Table 3, and three representative cases were shown in Figs. 2–4. For the LGG group, $APTW_{\text{tumor}}$ and D_{tumor} values were significantly larger than the $APTW_{\text{CNAWM}}$ and the D_{CNAWM} ($p < 0.001$), and there was no statistical difference for f and D^* . For the HGG group, $APTW_{\text{tumor}}$, f_{tumor} and D_{tumor} were significantly higher and D^*_{tumor} was significantly lower than those in the CNAWM, all p values were less than 0.001. When comparing these two groups, APTW, r APTW, and f values in tumors were significantly larger, while D was significantly lower ($p < 0.001$) in the HGG group than in the LGG group ($p < 0.001$). There was no significant statistical difference between D^* values in the two

groups ($p > 0.05$). Except APTW, none of these parameters for the CNAWMs was different in the two groups ($p > 0.05$).

Table 4 showed the comparisons of MRI parameters for WHO grade-II, -III, and -IV gliomas. Comparing to grade-II gliomas, grade-III gliomas had larger APTW, rAPTW, f, and D^*_{CNAWM} , and lower D and $\text{APTW}_{\text{CNAWM}}$ ($p < 0.05$), while there were no statistical difference for D^* , D_{CNAWM} , and f_{CNAWM} ($p > 0.05$). Comparing to grade-II gliomas, grade-IV gliomas had larger APTW, rAPTW, f, and lower D ($p < 0.05$), while there were no statistical difference for D^* , $\text{APTW}_{\text{CNAWM}}$, D_{CNAWM} , f_{CNAWM} and D^*_{CNAWM} ($p > 0.05$). There were no statistical difference for all measured parameters within WHO grade-III and -IV gliomas ($p > 0.05$).

Table 5 and Fig. 5 showed the diagnostic performance of APTW and IVIM parameters in differentiating HGG from LGG. The results of the ROC analysis showed that rAPTW had an AUC of 0.96, with a sensitivity of 100%, specificity 84.6%, followed by APTW, f, D, and D^* . The AUC, sensitivity, and specificity of the combination of rAPTW, D and f were 0.986, 96.0% and 96.2%, respectively.

4 DISCUSSION

In this study, five APTW and IVIM parameters (APTW, rAPTW, D, f, and D^*) were used to explore the diagnostic performance in differentiating between low- and high-grade gliomas. Demographically, males tended to have a higher morbidity than females. The mean age of LGG cases was lower, while HGG more often attacked the elderly. These findings were highly consistent with the former epidemiologic study¹. Postsurgical pathology is the gold standard for grading glioma. Both histology features (cellularity, vascularity, heterogeneity and mitotic activity) and molecular genetic features are crucial for glioma grading. APTW, rAPTW, D, and f, to some extent, were assumed to reflect some of the aforementioned histopathological properties.

In our study, minimum D showed a moderate diagnostic performance. Its value was lower in HGG than in LGG, presumably because of the higher cell density, increased cell membranes, extracellular space volume, and fraction of intracellular space in HGG, which thus provides more restriction of water movement^{30, 39}. Thus far, both human and animal studies have revealed that minimum ADC correlated negatively with tumor cellularity, and a very low pretreatment minimum ADC is usually associated with aggressive malignant tumors^{39–41}. However, several studies^{27, 29, 30} have demonstrated that minimum D is smaller and more precise than minimum ADC, mainly because any ADC estimated by a mono-exponential model with two b values (usually 0 and 1000 sec/mm²) in clinical studies would miss the curvature and include perfusion effects, which would result in an overestimation of ADC. Given this, we infer that the minimum D correlates negatively with tumor cellularity and malignancy. As to D^* , because of its low signal-to-noise ratio, which was easily affected by the circulation⁴², there were no statistical differences among any comparison, and, in fact, a study in the liver showed a similar less reproducible D^* value⁴³.

Protein makes up about 18% of the total mass of a cell in mammals, and executes almost all the cellular functions. These proteins can be divided roughly into two types, semi-solid proteins and mobile proteins. The latter are the basis of APTW imaging. The observed APTW hyperintensity in tumor is mostly dominated by the increased amide proton concentration related to mobile cellular proteins (such as cytosolic proteins, many endoplasmic reticulum proteins, and secreted proteins⁴⁴, but an extra contribution from the possibly alkaline intracellular pH may exist. We have demonstrated that APTW in HGG was higher than that in LGG or in CNAWM, which is consistent with the results of previous researches^{5, 21, 45}. Previous studies using MR spectroscopy *in vivo* and MRI-guided proteomics revealed that HGGs are highly cellular tumors and have a higher cellular content of proteins and peptides. Since the protein concentration and cellularity were linked, we infer that the high cellularity was related to high intensity on APTW images. Notably, Togao *et al.*²⁰ and Jiang *et al.*²⁴ found positive correlations between APTW and Ki-67 and cell density.

Another important diagnostic factor in pathology is high vascularity. Neoangiogenesis is an important property of malignant tumors, and higher blood vessel numbers indicate a higher glioma grade. Many studies chose contrast-enhanced measurements of cerebral blood volume (CBV) as a marker to reflect glioma neoangiogenesis. An increased CBV has been reported in glioblastoma compared to low-grade glioma^{27, 30}. Technically, *f* is based on the microvascular network structure, and thus, it mainly reflects the vascular compartment. In our study, *f* in HGG was about 2–3 times higher than that in LGG. In addition, mean *f* in LGG was slightly higher (but with no statistical significance) than that in the CNAWM, and this may explain the slight or non-enhancement in LGGs. Several studies have demonstrated that the *f* value showed a positive correlation to CBV. Therefore, *f* may be a promising surrogate parameter for the CBV²⁵ in the future.

Due to the inherent heterogeneity of glioma, the location and size of ROI placement can be challenging. In this study, the ROI selection was primarily based on the co-registered T2W and Gd-enhanced T1W images. When there was no contrast enhancement, only T2W hyperintensity was used to select the ROIs. We placed five small approximately circular ROIs on the maximum slice of the tumor to obtain maximum APTW and *f*, and minimum *D* and *D**. We speculate that the maximum APTW and *f*, and minimum *D* and *D** regions represent the most active part of the tumor, and could reflect tumor core portions and the actual pathological grade. From this aspect, these two functional modalities showed large advantages for routine MR imaging in grading gliomas.

The APTW images constructed with the MTR_{asym} (3.5 ppm) were used in this study²¹. In vivo, multiple pools on both sides of the water peak may interfere when applying the MTR asymmetry approach. Notably, according to previous research, the APTW intensity has multiple contributions including the upfield nuclear Overhauser effect and some conventional semisolid MT asymmetry^{46–48}. To solve this problem, several alternative approaches, such as the Lorentzian difference (LD) analysis^{17, 48}, multiple-pool Lorentzian fit^{49, 50}, three-point method^{51, 52}, and extrapolated semisolid magnetization transfer reference (EMR)^{53, 54}, were proposed and applied in patients. However, a few recent studies showed that, for the saturation parameters used in this study, the APT effect would be the

major contributor to the relative APTW image signal in tumor with respect to normal brain tissue^{36–38}.

There are still some limitations to this study. (1) The sample size of the study is relatively small, and larger sample size studies are still needed in the future. (2) A bi-exponential IVIM model was used in this study, but it is still not the perfect model to simulate the actual situation in the human body. A more optimized model needs to be developed in the future to solve this issue. (3) The two-dimensional APTW scan covered only one slice, and the single slice acquisition might miss the maximum diameter or largest viable tumor parts in the present study. To address this issue, 3D APTW scanning should be introduced in the future^{9, 55}. (4) Finally, the performed ROI approach is relatively hard to reproduce, although areas of hemorrhage, liquefactive necrosis, cystic changes, and cerebrospinal fluid-fill can be well avoided. On the other hand, it would be desirable to use the histogram analysis of the whole tumor area as displayed on T2W images (since both high- and low-grade tumors display hyperintense on T2W)⁵⁶.

In conclusion, APT and IVIM are two promising molecular and functional imaging modalities that could assess glioma at the cellular and molecular level. Our results showed that they could provide more precise diagnostic information in the clinical settings. These important supplementary methods would be valuable in differentiating low- from high-grade gliomas.

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Abbreviations used

ADC	apparent diffusion coefficient
APT	amide proton transfer
APTW	amide proton transfer-weighted
AUC	area under the curve
CBV	cerebral blood volume
CNAWM	contralateral normal-appearing white matter
CNS	central nervous system
FOV	field of view
HGG	high-grade glioma
IVIM	intravoxel incoherent motion
LGG	low-grade glioma

rAPTW relative amide proton transfer-weighted

ROI region of interest

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Figure 1.

Examples of the placement of ROIs. Five small approximately circular ROIs (red circles) were placed based on co-registered T2W and Gd-enhanced T1W images.

Figure 2.

A 24-year-old male with an oligodendroglioma (WHO II) in the left frontal lobe. The non-Gd-enhanced tumor core had a significant hyperintensity on the D-map, while on D*, f, and APTW images, there was a relatively homogeneous signal intensity (white arrow). H&E staining (original magnification, $\times 200$) showed a relatively low cell density with microcytic and less nuclear atypical tumor cells.

Figure 3.

A 59-year-old male with an anaplasia oligodendroglioma (WHO III) in the right parietal lobe. T1WI and T2WI demonstrated a large mass in the right parietal lobe with heterogeneous intensity, unenhanced on the Gd-T1W image. The D value in the solid part of the tumor was $1.02\text{--}1.33 \times 10^{-3} \text{ mm}^2/\text{s}$, which was close to the cut-off value ($1.15 \times 10^{-3} \text{ mm}^2/\text{s}$). The f map and APTW images showed significant hyperintensity in the lesion, 9.8–16.0% and 2.41–3.24%, respectively, compared to the cut-off value (7.60% and 2.34%). The tumor was almost isointense on the D* map. H&E staining (original magnification, $\times 200$) showed increased cellularity, more nuclear atypia, and pleomorphism.

Figure 4.

A 26-year-old male with a gliosarcoma (WHO IV) in the right parietal lobe and the left frontal lobe. T1WI and T2WI images showed two oval masses on the right and left hemicerebrum. The mass in the right was unenhanced, while the left was obviously enhanced. They were both hypointense ($0.65\text{--}0.69 \times 10^{-3} \text{ mm}^2/\text{s}$) on the D-map and hyperintense (2.47–3.12%) on the APTW image, and isointense on the f and D* maps. H&E staining (original magnification, $\times 400$) showed dense packed long bundles of spindle cells.

Figure 5.

Diagnostic performance of APT and IVIM parameters in differentiating HGG from LGG. For the single parameter, rAPTW showed the best diagnostic performance, with an AUC of 0.957, followed by APTW 0.935. *f* and *D* showed moderate diagnostic performance with AUCs = 0.826 and 0.765, respectively. The combination of rAPTW, *D*, and *f* showed the best diagnostic performance, with an AUC of 0.986. *D** showed the lowest diagnostic performance, with an AUC = 0.603.

Table 1

Reliability analysis for the two observers

	Cronbach alpha	Standardized Cronbach alpha
APTW _{tumor}	0.984	0.986
APTW _{CNAWM}	0.933	0.941
rAPTW	0.979	0.982
D _{tumor}	0.951	0.952
f _{tumor}	0.948	0.952
D* _{tumor}	0.944	0.945
D _{CNAWM}	0.919	0.926
f _{CNAWM}	0.918	0.925
D* _{CNAWM}	0.924	0.930

Table 2

Demographic data for all patients

Variable	LGG	HGG	<i>p</i>
Sex distribution			0.023 *
No. of Male	11	19	—
No. of Female	15	6	—
Mean age (y)	36.4 ± 11.3	45.7 ± 15.1	0.017

Note:

* Comparison of morbidity within male and female for all gliomas (including LGG and HGG)

Table 3

Comparisons of MRI parameters for the LGG and HGG groups

	LGG			HGG			p^c
	tumor	CNAWM	p^a	tumor	CNAWM	p^b	
APTW (%)	1.98 ± 0.58	0.59 ± 0.20	< 0.001	2.77 ± 0.35	0.45 ± 0.17	< 0.001	< 0.001
rAPTW	1.39 ± 0.57			2.31 ± 0.37			< 0.001
f (%)	6.22 ± 6.75	4.06 ± 1.97	0.107	14.73 ± 5.90	3.44 ± 1.62	< 0.001	< 0.001
D ($\times 10^{-3}$ mm ² /s)	1.31 ± 0.36	0.71 ± 0.03	< 0.001	0.97 ± 0.23	0.72 ± 0.08	< 0.001	< 0.001
D* ($\times 10^{-2}$ mm ² /s)	7.61 ± 6.13	8.91 ± 3.80	0.189	5.17 ± 4.75	10.87 ± 5.35	< 0.001	0.121

Note:

^aFor parameters in tumors and CNAWM within the LGG group;

^bFor parameters in tumors and CNAWM within the HGG group;

^cFor parameters in tumors between the HGG and LGG groups.

Table 4

Comparisons of MRI parameters for WHO grade-II, -III and -IV gliomas

	Grade-II	Grade-III	Grade-IV	p_{II-III}	p_{II-IV}	p_{III-IV}
APTW (%)	1.98 ± 0.58	2.71 ± 0.39	2.84 ± 0.30	< 0.001	< 0.001	0.524
rAPTW (%)	1.39 ± 0.57	2.26 ± 0.40	2.37 ± 0.32	< 0.001	< 0.001	0.581
D (× 10 ⁻³ mm ² /s)	1.31 ± 0.36	0.97 ± 0.22	0.98 ± 0.26	0.001	0.004	0.923
f (%)	6.22 ± 6.75	14.68 ± 6.36	14.79 ± 5.55	< 0.001	0.001	0.965
D* (× 10 ⁻² mm ² /s)	7.61 ± 6.13	5.20 ± 5.48	5.14 ± 3.90	0.197	0.224	0.980
APTW _{CNAWM} (%)	0.59 ± 0.20	0.45 ± 0.14	0.46 ± 0.21	0.024	0.063	0.826
D _{CNAWM} (× 10 ⁻³ mm ² /s)	0.71 ± 0.03	0.71 ± 0.06	0.73 ± 0.10	0.868	0.431	0.570
f _{CNAWM} (%)	4.06 ± 1.97	3.35 ± 1.53	3.56 ± 1.79	0.245	0.441	0.785
D* _{CNAWM} (× 10 ⁻² mm ² /s)	8.91 ± 3.80	12.56 ± 5.91	8.99 ± 5.76	0.018	0.912	0.051

Table 5

Diagnostic performance of MRI parameters in differentiating HGG from LGG

	Cut-off value	Sensitivity (%)	Specificity (%)	AUC
APTW (%)	> 2.34	100	88.5	0.935
rAPTW (%)	> 1.71	100	84.6	0.957
D ($\times 10^{-3}$ mm ² /s)	1.15	84.0	65.4	0.765
f (%)	> 7.60	92.0	80.8	0.826
D* ($\times 10^{-2}$ mm ² /s)	6.12	72.0	57.7	0.603
rAPTW + D	—*	96.0	88.5	0.975
rAPTW + f	—*	96.0	92.3	0.957
rAPTW + D + f	—*	96.0	96.2	0.986

Note:

* The combined cut-off values were the same as the individual index above.