T1ρ 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 and multiparametric MR analysis based on T1, T2 and Apparent Diffusion Coefficient (ADC) data 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 T1ρ imaging. Previously, changes in tumor T1ρ after gene therapy and chemotherapy have been reported. The goal of the present study was to assess whether T1ρ also 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=14x6 cm², matrix=128x128) consisted of T2-weighted imaging (TE=30 ms, TR=2000 ms, NA=1) and T2 mapping (B1- and B2-compensated spin-lock preparation (spin-lock amplitude B1=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 Tρ measurement at B1=0 Hz is equivalent to a T2 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 T2-weighted images. This was confirmed by absence of visible changes after HIFU in the T2ρ maps at B1=0 Hz, which essentially represent T2 maps. Before HIFU, T2ρ maps at B1=2000 Hz had a slightly more heterogeneous appearance than those at B1=0 Hz, indicative of a larger variation in tumor T2ρ at higher amplitudes. At both time points after HIFU, a large region of decreased T2ρ was observed at B1=2000 Hz. Histology confirmed extensive necrosis in the tumor tissue. Average tumor T2ρ distributions indeed showed a larger spread in tumor T2ρ at higher spin-lock amplitudes before HIFU (Figure 2). Furthermore, a shift toward lower T2ρ values after HIFU was observed for all spin-lock amplitudes. The shift in T2ρ values at 3 days after HIFU treatment was larger with increasing spin-lock amplitude. Quantitative analysis of the average T2ρ value in the tumors at the different experimental time points (Figure 3A) showed a significant decrease in the average T2ρ at 3 days after HIFU treatment as compared to baseline for spin-lock amplitudes higher than or equal to 100 Hz. The average ΔT2ρ 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 ΔT2ρ at 3 days after HIFU (ANOVA for repeated measures, P=0.048). At 3 days after treatment, the ΔT2ρ values at B1 strengths above 100 Hz were significantly lower (more negative) than at B1=0 Hz. Furthermore, the ΔT2ρ value at 2000 Hz was significantly lower than the ΔT2ρ values at B1 strengths between 0 and 1000 Hz.

Discussion and Conclusion
The data provide evidence that T1ρ mapping gives superior contrast between HIFU-treated and non-treated tumor tissue at 3 days after HIFU as compared to T2ρ mapping. Although only partial tumor ablation was performed, global analysis of the average T2ρ values in the whole tumor already showed a significant difference between tumor T2ρ before and at 3 days after HIFU, indicative of substantial T2ρ contrast between HIFU-treated and non-treated tumor tissue. T2ρ 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 B1=100 Hz, which is compatible with clinical SAR constraints.

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References
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Figure 1 A) Representative examples of MRI of tumor-bearing legs before and after HIFU treatment. T2ρ values at B1=0 Hz and B1=2000 Hz are overlaid on the tumor pixels obtained 3 days after HIFU at approximately the same location within the tumor.

Figure 2 Average tumor T2ρ distributions at the different experimental time points for all assessed spin-lock amplitudes. The transparent grey bands represent the standard error.

Figure 3 A) Mean±SD tumor T2ρ at the different experimental time points as function of the B1 strength. * denotes a significant difference between before and after HIFU (P<0.05, two-sided paired t-test). B) Mean±SD ΔT2ρ values between both time points after HIFU and before HIFU as function of the B1 strength. * indicates a significantly lower (more negative) ΔT2ρ value than at B1=0 Hz (P<0.05, one-sided paired t-test). # indicates a significantly lower ΔT2ρ value than at all other spin-lock amplitudes except 1500 Hz (P<0.05, one-sided paired t-test).