

# Molecular imaging of high-grade brain tumors using endogenous protein and peptide-based contrast

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## Introduction

High grade gliomas are invasive and histologically heterogeneous, usually consisting of a core mass mixed with necrosis, and surrounded by infiltrating cells in edematous or even normal appearing brain. Currently, these brain tumors are generally evaluated using gadolinium (Gd)-contrast enhanced MRI in combination with T<sub>2</sub>-weighted (T<sub>2</sub>w) or fluid-attenuated inversion recovery (FLAIR) MRI, which are used to localize the core of the tumor and to determine the extent of involvement. However, existing MRI techniques are not sufficiently tissue-specific and suffer from several limitations.<sup>1</sup> Amide proton transfer (APT) imaging<sup>2,3</sup> is a new molecular-MRI technique that detects endogenous mobile proteins and peptides in tissue via saturation of the amide protons in the peptide bonds. Its detection mechanism is based on the chemical exchange saturation transfer (CEST) approach. The purpose of this abstract is to demonstrate that APT can potentially provide information about the presence and heterogeneity of high grade brain tumors based on increased cellular content of proteins and peptides, as revealed by MRI-guided proteomics<sup>4</sup> and in vivo MR spectroscopy.<sup>5</sup>

## Materials and Methods

Experiments were performed on a Philips 3T MRI scanner using a body coil for RF transmission and an 8-channel SENSE coil for reception. Four brain tumor patients were scanned in this study. For APT imaging, RF saturation power and time were 3  $\mu$ T and 500 ms, respectively. Other imaging parameters were TR 3 sec, TE 30 ms, matrix 128×64, FOV 230×230 mm<sup>2</sup>, and slice thickness 6 mm. A full MT-spectrum (offsets -6 to 6 ppm, interval 0.5 ppm) was acquired ( $S_{sat}$ ). One unsaturated image (no saturation pulses added) was acquired for control ( $S_0$ ). To increase the SNR, the images at and around the offset of  $\pm 3.5$  ppm were acquired with 8 averages. The scanning time for this APT scan was about 5 min. In data analysis, the MT-spectrum was corrected for the  $B_0$  inhomogeneity effect on a pixel-by-pixel basis according to the procedure previously reported in the literature.<sup>2,3</sup> Finally, the APT effect was quantified using an MT-ratio asymmetry analysis at the offset of 3.5 ppm:  $MTR_{asym}(3.5\text{ppm}) = S_{sat}(-3.5\text{ppm})/S_0 - S_{sat}(+3.5\text{ppm})/S_0$ . The Gd-T<sub>1</sub>w images were used as the reference of ROI analysis.

## Results and Discussion

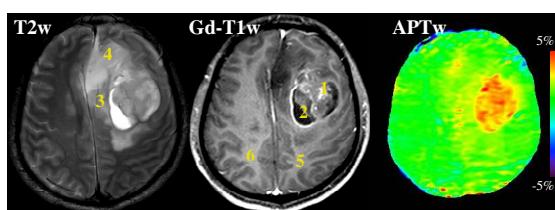
Fig. 1 shows an example of the APTw and standard MR images for a patient with mixed WHO grade-III/IV oligodendro-astrocytoma. There is a large APT intensity increase in the entire Gd-enhancing tumor area compared to peritumoral edema and normal-appearing white matter. The area of the highest intensity on APT corresponds well to the area of maximal Gd-enhancement on T<sub>1</sub>w with slightly decreasing intensity in the non-enhancing portion (likely necrosis) of the tumor core. The clear APT hyperintensity is a typical feature of the tumor, suggesting increased content of mobile proteins and peptides.<sup>4,5</sup> Further, regions of increased APT extend outside of the tumor core (signified by Gd-enhancement) and into the peripheral brain zones (likely tumor infiltration, which could not be identified by Gd-MRI). However, the hyperintense APT area is generally smaller in size than the lesion identified on T<sub>2</sub>w.

Table 1 summarizes the results for four patients with high-grade gliomas (all with Gd contrast enhancement). These initial data show that APT image intensity is consistently higher in Gd-enhancing tumor core than in immediate (two-tailed paired Student's t-test,  $p = 0.01$ ) and peripheral edema ( $p = 0.02$ ), as well as ipsilateral ( $p = 0.0006$ ) and contralateral normal-appearing white matter ( $p = 0.007$ ). Thus, APT may help better distinguish the heterogeneous portions of tumor (including mixed grades within a single tumor and completely non-enhancing high-grade tumors<sup>1</sup>) to assist with treatment planning by providing targets for tissue sampling to yield the most accurate diagnosis.

## Conclusions

Early results suggest that APT imaging may be able to identify the most active parts of the tumor without the need of exogenous contrast agents. These unique capabilities of APT imaging may be very important for increasing diagnostic accuracy and safety of MRI for human brain tumors.

**References:** (1) Scott et al. Neurology 2002;59:947. (2) Jones et al. MRM 2006;56:585. (3) Zhou and van Zijl Progr. NMR Spec. 2006;48:109. (4) Hobbs et al. JMRI 2003;18:530. (5) Howe et al. MRM 2003;49:223.



**Fig. 1.** MR images for a patient with oligodendro-astrocytoma (mixed WHO III/IV) and ROIs locations.

**Table 1.**  $MTR_{asym}(3.5\text{ppm})$  in several areas for four patients (mean  $\pm$  sd).

Tumor grade	CE (1)	NE (2)	Immediate edema (3)	Peripheral edema (4)	INAWM (5)	CNAWM (6)
III/IV	3.7 $\pm$ 0.4	3.5 $\pm$ 0.3	2.4 $\pm$ 0.4	2.2 $\pm$ 0.4	1.8 $\pm$ 0.6	1.3 $\pm$ 0.3
III/IV	4.2 $\pm$ 0.4	4.0 $\pm$ 0.3	2.6 $\pm$ 0.8	1.7 $\pm$ 0.9	2.4 $\pm$ 0.4	2.1 $\pm$ 0.5
III/IV	4.0 $\pm$ 1.2	--	2.2 $\pm$ 0.3	1.7 $\pm$ 0.5	1.7 $\pm$ 0.4	1.7 $\pm$ 0.2
III	2.8 $\pm$ 0.4	1.8 $\pm$ 0.2	2.1 $\pm$ 0.7	2.2 $\pm$ 0.4	1.1 $\pm$ 0.3	1.7 $\pm$ 0.2

CE: Gd-contrast enhancing core, NE: non-Gd enhancing core, INAWM: ipsilateral normal-appearing white matter, CNAWM: contralateral normal-appearing white matter.