Non-Invasive Histotripsy Promotes Local Tumor Regression in an In Vivo, Orthotopic Rodent Liver Tumor Model

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Background, Motivation and Objective

Current locoregional thermal ablative therapies for liver cancer inherently exhibit inconsistent tissue ablation due to irregular heat dissipation. Histotripsy therapy mechanically ablates tissue through precisely controlled, noninvasive acoustic cavitation. Previous large animal studies have demonstrated that histotripsy can uniformly ablate the target liver tissue with millimeter accuracy with no damage to surrounding blood vessels. This study evaluates the potential of histotripsy to reduce local tumor progression in an in vivo orthotopic, immunocompetent rat hepatocellular carcinoma (HCC) model.

Statement of Contribution/Methods

HCC tumors were generated by injecting 2-4 million rat-derived N1-S1 cells into the livers of n=21 immunocompetent Sprague-Dawley rats (n=6, control and n=15, treatment). The treatment cohort was further classified based on the tumor volume targeted for ablation; partial treatment (n=6, 50-75% tumor volume) and complete treatment (n=9, 100% tumor volume + 2 mm margin). 1-2 cycle histotripsy treatment pulses were delivered at 100 Hz PRF (P- >30 MPa) using a custom-built 1 MHz therapy transducer equipped with real-time ultrasound guidance. Volumetric ablation was achieved by mechanically steering the histotripsy focus to cover the target volume using a robotic positioner. Animals were monitored weekly using T2-weighted MRI (Magnetic Resonance Imaging) for 3 months or until tumors reached ~2.5cm.

Results/Discussion

Histotripsy-generated cavitation cloud ablated the targeted tumor regions guided by real-time ultrasound imaging. MRI monitoring revealed effective post-histotripsy reduction of tumor burden with near-complete resorption of the ablated tumor in 14/15 (93.3%) animals in both complete and partial treatment groups. Gross morphology showed shrunken, non-tumoral, fibrous tissue at the site of original tumor. 3/6 control and 1/15 treatment animals were euthanized early at 3 weeks due to increased tumor burden. In other 3/6 controls, gross evaluation at 3 months revealed residual tumor not detected on MRI. There was no evidence of histotripsy-induced adjacent tissue injury. Complete and partial histotripsy ablation enabled tumor removal, with no evidence of local tumor progression or recurrence in orthotopic rat liver tumor model. Additional work is ongoing to evaluate the immune response of histotripsy.

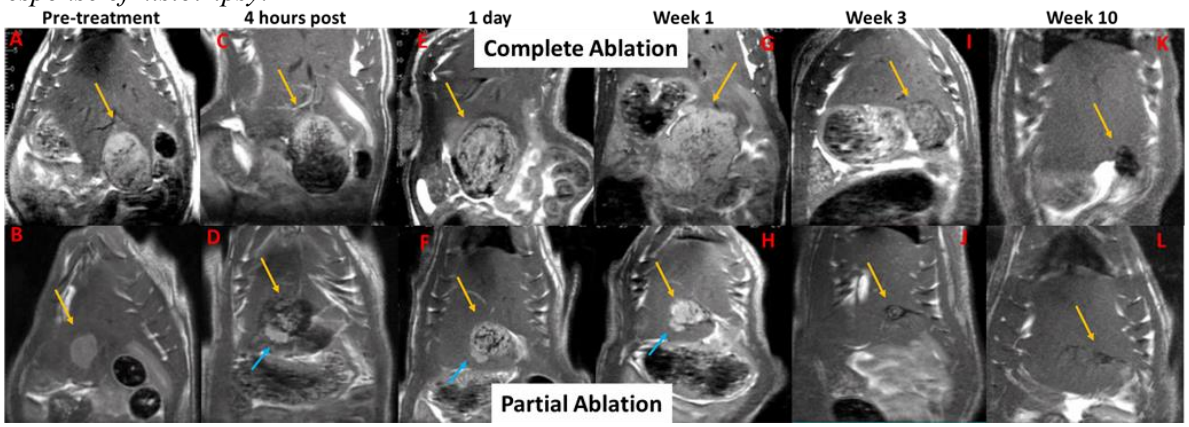

Figure 1. Local tumor regression is observed in complete and partial histotripsy (*non-targeted tumor, blue arrow*) cases without radiographic evidence of tumor by week 10 on T2-weighted MRI. At week 10, the observation of T2-hypointense tissue at original treatment site (*yellow arrow*) corresponded to shrunken, non-tumoral fibrous tissue observed on gross morphology.