

Amide Proton Transfer Imaging of Human Brain Tumors Distinguishes Tumor from Brain Tissue at the Periphery

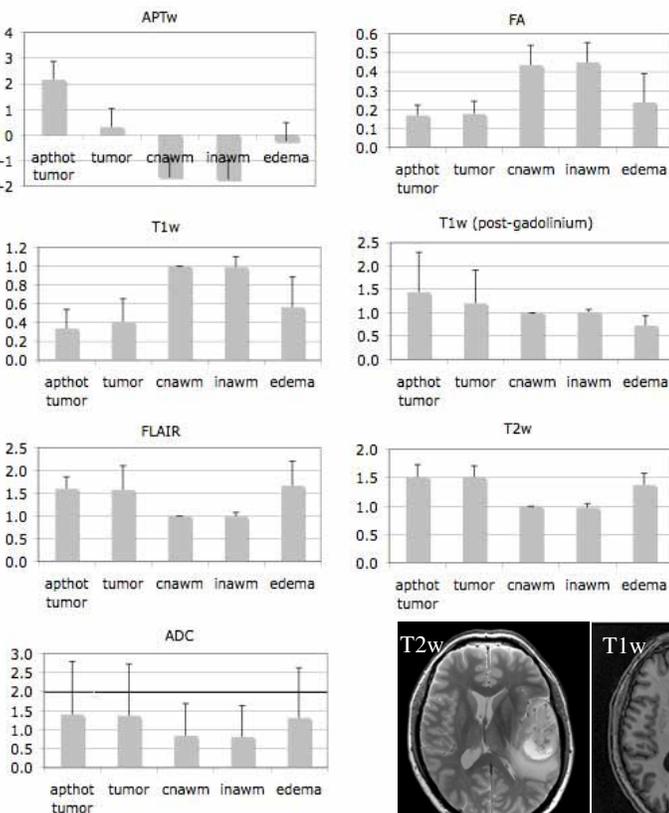
C. K. Jones^{1,2}, M. J. Schlosser³, P. C. van Zijl^{1,2}, M. G. Pomper², J. Zhou^{1,2}

¹F.M. Kirby Center, Kennedy Krieger Institute, Baltimore, MD, United States, ²Department of Radiology and Radiological Sciences, Johns Hopkins University, Baltimore, MD, United States, ³Department of Neurology/Neurosurgery, Johns Hopkins University, Baltimore, MD, United States

Introduction: Recently, we developed a chemical exchange saturation transfer (CEST)¹-type MRI methodology called APT imaging, in which the interaction between protons of free tissue water and the amide groups of endogenous mobile proteins and peptides is imaged². Protons on the amide groups exchange with free water at a rate of approximately 28 Hz, so to measure the APT effect, a long saturation pulse is applied at the amide frequency of 3.5ppm from water which results in a measurable difference in the water signal due to the saturated protons exchanging with free water protons. In a typical in vivo APT experiment, the saturation pulse is applied at ± 3.5 ppm and the resulting images are subtracted to create an APT-weighted magnetization transfer asymmetry (MTR_{asym}) measure with minimal other disturbing effects. When applied to rats implanted with gliosarcoma tumors³, APT was able to distinguish between regions of tumor and edema, which could not be accomplished using standard T1-weighted, T2-weighted, and diffusion-weighted imaging, for which the tumor border appeared diffuse. The method has now been implemented on a clinical 3T scanner for patients with brain tumors. In this work, the APT measure is quantitatively compared to standard MRI contrast mechanisms, and the potential diagnostic specificity of APT for brain tumor patients is evaluated.

Methods: Ten patients with brain tumors were scanned on a 3T Philips Intera system using an APT pulse sequence (turbo spin-echo factor = 32, TR = 6 sec, TE = 30 ms, matrix 128x128, FOV 230x230 mm, slice thickness 5 mm, single slice) with two offsets (± 3.5 ppm relative to the water frequency) and 8 averages to increase the SNR. A control image without the saturation RF pulse was also acquired. Other pulse sequences included: T₂-weighted (TR = 4 sec, TE = 80 ms, 60 slices, 2.2 mm thick), T₁-weighted MPRAGE (3D fast field echo, TR/TE = 8.33/3.9 ms, flip angle = 8°, 120 slices, 1.1 mm isotropic voxels), FLAIR (inversion delay = 2800 ms, TR/TE = 11,000/120 ms, 60 slices, 2.2 mm thick), diffusion tensor (single-shot SE EPI, TR/TE = 9699/63 ms, 30 gradient directions with b = 700 s/mm² and reference, 60 slices, 2.2 mm thick), and gadolinium-enhanced T₁-weighted MPRAGE (parameters as MPRAGE) images. For APT data, the $MTR_{asym}(3.5 \text{ ppm}) = (S_{sat}(-3.5\text{ppm}) - S_{sat}(3.5\text{ppm}))/S_0$ was calculated for each voxel in the brain. A single slice from the other pulse sequences was matched for quantitative analysis. Five regions of interest (ROI) were drawn by a neurosurgeon: 1) brain tumor where the region had high APT compared to the rest of the tumor region (APT-hot tumor), 2) region encompassing the whole brain tumor (tumor), 3) contralateral normal appearing white matter (CNAWM), 4) ipsilateral normal appearing white matter (INAWM), and 5) edema. The tumor, CNAWM, INAWM, and edema regions were drawn based on the T2w, T1w and FLAIR images. For APT, FA and ADC, the mean and standard deviation for the absolute measures were calculated. For the FLAIR, pre- and post-gadolinium T1-weighted MPRAGE, and T2-weighted images, the signal intensity in each of the regions was normalized by the signal intensity in the CNAWM for ease of comparison across subjects, and then the mean and standard deviation were calculated.

Results and Discussion: For the ten patients an APT image was generated and compared to the results of the other MRI sequences. Based on the APT measure, the APT hot tumor region was statistically different from the CNAWM (p = 0.0097), INAWM (p = 0.0023), and edema (p = 0.035). For the T2W, ADC and FA measures the APT-hot region was not significantly different from the CNAWM, INAWM, nor edema. For FLAIR the APT hot region was not different from CNAWM (p = 0.055), nor edema (p = 0.70) and just reached significance for INAWM (p = 0.046). For the T1w scan the APT hot region was different from edema (p=0.042). In addition, the APT hot region compared to the T1w scan with gadolinium contrast was not statistically different. It is important that the APT measure was able to further separate the tumor into two significantly different regions while all other measures were not. Images below show that there is a clear intensity increase in the tumor in the APT-weighted image, but a lack of APT enhancement in the hyperintense edema region occurring in several conventional MRI images. APT contrast (yellow/red region on middle, right side of APT image) distinguished tumor from edema and normal appearing tissue.



Conclusions: In this study of 10 patients, the amide proton transfer imaging was better able to distinguish between tumor and normal appearing white matter or peritumoral edema compared than standard MRI contrast. This will have to be confirmed in a larger independent study with tissue biopsy data as a golden standard.

References: 1) Ward KM, et al., JMR 2000;143:79-87. 2) Zhou J, et al., Nat Med 2003;9(8):1085-1090, 3) Zhou J, et al., MRM 2003;50(6):1120-1126.

