Feasibility of MRI-guided focused ultrasound ablation in an orthotopic mouse brain tumor model

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Background, Motivation and Objective

Glioblastoma multiforme (GBM) has a dismal prognosis and significant efforts are being made to develop more effective treatments. MRI-guided focused ultrasound (MRgFUS) has been demonstrated in human GBM, but there is interest in combining ablation with other therapies (especially immunotherapies) to further improve patient outcomes. Therefore, preclinical studies investigating such combinations are of interest, particularly in mouse models. Ablating mouse brain tissue is technically challenging due to the small spatial scale of the target anatomy and the presence of the surrounding skull bone. The objective of this work is to develop a robust method of ablating mouse brain tumor tissue with MRgFUS through a parameter investigation with the eventual goal of evaluating the immune response of gliomas in mice following ablative MRgFUS treatments.

Statement of Contribution/Methods

Experiments were performed using a GL261 intracranial tumor model in immune-competent C57 BL/6 albino mice. To reduce superficial heating craniotomies were performed before tumor cell implantation. Tumors then grew for 14 days whereupon experiments commenced. Ultrasound exposures were carried out in a 7T MRI scanner and MR thermometry was used to monitor temperatures during sonication. In order to determine the appropriate settings for mouse glioma ablation, the focused transducer (focal length 20 mm; *f*# 0.8) was driven at 3.3, 5.5 or 7.7 MHz. Data was acquired at day 21 (7 days post ablation or sham treatment) for tumor growth and immunohistochemistry (IHC) analysis (n = 19). IHC focused on the distribution of $CD4^+$ and $CD8^+$ T-cells within tumors.

Results/Discussion

Lesions in the brain were induced at all three frequencies assessed. The bulk of experiments comprised of 15 s sonications at an acoustic power level of 2.45 W at 5.5 MHz. These parameters produced heating within the desired depth range where either single or multiple exposures were performed within tumors. Normalized tumor volumes were significantly reduced in animals that received MRgFUS ablation compared to sham controls. IHC analysis did not find any significant differences between the two groups, but future work will involve flow cytometry in order to inform the distribution of T-cells within treated tumors that may provide a rational basis for combining ablation with immunotherapies in patients with GBM.

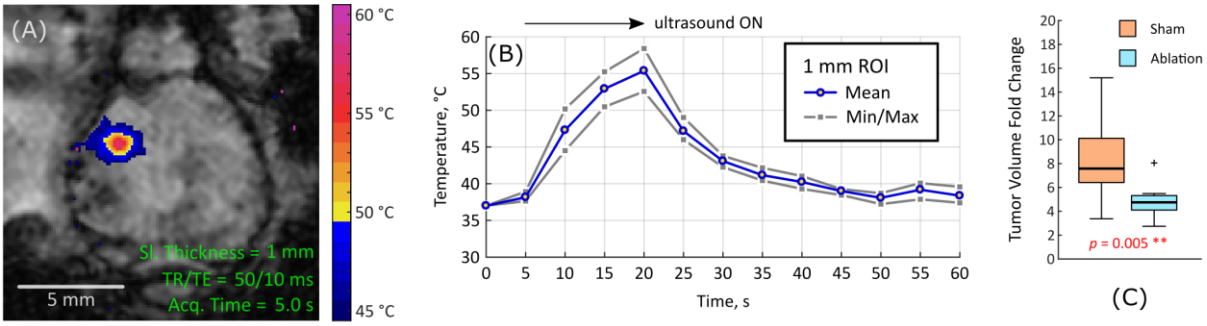

Fig. 1: (A) MR thermometry image illustrating the distribution of temperatures within the mouse brain. (B) Temperature versus time within a 1 mm diameter region-of-interest (ROI) during a 15 s sonication at 5.5 MHz targeting an orthotopic mouse glioma. (C) Normalized tumor volume fold change, calculated by taking the ratio of tumor volumes at day 14 and at day 21 following MRgFUS brain tumor ablation or sham control treatments of mouse gliomas. Tumor volumes were compared with a *t*-test.