Amide Proton Transfer Imaging of High Intensity Focused Ultrasound-treated Tumor Tissue

Stefanie J. Hectors[1], Igor Jacobs[1], Gustav J. Strijkers[1], and Klaas Nicolay[1]
[1]*Biomedical NMR, Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, Netherlands*

Introduction High Intensity Focused Ultrasound (HIFU) is an emerging technique for the thermal treatment of solid tumors. Recently we showed that HIFU-treated tumor tissue can be distinguished from non-treated tumor tissue by means of an endogenous multiparametric MRI protocol, consisting of assessment of T_1, T_2 and the Apparent Diffusion Coefficient (ADC).[1] The goal of the present study was to investigate whether Amide Proton Transfer (APT) imaging gives complementary yet distinct information on tumor tissue status. It has been shown that APT imaging is a promising biomarker for the differentiation between viable tumor and radiation injury.[2] As a first step, it was assessed whether APT imaging is also sensitive to HIFU-induced necrosis in tumor tissue.

Methods Tumor-bearing (CT26 colon carcinoma, s.c. in hind limb) Balb/c mice were subjected to MRI (6.3 T) 24 h before (n=15), 1 h after (n=15) and 72 h after (n=8) HIFU treatment (TIPS, Philips). The HIFU treatment consisted of partial ablation of the tumor. The multi-slice imaging protocol (10-14 1 mm slices, matrix 128x128, FOV=40x40 mm^2), with whole tumor coverage, consisted of T_2-weighted (TR/TE 1 s/30 ms), APT (TR/TE 10 s/8 ms, GE-EPI read-out, 4 s block pulse irradiation (1.3 μT) at offsets of ±3.5 ppm with respect to water, NA=8) and gadolinium-enhanced (Dotarem, 0.3 mmol Gd/kg) T_1-weighted (TR/TE 0.8 s/8 ms) imaging. Prior to the APT acquisition, higher-order local shimming was performed to optimize B_0 homogeneity. After sacrifice, tumors were dissected and processed for histological analysis. Sections were obtained every 300 μm covering the whole tumor. NADH-diaphorase and H&E staining were performed on selected sections.

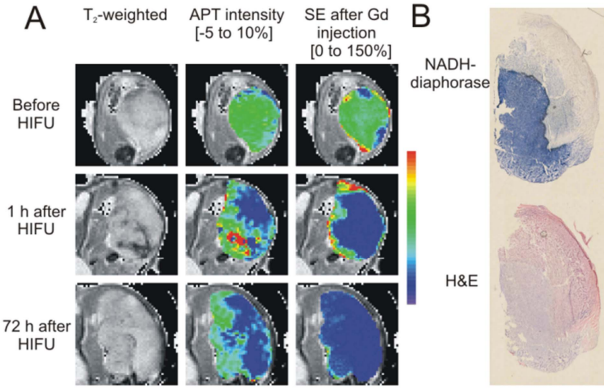

Figure 1 A) Representative examples of MRI of tumor-bearing legs before and after HIFU treatment. APT intensity values and signal enhancement (SE) values after Gd injection are overlaid on the tumor in the T_2-weighted images. B) NADH-diaphorase and H&E stained tumor sections obtained 72 h after HIFU at approximately the same location within the tumor. A region of non-viable (NADH-diaphorase negative), necrotic (H&E) tumor tissue is clearly visible.

Results Representative MRI scans of tumor-bearing legs after HIFU treatment are shown in Figure 1A. T_2-weighted images revealed a heterogeneous appearance of the tumor tissue after HIFU treatment. Both at 1 h and 72 h after HIFU regions with decreased APT intensity were observed. Furthermore, regions of decreased signal enhancement after Gd injection were present at both time points after HIFU treatment. These regions were distinctly larger than the regions with decreased APT effect. MRI results were compared with histology of the tumor tissue. Regions with decreased APT effect spatially corresponded to non-viable tumor tissue (NADH-diaphorase negative, Fig. 1B top) with extensive necrosis (H&E, Fig. 1B bottom). Figure 2A shows the average APT intensity distribution in the tumor pixels at the different time points. A clear shift towards lower APT intensity values was observed at 1 h after HIFU and to an even larger extent at 72 h. Figure 2B shows the difference in APT intensity distribution between baseline values and 1 h and 72 h after HIFU treatment. A clear increase in fraction of pixels with an APT intensity in the range between -10 and -2 % was observed at both time points after HIFU. This APT intensity range can be attributed to HIFU-induced changes in the tumor tissue. A highly significant increase in the fractions of pixels within this HIFU-related APT intensity range was observed at 1 h and 72 h after HIFU as compared to baseline (Figure 2C).

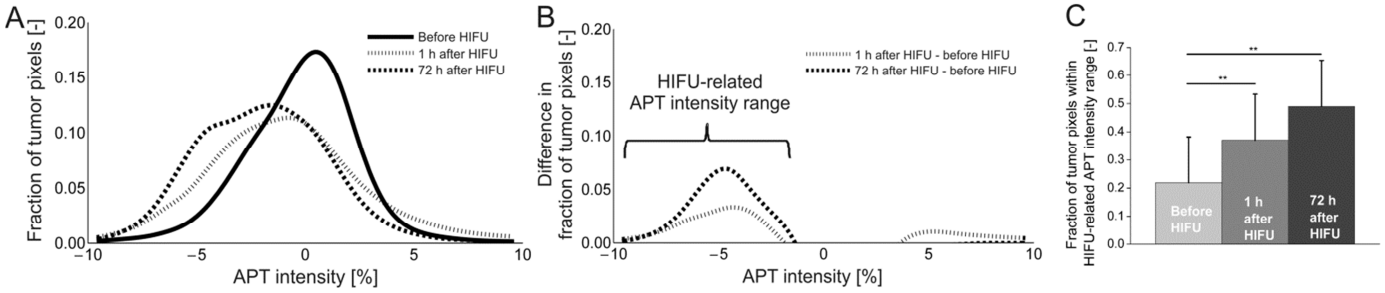

Figure 2 A) Average distributions of APT intensity values in tumor tissue before, 1 h and 72 h after HIFU treatment. B) Difference in distribution of APT intensity values after HIFU (1 h and 72 h) with respect to baseline values. C) Fractions of the pixels within HIFU-related APT intensity range before, 1 h and 72 h after HIFU. Data are presented as mean±SD. ** denotes a significant difference (paired Student's t-test, $p<0.001$).

Discussion and Conclusion Regions with substantially decreased APT intensity were observed after HIFU treatment. These regions corresponded spatially to non-viable, necrotic tumor regions observed in histology. Analysis of the tumor APT intensity distribution showed a pronounced shift towards lower APT intensity values after HIFU. The fractions of pixels within the defined HIFU-related APT intensity range (-10 to -2%) significantly increased by HIFU treatment. These results provide evidence that APT imaging may serve as a new biomarker for identification of HIFU-treated tumor tissue. In the near future, APT imaging will be added to the previously described multiparametric protocol[1] to assess its complementary value for HIFU treatment evaluation.

Acknowledgement This research was supported by the Center for Translational Molecular Medicine (VOLTA)

[1]Hectors et al. *Proc Ann Meeting ISMRM* 2012:4626 [2]Zhou et al. *Nat Med* 2010;17;130-134