Predicting Glioma Response to Radiotherapy with Amide Proton Transfer (APT) MRI

J. Zhou[1,2], S. Wang[1], B. Tyler[3], R. Grossman[3], E. Tryggestad[4], E. Ford[4], M. Armour[4], K. Yan[1], B. Lal[5], P. C. van Zijl[1,2], and J. Laterra[5]

[1]Department of Radiology, Johns Hopkins University, Baltimore, MD, United States, [2]F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD, United States, [3]Department of Neurosurgery, Johns Hopkins University, Baltimore, MD, United States, [4]Department of Radiation Oncology, Johns Hopkins University, Baltimore, MD, United States, [5]Department of Neurology, Kennedy Krieger Institute, Baltimore, MD, United States

Introduction

Currently, there is a shortage of MRI techniques to differentiate tumor progression from radiation necrosis after brain tumor therapy. This complicates daily patient care, and is a critical barrier to investigating the efficacy of new therapies for brain tumors.[1] Recently, we have designed a new molecular MRI technique, dubbed APT imaging,[2] which detects amide protons of endogenous mobile proteins and peptides in tissue. Previous data have shown an increased APT signal in gliomas that provides unique information about the presence and grade of brain tumors. In this abstract, we demonstrate that the APT signal is a potential biomarker for differentiation between viable tumor and radiation necrosis.

Materials and Methods

Five U87MG tumor-bearing rats were irradiated using a small animal radiation research platform (single dose, 40 Gy; 10×10 mm^2). APT imaging was acquired at 4.7T, using labeling offsets of ±3.5 ppm with respect to water (raw image intensity S_{sat}; TR/TE = 10 s/30 ms; RF saturation power/time 1.3 µT/4 s; slice thickness = 1.5 mm; NA = 16). A control image (S_0) in the absence of RF saturation was acquired for signal normalization. APT images were quantified using the magnetization transfer-ratio asymmetry: $MTR_{asym}(3.5ppm) = 100\% \times [S_{sat}(-3.5ppm) - S_{sat}(3.5ppm)]/S_0$, and displayed using a window of -10% to 10%.

Results and Discussion

The APT-MRI signal in tumor decreased following radiation. At baseline, the U87MG tumors were hyperintense (compared to contralateral brain tissue) with minimal heterogeneity on the APT images. Although the irradiated tumors appeared to enlarge during the first several days post-radiation, their APT signals gradually decreased following therapy (**Fig. 1**). These irradiated tumors clearly showed the presence of large necrotic areas upon histopathological analysis, in contrast to non-irradiated U87MG tumors that typically display no spontaneous necrosis. Quantitative analysis shows that the average APT signal intensities in the lesion significantly decreased at 3 and 6 days post-radiation ($P <$ 0.05 or 0.001, respectively). The results show that APT-MRI signals after radiation are closely associated with early tumor response.

Changes in ADC and APT histograms following radiation. During the first days post-radiation, the tumor continued to grow in size, as reflected by increased areas under the histograms (**Fig. 2**). The tumor was relatively homogenous and histograms showed a relatively narrow distribution. Starting from day 9 post-radiation, this irradiated tumor became very heterogeneous, as characterized by widened histograms. Both ADC and APT demonstrate larger changes in response to therapy. It is widely realized that ADC is an effective early biomarker for tumor response to therapy and successful treatment is associated with increases in ADC values (mainly due to tumor cell loss).[3-5] APT-MRI would provide **independent (not duplicated)** information for the early prediction of cancer treatment outcome.

Conclusions

The preliminary results clearly show that the amide protons detected by APT constitute a biomarker for the presence of the tumor, which can be used to distinguish between viable tumors and treatment-induced necrosis and to predict tumor response to therapy.

(1) Yang & Aghi, *Nature Rev. Clin. Oncol.* 2009;6:648-657. (2) Zhou et al. *MRM* 2003;50:1120-1126. (3) Chenevert et al. *J. Nat. Cancer Inst.* 2000;92:2029-2035. (4) Moffat et al. *PNAS* 2005;102:5524-5529. (5) Padhani et al. *Neoplasia* 2009;11:102-125.
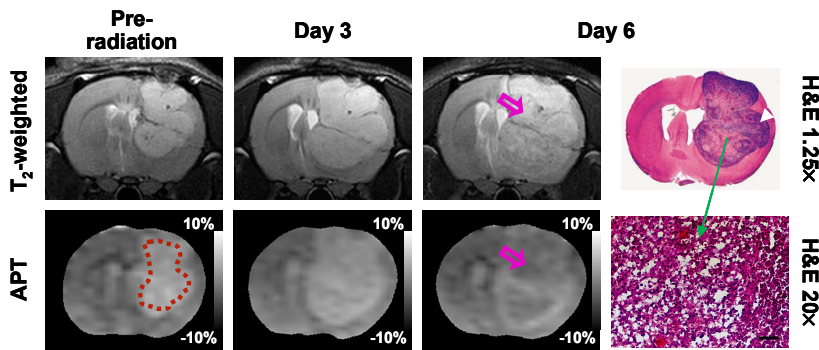
Fig. 1. Changes in APT signal intensity in a radiated U87MG tumor as a function of time post-radiation. APT signals show a clear decrease following therapy. At 6 days post-radiation, the image intensity of the mass is very heterogeneous with an area that is almost isointense to contralateral (pink arrow). At this time point, the presence of severe radiation necrosis was confirmed on histology. Low-density tumor cells were also found, mainly on the edge of the lesion (white arrowhead). Example of tumor ROIs for quantitative image analysis is shown with a red dotted line.
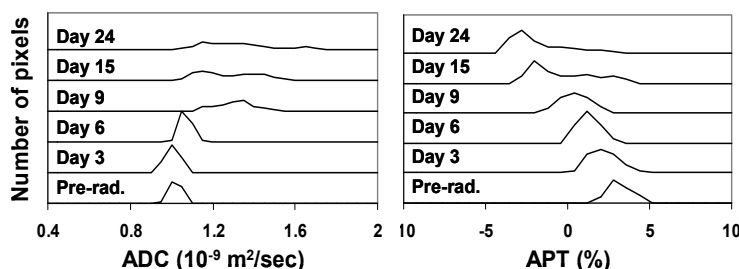
Fig. 2. Histogram analysis of ADC and APT intensities obtained pre-radiation and at 3−24 days post-radiation for another irradiated U87MG glioma. The ADC histogram has a right shift (**except at day 3**), showing a similar pattern to that observed previously in the 9L brain tumor following chemotherapy.[3] The APT histogram has a consistent left shift at all time points.