Multi-parametric MRI Assessment of Tumor Response to High-Intensity Focused Ultrasound in a Rat Glioma Model

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Target audience: Researchers interested in assessing thermoablative tumor treatment response with multiparametric MRI.

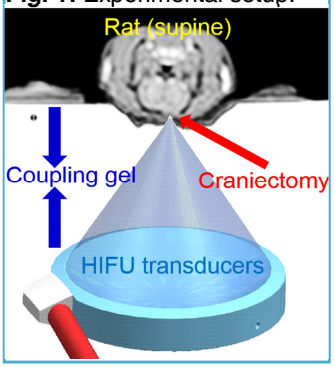
Purpose

High-intensity focused ultrasound (HIFU) is an emerging non-invasive thermal procedure for treating various solid tumors[1]. MRI plays a key role in therapy planning before HIFU treatment, monitoring temperature change during therapy, and assessing efficacy afterwards. Amide proton transfer weighted (APTw) MRI has expanded the achievable MRI contrast, and may offer a powerful aid to molecular diagnosis of malignancies and assessing their treatment response[2,3]. We hypothesized that coagulative necrosis in the tumor induced by HIFU, is associated with a decrease in blood flow and APTw-MRI signal, and an increased magnetization transfer ratio (MTR). This was tested in a pilot study of a rat glioma model with a clinical MR HIFU system.

Methods

Eight adult nude rats were implanted with human glioblastoma cells in the right forebrain. To facilitate ultrasound penetration, a ~8 mm diam. craniectomy was performed 1 wk. after tumor implantation. The skin was sutured over the craniectomy and allowed to heal for 1 wk. At ~5 wks post-implantation, HIFU was done in a clinical 3T MRI based HIFU system (Sonalleve V2, Philips Healthcare, Vantaa, Finland; 14cm focal length; 1.2 MHz acoustic frequency; 150 W acoustic power applied for 16 s; treatment cell diameter/length = 4/10 mm; 1-2 treatment cells/rat, depending on the tumor size). The rats were oriented supine on top of a home-made gel phantom that was acoustically coupled to the HIFU transducers (**Fig. 1**).

Fig. 1: Experimental setup.



Quantitative MRI were performed on a Bruker 4.7T animal system: T_2 (spin-echo EPI; TE = 30, 40, 50, 60, 70, 80 and 90 ms), T_1 (inversion recovery; TI = 50, 300, 600, 1200, 1800, 2500 and 3500 ms), diffusion (trace diffusion weighting; b = 0, 145, 290, 435, 581, 726, and 871 s/mm^2), perfusion (continuous arterial spin labeling duration=2 s), APTw (offsets = ±3.5 ppm, unsaturated and saturation duration/power=4 s /1.3 uT; quantified by MTR_{asym} at 3.5ppm), and MTR (offsets = ±10 ppm unsaturated and saturation duration/power=4 s/1.3 uT).

Animals were assessed by MRI at five different time points: one day before HIFU treatment (n = 8); and 2 hr (n = 4), 1 day (n = 8), 3 days (n = 8), and 6 days (n = 7) post-treatment. Tumor-average MRI indices were measured for each rat at each time point. The difference between pre- and post-HIFU values was statistically tested (unpaired t-test for 2 hr and paired for 1 d, 3 d, and 6 d).

Results and Discussion

Fig. 2 shows example multiparametric MRI maps from a rat. Quantitative analysis shows that, at one or two late time points post-treatment, T2 (3 days), T1 (3 days and 6 days), and MTR (3 days and 6 days) values increased significantly, while CBF (3 days and 6 days) decreased significantly, compared to pre-treatment (**Fig. 3**). Notably, APTw values were significantly decreased at all time points post-treatment. As observed previously in the U87 radiotherapy model[2], the apparent diffusion constant (ADC) decreased and then increased slightly at two early time points, albeit not significantly. The change in CBF (43%) and APTw (32%) was much greater than in T_1, T_2, ADC, and MTR.

Fig. 2: Example multiparametric MR maps at 2 hours post-HIFU.

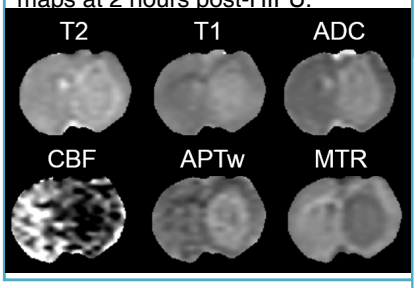
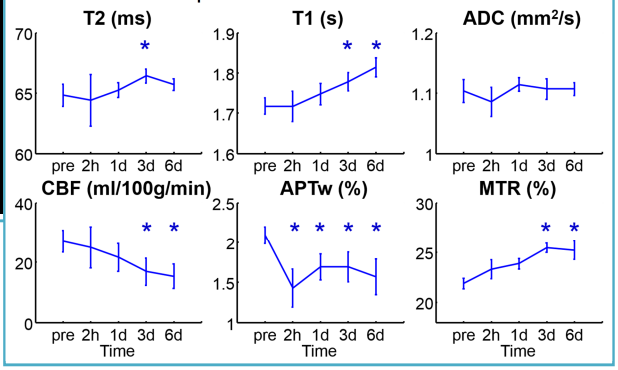


Fig. 3: Multiparametric MR indices (mean ± SE) at different time points before and after (2 h, 1 d, 3 d, 6 d) HIFU treatment. Blue stars denote significant differences from pre-HIFU indices.



The APTw signal decreased substantially after HIFU, possibly reflecting heat-induced protein cross-linking (as observed previously in the cooked eggwhite experiment[4]) and coagulative necrosis, consistent with a recent study in a mouse leg tumor model with a pre-clinical HIFU system[5]. The APTw signal may be an earlier and more sensitive index than other MRI parameters for HIFU treatment assessment.

Conclusion

Multiple MRI signals are useful noninvasive biomarkers with which to assess glioma response to thermoablative HIFU therapy. The APTw signal could be a promising biomarker for early predicting HIFU treatment effects.

References

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