Therapeutic efficacy of thermosensitive liposomal doxorubicin and short duration MRI-guided focused ultrasound hyperthermia in rabbit Vx2 tumors

Marc A. Santos[1,2], Sheng-Kai Wu[1,2], Maximilian L. Regenold[2], Lucy Wang[2], Christine J. Allen[2], David E. Goertz[1,2], Kullervo Hynynen[1,2], [1]Sunnybrook Research Institute, Toronto, Canada, [2]University of Toronto, Toronto, Canada

Background, Motivation and Objective

There is an urgent need to improve the delivery of chemotherapy to solid tumors while minimizing harmful side effects. One promising strategy is to combine MRI-guided focused ultrasound (MRgFUS) hyperthermia with thermosensitive liposomal doxorubicin (TSL-Dox) to achieve localized release at the tumor site. The current approach is to maintain hyperthermic conditions in target regions for long periods (>10 min). In many circumstances this is impractical for realistic tumor volumes due to the issues of respiratory motion, bone shielding and large blood vessel cooling. We have previously shown that using FUS for shorter durations can reduce the impact of blood vessel cooling and can be applied during a breath hold to limit motion effects. It remains an open question whether short duration MRgFUS hyperthermia can release enough drug from TSL-Dox to have a therapeutic effect. In this work we investigated short duration MRgFUS hyperthermia with TSL-Dox on its ability to treat rabbit Vx2 tumors.

Statement of Contribution/Methods

Vx2 tumors were initiated in New Zealand white rabbit thighs and grown for 12 days whereupon experiments commenced. TSL-Dox was manufactured in-house and given at a dose of 1.67 mg/kg of doxorubicin. Rabbits were assigned into 1 of 3 treatment groups: MRgFUS alone (n = 5), TSL-Dox alone (n = 6) or MRgFUS+TSL-Dox (n = 6). Acute histologic examination of heated and unheated bilateral Vx2 tumors was performed (n = 1). Sonications were conducted to heat discrete 4 mm diameter regions-of-interest (ROI) that covered the tumor. Each ROI was sonicated for 30 s to a temperature of 42 °C a total of 10 times. Tumor volumes were measured with MRI on a weekly basis following treatment to evaluate antitumor efficacy.

Results/Discussion

At 14 days post treatment, tumor volumes in the group receiving MRgFUS+TSL-Dox were reduced 16-fold compared to MRgFUS alone and reduced 13-fold compared to TSL-Dox alone. Survival also significantly improved with MRgFUS+TSL-Dox. This provides the first *in vivo* demonstration of the therapeutic effect of short duration MRgFUS hyperthermia combined with TSL-Dox. The profound antitumor effects observed in this study suggest that short duration MRgFUS hyperthermia may be a viable new method to overcome longstanding issues that have inhibited the clinical adoption of FUS-mediated hyperthermia for a broad spectrum of tumor types and sizes.

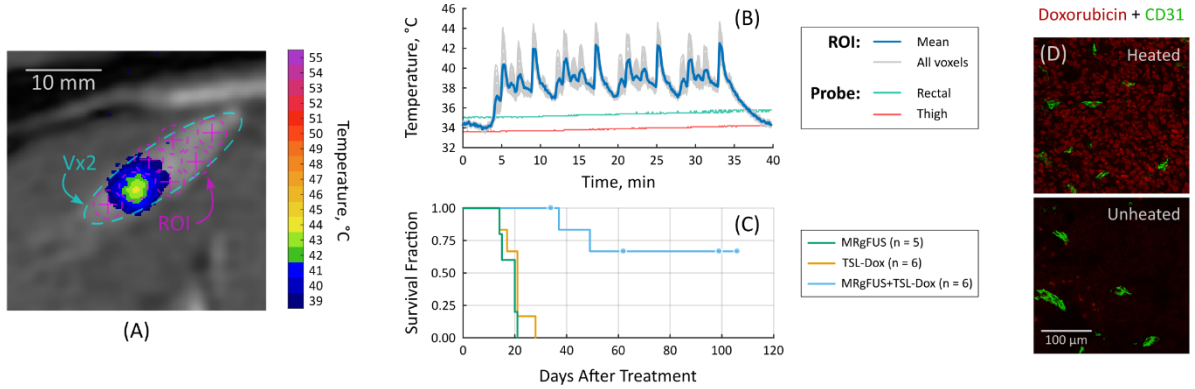

Fig. 1: (A) MR thermometry image illustrating the temperature distribution within the heated Vx2 tumor. (B) Representative Vx2 tumor ROI temperature as a function of time during short duration MRgFUS hyperthermia. (C) Kaplan-Meier plot of rabbit survival, data points represent animals with tumors that have not reached humane size-related endpoints and remain under observation. (D) Fluorescent microscopy of Vx2 tumor sections in heated (top) and unheated (bottom) tumors highlighting the difference in doxorubicin fluorescence intensity and the increased accumulation of the drug within heated tumors.