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Amide proton transfer imaging to discriminate between low- and high-grade gliomas: added value to apparent diffusion coefficient and relative cerebral blood volume

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Abstract

Objectives—To evaluate the added value of amide proton transfer (APT) imaging to the apparent diffusion coefficient (ADC) from diffusion tensor imaging (DTI) and the relative cerebral blood volume (rCBV) from perfusion magnetic resonance imaging (MRI) for discriminating between high- and low-grade gliomas.

Methods—Forty-six consecutive adult patients with diffuse gliomas who underwent preoperative APT imaging, DTI and perfusion MRI were enrolled. APT signals were compared according to the World Health Organization grade. The diagnostic ability and added value of the APT signal to the ADC and rCBV for discriminating between low- and high-grade gliomas were evaluated using receiver operating characteristic (ROC) analyses and integrated discrimination improvement.

Results—The APT signal increased as the glioma grade increased. The discrimination abilities of the APT, ADC and rCBV values were not significantly different. Using both the APT signal and ADC significantly improved discrimination vs. the ADC alone (area under the ROC curve [AUC], 0.888–0.910; $P=0.007$), whereas using both the APT signal and rCBV did not improve discrimination vs. the rCBV alone (AUC, 0.927–0.923; $P=0.222$).

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Conflict of interest

The scientific guarantor of this publication is Sung Soo Ahn. The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Compliance with ethical standards

No complex statistical methods were necessary for this paper. Institutional review board approval was obtained. Written informed consent was waived by the institutional review board. No study subjects or cohorts have been previously reported. Methodology: retrospective, observational, performed at one institution.

Conclusions—APT imaging may be a useful imaging biomarker that adds value to the ADC for discriminating between low- and high-grade gliomas.

Keywords

Amide proton transfer imaging; Chemical exchange saturation transfer; Magnetic resonance imaging; Brain tumour; Glioma

Introduction

The ability to discriminate between low- and high-grade gliomas is clinically relevant, since the prognosis and treatment strategies differ according to the glioma grade [1]. Surgical resection followed by concurrent chemoradiation with temozolomide is the standard treatment for glioblastomas [1], and undergrading high-grade gliomas as low-grade gliomas can lead to insufficient and less-aggressive treatment. The gold standard for glioma grading is surgical sampling, an invasive procedure that carries the risk of sampling from a suboptimal site, where the intratumoral heterogeneity of high-grade gliomas can result in undergrading. Thus, advanced magnetic resonance techniques like dynamic susceptibility contrast-enhanced (DSC) perfusion magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) have been utilized as noninvasive imaging biomarkers for glioma grading [2–9].

Amide proton transfer (APT) imaging is a subtype of chemical exchange saturation transfer imaging that reflects the concentration of endogenous peptides or proteins without the need for contrast agent administration [10–12]. In APT imaging, a radiofrequency (RF) pulse corresponding to the amide (–NH) protons (3.5 ppm) in peptides and proteins selectively saturates their signal, and these saturated amide protons exchange with protons from bulk water, reducing the signal from water protons. Hence, the peptide and protein concentrations can be indirectly assessed by calculating the asymmetric signal decrease of bulk water at an offset frequency of ± 3.5 ppm [10–14]. A previous study reported that APT imaging is useful for predicting the histopathological glioma grade [15]. However, the clinical applications of APT imaging are limited by technical challenges including long scan times, limited coverage and high RF power. Additionally, given that DTI and perfusion MRI are commonly used to evaluate gliomas, whether APT imaging is compatible with or is of added value to these modalities for discriminating between low- and high-grade gliomas is of clinical importance.

Therefore, we aimed to evaluate whether APT imaging provides added value to the ADC obtained with DTI and the relative cerebral blood volume (rCBV) obtained with perfusion MRI for discriminating between high- and low-grade gliomas. We hypothesized that the combination of APT with ADC and/or rCBV would improve the diagnostic ability compared to each technique alone. Since gliomas are the most common primary brain tumour, we confined our cohort to individuals with diffuse gliomas.

Materials and methods

Our institutional review board approved this retrospective study, and the requirement of informed consent was waived.

Phantom experiment

To validate the APT imaging protocol in vitro, a phantom (Fig. 1a) with variable bovine serum albumin (BSA) concentrations and pH values (2%, 4%, 8% and 16% BSA at pH 7.4, and 16% BSA at pH 6, 6.5, 7 and 7.4) was used. This phantom was scanned with the same APT imaging sequence as that for humans (described below), which utilized a three-dimensional gradient- and spin-echo approach and fixed RF durations of 200 ms, except for varying RF powers of 1 μ T, 2 μ T, 3 μ T and 4 μ T and a full z spectrum with offset frequencies ranging from -5 ppm to 5 ppm at 0.5-ppm steps. APT signals were calculated from magnetization transfer ratio asymmetry (MTR_{asym}) at an offset frequency of ± 3.5 ppm. A fixed circular region of interest (ROI) was drawn at each BSA concentration and pH on the representative section of the scanned images. The correlation between the APT signal and the BSA concentration and pH was assessed using linear regression.

Study population

From November 2014 to August 2015, 225 adult patients with suspected brain tumours underwent preoperative APT imaging. Inclusion criteria were as follows: (1) pathologically confirmed diffuse glioma and available World Health Organization (WHO) grade in the pathological report, (2) no surgery or treatment prior to APT imaging and (3) preoperative perfusion MRI and DTI performed within 7 days before APT imaging. Of the 47 patients who met the inclusion criteria, one was excluded owing to loss of perfusion MRI data. Thus, 46 consecutive patients with diffuse gliomas were enrolled. The mean age of the cohort was 44.2 ± 14.5 years, and the male-to-female ratio was 25:21. The mean interval from APT imaging to operation was 0.8 ± 0.4 days. All 46 patients underwent at least partial resection of the tumour.

Image acquisition

MRI studies were performed using a 3-Tesla system (Achieva, Philips Healthcare, Best, Netherlands) and a 32-channel receiver head coil with a body transmit coil. APT imaging was acquired using the three-dimensional gradient- and spin-echo approach [15] with the following parameters: voxel size, 2.2×2.2 mm; slice thickness, 4.4 mm; repetition time (TR), 3000 ms; echo time (TE), 17 ms; turbo spin echo factor, 22; echo planar imaging factor, 7; and number of slices, 15 to cover the entire tumour volume. Using four repetitions at six saturation-frequency offsets (± 3.0 , ± 3.5 and ± 4.0 ppm), a sufficient signal-to-noise ratio could be achieved within a clinical time frame. APT imaging was conducted with an RF saturation amplitude of 2 μ T and a total duration of 800 ms, which consisted of a four-block pulsed saturation scheme. The water frequency shift due to field inhomogeneity was measured in a separate scan using the water saturation shift referencing method [16] with 21 offset frequencies ranging from -1.25 ppm to 1.25 ppm at a step of 0.125 ppm (16 Hz) and one reference scan without a saturation RF pulse resulting in a full z spectrum within the offset range. This scan was acquired with a TR/TE of 1250 ms/17 ms, RF saturation

amplitude of 0.5 μ T, total duration of 400 ms consisting of a two-block pulsed saturation scheme, and the same imaging parameters as those used in APT imaging. Both the APT and water saturation shift referencing scans were performed prior to the contrast-enhanced T1-weighted scan and had a total acquisition time of 7 min 36 s.

DTI was performed with b values of 600 s/mm^2 and 0 s/mm^2 , 32 directions and the following parameters: TR/TE, 8413.4 ms/77 ms; field of view (FOV), 220 mm; slice thickness, 2 mm; and 112×112 matrix. For DSC perfusion MRI, the T2*-weighted gradient-echo echo planar imaging sequence was used during gadolinium-based contrast bolus injection (0.1 mL/kg gadobutrol; Gadovist, Bayer Schering Pharma) at a rate of 4 mL/s, followed by a bolus injection of saline (total 20 mL at 4 mL/s). DSC perfusion MRI was performed with the following parameters: TR/TE, 1600 ms/30 ms; flip angle, 40°; FOV, 220 mm; slice thickness, 5 mm; 128×128 matrix; and echo train length, 53.

The conventional MR imaging sequences included T1-weighted (TR/TE, 2000 ms/10 ms; FOV, 240 mm; slice thickness, 5 mm; matrix, 256×256), T2-weighted (TR/TE, 3000 ms/80 ms; FOV, 240 mm; slice thickness, 5 mm; matrix, 256×256) and fluid-attenuated inversion recovery imaging (TR/TE, 10,000 ms/125 ms; FOV, 240 mm; slice thickness, 5 mm; matrix, 256×256). Three-dimensional postcontrast T1-weighted images (TR/TE, 6.3 ms/3.1 ms; FOV, 240 mm; slice thickness, 1 mm; matrix, 192×192) were acquired after DSC perfusion MRI.

Image postprocessing analysis

After water frequency shift correction, MTR_{asym} values at ± 3.5 ppm with respect to the water frequency, the so-called APT-weighted signal values, were calculated as follows [13, 14]:

$$\text{MTR}_{\text{asym}}(+3.5\text{ppm}) = \frac{S_{\text{sat}}(-3.5\text{ppm}) - S_{\text{sat}}(+3.5\text{ppm})}{S_0}$$

where S_0 and $S_{\text{sat}}(\pm 3.5 \text{ ppm})$ are the signal without and with the RF saturation pulse at the offset frequency downfield (+3.5 ppm) and upfield (−3.5 ppm) from the water centre frequency, respectively. All postprocessing of APT images was performed with Matlab (MathWorks, Natick, MA). The full water saturation shift referencing z spectrum was then fitted to a 12th-order polynomial at each voxel, and the lowest signal in the fit after interpolation at a higher spectral resolution (1 Hz) was assumed to be the actual water resonance frequency resulting in a water centre frequency offset at a corresponding voxel. The acquired APT data were organized according to the offsets, and the saturation images with the same offsets were averaged. The data for the offsets (+4, +3.5, +3 ppm) and (−3, −3.5, −4 ppm) for each voxel were interpolated to 385 points over a frequency offset range from +5 to +2 ppm and from −2 to −5 ppm, respectively, and shifted using the fitted water saturation shift referencing central frequency offset at the same voxel. Based on the shift-corrected data, the APT-weighted signal parameter map was generated using an MTR_{asym} at ± 3.5 ppm.

Several circular ROIs were placed manually on the areas of high signal intensity on APT and rCBV maps and on areas with low signal intensity on ADC maps that corresponded to solid components (Supplementary Fig. 1), by using the Medical Image Processing, Analysis, and Visualization software package (MIPAV, version 7.0; National Institutes of Health). The mean values of the ROIs on APT, ADC and rCBV maps were statistically analysed, with rCBV values normalized to the signal intensity of the contralateral normal-appearing white matter. The ROI size at each lesion ranged from 18.1 to 49.3 mm².

Statistical analysis

The inter-rater reliability of the APT signal measurements between the two radiologists (Y.S.C. and S.S.A.) was evaluated by calculating the intraclass correlation coefficient using a two-way random model with absolute agreement on average measures. The intraclass correlation coefficient for the APT signal measurements was 0.96 (95% confidence interval, 0.93–0.98). The APT signals were compared according to the WHO grade (II, III or IV) using one-way analyses of variance and post hoc comparisons with Bonferroni correction. The significance in the trend of APT signal changes according to the WHO grade was evaluated using linear regression. The APT signal, ADC and rCBV values were compared between low-grade (WHO grade II) and high-grade (WHO grade III or IV) gliomas using Student's *t* tests or Wilcoxon rank-sum tests according to the results of the Shapiro–Wilk test for normality. The abilities of the APT, ADC and rCBV to discriminate high-grade from low-grade gliomas were compared using receiver operating characteristic (ROC) analyses and methods reported by DeLong et al. [17]. The area under the ROC curve (AUC) and the optimal cutoff values according to Youden's index were then calculated. Additionally, the AUC after leave-one-out cross-validation was calculated to prevent overfitting. The added value of APT imaging to ADC and rCBV was assessed by measuring the integrated discrimination index (IDI), as described by Pencina et al. [18]. A positive IDI value indicates improved discrimination following the addition of a new parameter. Statistical analyses were performed with the Stata software package (version 12.1; StataCorp, College Station, TX). *P* values of less than 0.05 were considered statistically significant.

Results

Phantom experiments

Figure 1 shows the scanned images of a phantom and the APT signals from various BSA concentrations and pHs. Table 1 summarizes the correlations between the APT signal and the BSA concentration and pH. The APT signal significantly increased as the BSA concentration increased (all *P* values for trend were less than 0.001). The β coefficients for the correlation between the APT signal and BSA concentration increased as the RF power increased. In contrast, the APT signal significantly decreased as the pH increased (all *P* values for trend were less than 0.001). The β coefficients of this trend were not correlated with RF power.

Differences in APT signal according to glioma grade

Among the 46 patients, 15 had grade II (5 diffuse astrocytomas, 7 oligoastrocytomas and 3 oligodendrogliomas), 10 had grade III (4 anaplastic astrocytomas, 3 anaplastic

oligoastrocytomas and 3 anaplastic oligodendrogliomas) and 21 had grade IV (20 glioblastomas and 1 glioblastoma with oligodendroglial component) gliomas. As shown in Fig. 2, the APT signals were higher for higher glioma grades ($0.84 \pm 0.60\%$ in grade II, $1.55 \pm 0.87\%$ in grade III and $2.53 \pm 0.70\%$ in grade IV gliomas; P for trend less than 0.001). The APT signals for grades III and IV were significantly different ($P = 0.002$), as were those for grades II and IV ($P < 0.001$), while the APT signals for grades II and III showed borderline significance ($P = 0.059$).

ROC analyses and added value of APT imaging

Table 2 summarizes the differences in the APT, ADC and rCBV values between low- and high-grade gliomas. The APT and rCBV values were significantly higher and the ADC values were significantly lower in high-grade gliomas than they were in low-grade gliomas (all $P < 0.001$). Table 3 summarizes the results of the ROC analyses for determining the discriminatory abilities of APT, ADC and rCBV values. The APT, ADC and rCBV values showed excellent diagnostic performance, with AUCs of 0.877, 0.888 and 0.927, respectively. No significant difference in the performance of these values was found ($P = 0.828$ for APT vs. ADC, and 0.443 for APT vs. rCBV). Representative images of the APT, ADC and rCBV parameter maps that were obtained from low- and high-grade gliomas are depicted in Figs. 3 and 4.

Table 4 summarizes the added value of the APT signal to the ADC and rCBV. By adding the APT signal to the ADC, the AUC increased from 0.888 to 0.910, and the AUC after leave-one-out cross-validation increased from 0.858 to 0.867 (Fig. 5). This improvement was significant ($P = 0.007$). In contrast, adding the APT signal to the rCBV value did not significantly improve the diagnostic ability compared to that of the rCBV value alone; specifically, the AUC changed from 0.927 to 0.923 ($P = 0.222$), and the AUC after leave-one-out cross-validation decreased from 0.882 to 0.837.

Discussion

Here, we found that APT imaging demonstrated higher signal intensities for higher-grade gliomas and was compatible with the ADC and rCBV as a tool for glioma grading. Moreover, the APT signal added value to the ADC, but not to the rCBV, for discriminating between low- and high-grade gliomas.

APT imaging indirectly provides information about the peptide or protein concentration within tissues [10–14]. Previous studies demonstrated that APT signal is positively correlated with the glioma grade and cell density [19–21]. However, the clinical feasibility of these studies was limited, since they scanned animal models using experimental MRI or assessed human patients using only one representative tumour slice. A recent clinical MRI study reported that APT imaging increased the accuracy of rCBV for differentiating contrast-enhanced low-grade from high-grade tumours [22]. Here, we restricted our cohort to cases with gliomas, the most common primary brain tumour, and we investigated the compatibility and added value of APT imaging to DTI and perfusion MRI.

In our phantom experiments, the APT signal was positively correlated with the BSA concentration, and the β coefficients of this correlation increased with higher RF powers, thus validating previous reports showing that APT imaging can indirectly measure the protein and peptide concentrations [10–14]. In contrast, the observed negative correlation between the APT signal and pH conflicts with studies showing increased APT signalling with increasing pH. However, these previous studies used a creatine phantom and measured the APT signal from mobile amine protons [22, 23], whereas we used a BSA phantom and measured the APT signal primarily from amide, intermixed with the signal from amine. Thus, the conflicting results may be partially attributed to the different phantoms and to the mobile proton sources for the APT signal, resulting in mixed effects of the amide, amine and other factors on the APT signal changes according to the pH. Our results are supported by other studies using BSA phantoms, in which the correlation between the APT signal and pH was not consistent with numerical simulations [24, 25]. Although the mechanisms underlying the APT signal change according to the pH change remain unclear, our phantom experiment confirmed that protein and peptide concentrations are major contributors to the APT signal. Considering the specific absorption rate for patient safety, the minimum RF power that showed acceptable contrast at different protein concentrations, specifically 2 μ T, was selected for clinical MRI. Additionally, conventional magnetization transfer effects are reported as negligible at 2 μ T or lower RF power [14], enabling the selective assessment of APT effects without conventional magnetization transfer interference.

Our results are consistent with the previous studies demonstrating higher APT signals for brain tumours than for normal tissue, which was mainly attributed to the higher mobile protein and peptide concentrations in the brain tumour, along with increased mobile protein and peptide concentrations, cell density and Ki-67 cellular proliferation index according to the glioma grade [21, 26–28]. Both the ADC and rCBV reportedly correlate with the glioma grade and reflect tumour microenvironmental factors including cellular-level water diffusion and tumour vascularity. Hence, we reasoned that the APT signal would complement the ADC and rCBV for glioma grading, particularly if the APT signal reflects a different aspect of the tumour microenvironment than the ADC and rCBV, namely the protein and peptide concentrations. Since degree of mitotic activity and cell density increases and cell metabolism is altered in high grade gliomas, the APT imaging may be able to detect the increased protein and peptide concentrations, produced by the abnormal tumour cell proteosynthesis [29, 30]. Our results showed that the APT signal improved the diagnostic ability when added to the ADC, but not when added to the rCBV. Given that neither APT imaging nor the ADC requires an exogenous contrast agent, our results imply that APT imaging is especially useful as an adjunct for glioma grading when the patients' condition is not appropriate for contrast agent administration. As an adjunct for glioma grading in patients whose conditions are not appropriate for contrast agent administration, carbon-11-methionine PET or fluorine-18-fluoro-ethyl-tyrosine PET was also reported to be useful [31, 32]. APT imaging has an advantage over these other adjuncts, because APT imaging can be performed along with the other routine conventional MRI, whereas these PET modalities should be performed separately, or by using PET-MR that is less widespread than MR or PET alone. However, the compatibility of APT imaging with those PET modalities should be assessed in future investigations. Considering that perfusion MR is commonly performed

in glioma patients, APT imaging may not have added value when it is applied to the entire glioma patients in clinical practice. Future investigation is mandatory to identify subsets of patients who might benefit from APT imaging, such as those who have high-grade glioma and atypically low rCBV values.

Aside from its retrospective design and small sample size, several limitations of our study should be noted. First, the APT signal was not matched to the WHO grades in a locus-specific manner. Considering the intratumoral heterogeneity in high-grade gliomas, the tumour grade of the ROIs on the APT maps may be discordant with that in the pathological report. Second, we used the hot spot method, with manually placed circular ROIs, instead of segmenting the entire tumour. We chose this method on the basis of a previous study [33], which did not identify any significant differences in the glioma grading ability among various ROI selection methods on APT images, including manually placed circular ROIs vs. whole-tumour segmentation and ROIs on a single representative slice vs. on all tumour slices. Although segmenting the entire tumour reportedly shows higher interobserver agreement than the hot spot method for ADC measurement [34], in our opinion, the resolution of APT imaging must be improved to achieve adequate coregistration with conventional MRI images and segmentation of the entire tumour.

In conclusion, we showed that APT imaging was compatible with the ADC and rCBV for glioma grading. APT imaging added value to the ADC, but not to the rCBV, for discriminating high-grade from low-grade gliomas. Our results suggest that APT imaging may serve as a useful noninvasive imaging biomarker of gliomas for clinical decision-making regarding surgical sampling sites and therapeutic strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and acronyms

ADC	apparent diffusion coefficient
APT	amide proton transfer
AUC	area under the curve
BSA	bovine serum albumin
DSC	dynamic susceptibility contrast-enhanced

DTI	diffusion tensor imaging
FOV	field of view
IDI	integrated discrimination index
MRI	magnetic resonance imaging
MTR_{asym}	magnetization transfer ratio asymmetry
rCBV	relative cerebral blood volume
RF	radiofrequency
ROC	receiver operating characteristic
ROI	region of interest
TE	echo time
TR	repetition time
WHO	World Health Organization

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Key points

- Higher APT values were correlated with higher glioma grades.
- Adding the APT signal to the ADC improved glioma grading.
- Adding the APT signal to rCBV did not improve glioma grading.
- APT is a useful adjunct to the ADC for glioma grading.

Fig. 1. Results of the phantom scans. **a** Schematic image of the phantom. **b** Scanned APT image with RF power of 2 μ T. **c**, **d** Boxplots showing APT signals according to four different BSA concentrations at pH 7.4 (**c**) and 16% BSA at four different pH levels (**d**)

Fig. 2.

APT signal changes according to the glioma grade. The boxplot shows the APT signal changes according to the WHO grade. The APT signals increased as the glioma grade increased; significant differences in the APT signals were noted between grades III and IV ($P = 0.002$) and between grades II and IV ($P < 0.001$), while grades II and III showed borderline significance ($P = 0.059$)

Fig. 3. Images obtained from a 52-year-old man with an oligoastrocytoma (WHO grade II). **a** Postcontrast T1-weighted image. **b** T2-weighted image. **c** ADC map. **d** rCBV map. **e** APT map. Although the rCBV value (9.0) was atypically high, the ADC value ($1260.5 \text{ mm}^2/\text{s}$) and APT signal (0.61%) were consistent with a low-grade glioma

Fig. 4. Images obtained from a 76-year-old man with a glioblastoma (WHO grade IV). **a** Postcontrast T1-weighted image. **b** T2-weighted image. **c** ADC map. **d** rCBV map. **e** APT map. Although the ADC value ($1420.0 \text{ mm}^2/\text{s}$) was atypically high, the rCBV value (8.1, *arrow*) and APT signal (2.66%) were consistent with a high-grade glioma

Fig. 5. ROC curves showing the ability of the APT signal, ADC and combination of the APT signal and ADC to discriminate between low- and high-grade gliomas. Adding the APT signal to the ADC improved the diagnostic performance (AUC = 0.910) compared to the ADC alone (AUC = 0.888)

Table 1

Correlations between APT signal and BSA concentration and pH

RF power (μ T)	BSA concentration		pH	
	β coefficient (95% CI)	<i>P</i> for trend	β coefficient (95% CI)	<i>P</i> for trend
1	0.01 (0.01–0.02)	<0.001	–0.21 (–0.26 to –0.16)	<0.001
2	0.38 (0.37–0.38)	<0.001	–1.10 (–1.16 to –1.05)	<0.001
3	0.67 (0.67–0.68)	<0.001	–1.09 (–1.14 to –1.03)	<0.001
4	0.86 (0.82–0.89)	<0.001	–0.35 (–0.46 to –0.25)	<0.001

APT amide protein transfer, *BSA* bovine serum albumin, *CI* confidence interval, *RF* radiofrequency

Table 2

Differences in APT, rCBV, and ADC values between low- and high-grade gliomas

	Low-grade gliomas (<i>n</i> = 15)	High-grade gliomas (<i>n</i> = 31)	<i>P</i> value ^a	for normality Shapiro–Wilk test
APT (%)	0.84 ± 0.60	2.21 ± 0.88	<0.001	0.015
ADC (10 ⁻⁶ mm ² /s)	1520.5 ± 296.6	982.7 ± 357.8	<0.001	0.785
rCBV	1.79 ± 2.19	8.34 ± 4.81	<0.001	<0.001

ADC apparent diffusion coefficient, *APT* amide proton transfer, *rCBV* relative cerebral blood volume^aCalculated from Student's *t* test or Wilcoxon rank-sum test according the result of the Shapiro–Wilk test

Table 3

ROC analysis and leave-one-out cross-validation of imaging parameters' ability to discriminate between high- and low-grade gliomas

Imaging parameters	AUC (95% CI)	Cutoff	Cross-validated AUC
APT (%)	0.877 (0.772–0.983)	1.53	0.837
ADC (10^{-6} mm ² /s)	0.888 (0.793–0.984)	<1220.6	0.858
rCBV	0.927 (0.834–1.000)	2.01	0.882

ADC apparent diffusion coefficient, *APT* amide proton transfer, *AUC* area under ROC curve, *CI* confidence interval, *rCBV* relative cerebral blood volume, *ROC* receiver operating characteristic

Table 4

Incremental diagnostic value of APT over ADC and rCBV for discriminating between high- and low-grade gliomas, as measured by IDI

		AUC (95% CI)	Cross-validated AUC	IDI
Over ADC	ADC	0.888 (0.793–0.984)	0.858	0.124 ($P=0.007$)
	ADC + APT	0.910 (0.815–1.000)	0.867	
Over rCBV	rCBV	0.927 (0.834–1.000)	0.882	0.040 ($P=0.222$)
	rCBV + APT	0.923 (0.845–1.000)	0.837	

ADC apparent diffusion coefficient, *APT* amide proton transfer, *AUC* area under receiver operating characteristic curve, *CI* confidence interval, *IDI* integrated discrimination index, *rCBV* relative cerebral blood volume