

Amide Proton Transfer Imaging in Grading Diffuse Gliomas: Comparison with Contrast-enhanced and Diffusion-weighted MR Imaging

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Target audience: Researchers and clinicians interested in CEST/APT imaging.

Purpose: Amide proton transfer (APT) imaging¹ employs the proton exchange between bulk water and the amide protons (-NH) in endogenous mobile proteins and peptides, imaged by a chemical exchange saturation transfer (CEST) technique. Previous reports demonstrated that APT was useful in grading diffuse gliomas², differentiation between tumor and radiation necrosis³, and evaluation of therapeutic effects⁴. We reported that APT SI increased with glioma grade in patients (grade II, $2.1 \pm 0.4\%$, grade III, $3.2 \pm 0.9\%$, grade IV, $4.1 \pm 1.0\%$) at 3T⁵. Currently, Gd-enhanced and diffusion-weighted (DW) imaging has been routinely used for grading in the clinical setting. Therefore, the purpose of our study is to prospectively assess the diagnostic performance of APT imaging for grading of diffuse gliomas by comparisons with Gd-enhanced and DW imaging.

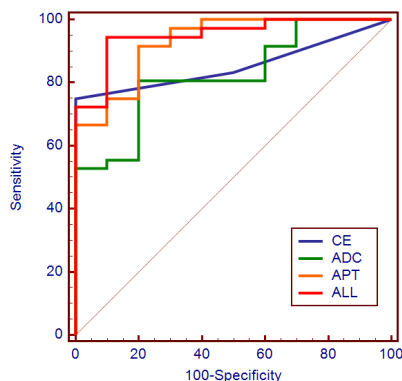
Methods: *Subjects:* Consecutive 46 patients with diffuse glioma (47.7±18.6 year-old, 21 males and 25 females) who underwent subsequent surgical resection or biopsy were included in the prospective study. Histological types of gliomas are as follows; 6 astrocytoma; 3 oligodendrogliomas; 1 oligoastrocytoma, 4 anaplastic astrocytomas; 6 anaplastic oligodendrogliomas; 2 anaplastic oligoastrocytoma, 24 glioblastoma multiforme (GBMs).

MRI: MRI was conducted in a 3T clinical scanner (Achieva TX 3.0T, Philips Healthcare, NL) using an 8-channel head coil for signal reception and 2-channel parallel transmission via the body coil. Acquisition software was modified to alternate the operation of the two transmission channels during the RF saturation pulse⁶ for an RF duty-cycle of 100% and to allow a special RF shimming for the saturation homogeneity of the alternated pulse (identical mean B1 level per channel)⁶. Saturation pulse: 40×50ms sinc-gaussian elements, $B_1=2.0\mu\text{T}$, $T_{\text{sat}}=2.0\text{s}$. 2D fast spin-echo sequences with driven equilibrium^{5,6} refocusing were used. The imaging parameters were as follows: TR/TE=5s/6ms, FOV (230 mm)², matrix 168², resolution $1.8 \times 1.8 \times 5 \text{ mm}^3$, 25 saturation frequency offsets $S[\omega]$, $\omega=-6$ to 6ppm (step 0.5ppm) and S_0 ($\omega=-160\text{ppm}$), affording 2 minutes scan time. B_0 maps for off-resonance correction were acquired separately (identical geometry, 2D GRE, $\Delta\text{TE}=1\text{ms}$, TR/TE=15ms/8ms, 16 averages, 33 sec). Maps of the MT asymmetry $\text{MTR}_{\text{asym}}=(S[-3.5\text{ppm}]-S[+3.5\text{ppm}])/S_0$ were calculated with a point-by-point B_0 correction. Four region-of-interests (ROIs) with a fixed area of 0.36 cm² were placed to measure maximum APT SI in the solid component of the gliomas. In addition, contrast enhancement (CE) on post-contrast T1-weighted imaging (2D spin-echo, TR=500ms, TE=10ms, Gd=0.01 mol/kg) of the tumor was visually graded into a 5-point scale, and minimum apparent diffusion coefficients (ADC) within solid components of the tumor were determined in 4 ROIs on DW imaging (single-shot spin-echo EPI, b=0,1000, mono-exponential fitting for ADC). Student's t-test, receiver-operating characteristics (ROC) analysis and logistic regression analysis were performed to evaluate and compare their diagnostic performance in grading gliomas

Results and Discussion: HGG (grade III and IV) showed greater CE ($P<0.001$), lower ADC ($P=0.01$) and higher APT signal ($P<0.0001$) than LGG (grade II). The area under curve (AUC), cutoff value, sensitivity, and specificity obtained in the ROC analysis for discriminating HGG from LGG are summarized in **Table 1**. The ROC analyses demonstrated that the APT signal provided the best AUC values in discriminating HGG from LGG (**Figure 1 and Table1**) and showed the highest AUC among the three parameters in the ROC analyses in differentiating the grades (II vs. III, II vs. IV, III vs. IV) among these three parameters (CE, ADC, APT). In the logistic regression analysis including all the three parameters, APT signal showed the largest Wald Chi-square (CE 0.02, ADC 2.22, APT 4.03) and was the only significant factor ($P<0.05$) among these parameters. Combination of all the three parameters obtained by the logistic analysis (**Figure 1**) improved the AUC (0.95) in the ROC analysis compared with CE alone (0.85, $P<0.05$) and ADC alone (0.82, $P<0.05$). A representative case in which only APT imaging is useful in grading is shown in **Figure 2**. APT imaging is based on the new contrast from mobile proteins and peptides in tissue and may provide different/additional information in grading gliomas and complement conventional imaging methods.

Conclusion: APT imaging showed high diagnostic performance to predict histopathological grades of diffuse gliomas compared with CE and DW imaging. APT has an additive value to other MR methods and is useful in accurate glioma grading.

References: 1. Zhou J et al., Nat Med (2003), 2. Zhou J et al., MRM (2008), 3. Zhou J et al., Nat Med (2010), 4. Sagiya K et al. ISMRM (2012), 5. Togao O et al., Neuro-Oncol (in press) 6. Keupp J et al. ISMRM (2011, 2012)



	AUC	Cutoff value	Sensitivity	Specificity
Contrast Enhancement	0.854	2	75.0%	100%
ADC	0.822	$1.16 \times 10^{-3} \text{mm}^2/\text{s}$	80.6%	80.0%
APT	0.931	2.63%	91.7%	80.0%

Table 1: Summary of the ROC analysis in differentiating HGG (grade III and IV) from LGG (grade II).

Figure 1: ROC analysis in differentiating HGG (grade III and IV) from LGG (grade II). APT achieved the best AUC among the 3 parameters. The combination of all the 3 parameters improved AUC compared with CE and ADC alone.

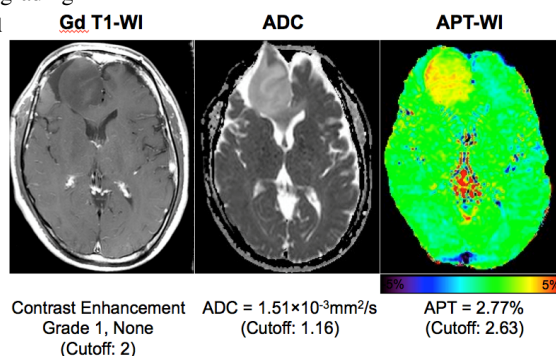


Figure 2: Anaplastic oligoastrocytoma, Grade III (HGG). The lesion in the right frontal lobe shows no contrast enhancement, high ADC and slightly high APT signal compared with the cutoff. Only APT signal is suggestive of HGG.