$T_{1\rho}$ Mapping for the Evaluation of High Intensity Focused Ultrasound Tumor Treatment

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Introduction For the clinical application of High Intensity Focused Ultrasound (HIFU) for the treatment of malignant lesions, it is of key importance that residual tumor tissue can be distinguished from successfully ablated tissue. We have recently shown that amide proton transfer (APT) imaging [1] and multiparametric MR analysis based on T_1, T_2 and Apparent Diffusion Coefficient (ADC) data [2] are both promising MRI methods for the segmentation of HIFU-treated and non-treated tumor tissue. Another MRI method with potential sensitivity to HIFU-induced changes in the tumor tissue, such as coagulative necrosis, is $T_{1\rho}$ imaging. Previously, changes in tumor $T_{1\rho}$ after gene therapy [3] and chemotherapy [4] have been reported. The goal of the present study was to assess whether $T_{1\rho}$ also provides contrast between HIFU-treated and non-treated tumor tissue.

Methods MRI (7T) of CT26 colon carcinoma-bearing (s.c. in hind limb) Balb/c mice was performed 1 day before (n=13), directly after (n=13) and 3 days after (n=7) HIFU treatment. The HIFU treatment consisted of partial ablation of the tumor with an 8-element therapeutic ultrasound transducer (TIPS, Philips). The multi-slice MRI protocol (FOV=4x4 cm^2, matrix=128x128) consisted of T_2-weighted imaging (TE=30 ms, TR=2000 ms, NA=1) and $T_{1\rho}$ mapping (B_0- and B_1-compensated [5] spin-lock preparation (spin-lock amplitude B_1=0, 100, 250, 500, 750, 1000, 1500 and 2000 Hz, spin-lock times TSL=5, 10, 20, 40, 80 ms) followed by GE-EPI read-out (TE=5 ms, TR=2000 ms, NA=2)). The $T_{1\rho}$ measurement at B_1=0 Hz is equivalent to a T_2 measurement. After sacrifice, tumors were dissected and processed for NADH-diaphorase and H&E staining.

Results Representative MRI results are shown in Figure 1. The HIFU treatment did not lead to contrast in the T_2-weighted images. This was confirmed by absence of visible changes after HIFU in the $T_{1\rho}$ maps at B_1=0 Hz, which essentially represent T_2 maps. Before HIFU, $T_{1\rho}$ maps at B_1=2000 Hz had a slightly more heterogeneous appearance than those at B_1=0 Hz, indicative of a larger variation in tumor $T_{1\rho}$ at higher amplitudes. At both time points after HIFU, a large region of decreased $T_{1\rho}$ was observed at B_1=2000 Hz. Histology confirmed extensive necrosis in the tumor tissue. Average tumor $T_{1\rho}$ distributions indeed showed a larger spread in tumor $T_{1\rho}$ at higher spin-lock amplitudes before HIFU (Figure 2). Furthermore, a shift toward lower $T_{1\rho}$ values after HIFU was observed for all spin-lock amplitudes. The shift in $T_{1\rho}$ values at 3 days after HIFU treatment was larger with increasing spin-lock amplitude. Quantitative analysis of the average $T_{1\rho}$ value in the tumors at the different experimental time points (Figure 3A) showed a significant decrease in the average $T_{1\rho}$ at 3 days after HIFU treatment as compared to baseline for spin-lock amplitudes higher than or equal to 100 Hz. The average $\Delta T_{1\rho}$ between 3 days after and before HIFU clearly decreased toward larger negative values with increasing spin-lock amplitude (Figure 3B). Statistical analysis confirmed a significant effect of spin-lock amplitude on $\Delta T_{1\rho}$ at 3 days after HIFU (ANOVA for repeated measures, P=0.048). At 3 days after treatment, the $\Delta T_{1\rho}$ values at B_1 strengths above 100 Hz were significantly lower (more negative) than at B_1=0 Hz. Furthermore, the $\Delta T_{1\rho}$ value at 2000 Hz was significantly lower than the $\Delta T_{1\rho}$ values at B_1 strengths between 0 and 1000 Hz.

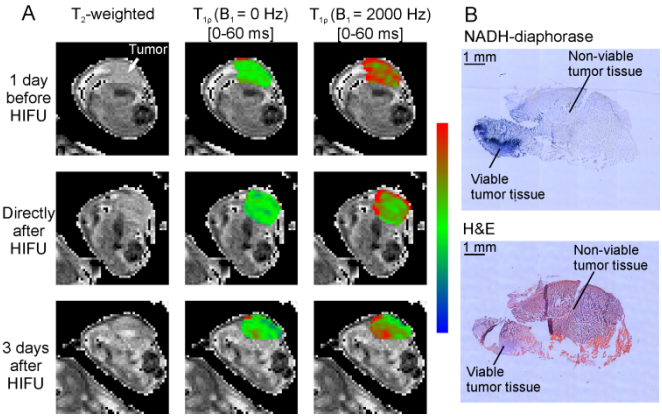

Figure 1 A) Representative examples of MRI of tumor-bearing legs before and after HIFU treatment. $T_{1\rho}$ values at B_1=0 Hz and B_1=2000 Hz are overlaid on the tumor pixels in the T_2-weighted images. B) NADH-diaphorase and H&E stained tumor sections obtained 3 days after HIFU at approximately the same location within the tumor.

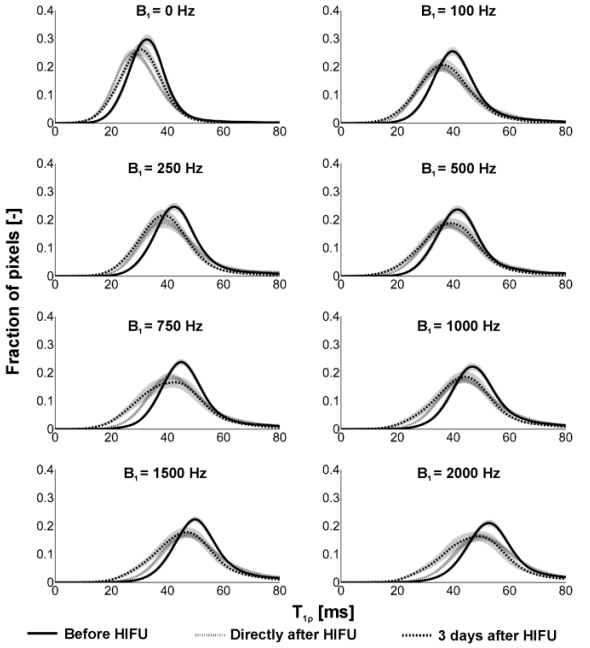

Figure 2 Average tumor $T_{1\rho}$ distributions at the different experimental time points for all assessed spin-lock amplitudes. The transparent grey bands represent the standard error.

Discussion and Conclusion The data provide evidence that $T_{1\rho}$ mapping gives superior contrast between HIFU-treated and non-treated tumor tissue at 3 days after HIFU as compared to T_2 mapping. Although only partial tumor ablation was performed, global analysis of the average $T_{1\rho}$ values in the whole tumor already showed a significant difference between tumor $T_{1\rho}$ before and at 3 days after HIFU, indicative of substantial $T_{1\rho}$ contrast between HIFU-treated and non-treated tumor tissue. $T_{1\rho}$ imaging may thus be a suitable MR method for the evaluation of HIFU treatment. Clinical translation of the method seems feasible, since significant contrast between HIFU-treated and non-treated tissue was already observed at B_1=100 Hz, which is compatible with clinical SAR constraints.

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References [1]Hectors et al. Magn Reson Med 2013;doi:10.1002/mrm.25000 [2]Hectors et al. Proc Ann Meeting ISMRM 2012:4626 [3]Kettunen et al. Radiology 2007;243:796-803. [4]Duvvuri et al. Cancer Res 2001;61(21):7747 7753 [5]Witschey et al. J Magn Reson 2007;186(1):75-85.

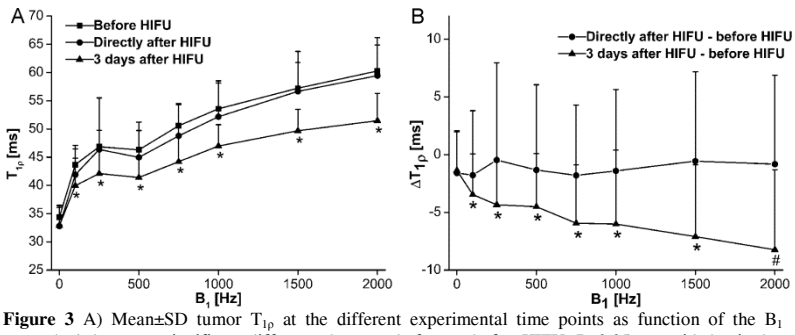

Figure 3 A) Mean±SD tumor $T_{1\rho}$ at the different experimental time points as function of the B_1 strength. * denotes a significant difference between before and after HIFU (P<0.05, two-sided paired t-test). B) Mean±SD $\Delta T_{1\rho}$ values between both time points after HIFU and before HIFU as function of the B_1 strength. * indicates a significantly lower (more negative) $\Delta T_{1\rho}$ value than at B_1=0 Hz (P<0.05, one-sided paired t-test). # indicates a significantly lower $\Delta T_{1\rho}$ value than at all other spin-lock amplitudes except 1500 Hz (P<0.05, one-sided paired t-test).