PET-MR-US in drug delivery

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Hypothesis: Precise three dimensional control of therapeutic ultrasound can be exploited to enhance cancer drug delivery.
Methods: Relevant parameters include the following**:** 16-element annular ultrasound array integrated with high speed motors, transducer diameter: 45 mm**,** radius of curvature: 35mm**,** acoustic efficiency > 65%**,** power rating: 50W**,** focal spot size (approx.): 1.5mm x 1.5mm x 2mm. Multiple planes of MR acquisition are sent in real time from the Bruker 70/30USR Biospin to the Thermoguide (Image Guided Therapy- IGT) thermal controller. The IGT system has multiple embedded algorithms for temperature estimation, motion correction and temperature display. In our study, temperature estimation was performed by a simple proton resonance frequency shift algorithm. With a Luxtron fiberoptic probe, we first validated ultrasound-induced temperature changes produced by 3-MHz ultrasound. A tight spiral trajectory was directed to a 3 mm ROI, increasing the temperature by 2-9ºC. For in vivo studies approved by the UC Davis Animal Use and Care Committee, we applied therapeutic ultrasound (1.5 MHz, 2 minutes, 32% duty cycle adjusted to maintain temperature, 1.3 MPa, temperature increase of 5°C) within tumors in the Met-1 mouse under ultrasound guidance. Fusion with PET was used to measure the accumulation of drug delivery vehicles, where MRI and PET image spaces are aligned by fiducial-based registration. For PET imaging, we have developed a surface chelation labeling method using ^{64}Cu (half life = 12.7 h), where ^{64}Cu is added to preformed particles which contain BAT(6-[*p*-(bromoacetamido)benzyl]-1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid)-lipids. This method provides fast and simple labeling of particles with ^{64}Cu.
Results: Using a 3 mm spiral trajectory, temperature increases of 2-9ºC were created using ultrasound (**Fig. 1a-c**). Insonation of ex vivo turkey breast demonstrated a localized temperature increase in the insonified region of interest (**Fig. 1b-c**). The phase and resulting temperature estimate maps (**Fig. 1b-d**) acquired using a TE of 7.4 ms correlated with the temperature increase as measured by the Luxtron (**Fig. 1a**). Preliminary studies insonifying the Met-1 tumor (**Fig. 1e**) with 1.5-MHz ultrasound demonstrated greater than 2-fold enhancement in the accumulation of PET-labeled vehicles in tumors using PET, achieving concentrations as high as 20% injected dose/gram-tumor (**Fig. 1f,** where the insonified region of interest is shown with an arrow).
Conclusion: We found that real time MR control of hyperthermia is feasible at high field with a temperature accuracy on the order of 1ºC. Local ultrasound hyperthermia can significantly increase the local accumulation of drug delivery vehicles within the Met-1 tumor; additional studies will be described using insonation of doxorubicin-loaded particles under MR guidance.

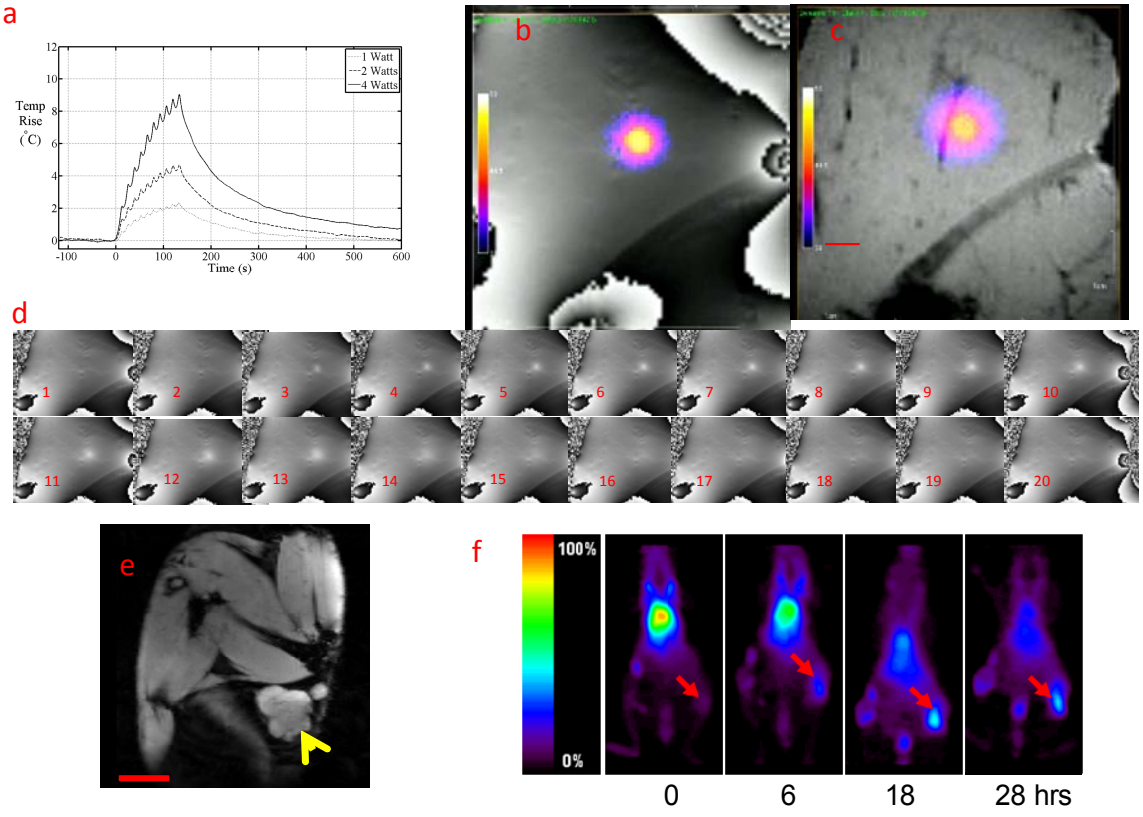

Fig. 1. Preliminary evaluation of MR temperature mapping at high field and the use of ultrasound to enhance drug delivery. **(a)** Temperature validation using the Luxtron during spiral US trajectories with 1, 2, or 4 acoustic Watts of transmission for 2 minutes. Small artifacts are observed as the US scans over the Luxtron. **(b-c)** Phase map **(b)** and magnitude image **(c)** with temperature overlay from IGT system resulting from FLASH sequence applied to turkey breast with TR of 44.7 ms, TE of 7.4 ms, FA 10º, matrix 128x64, slice thickness 2 mm, FOV 8 cm. Ultrasound (3 MHz, 4W) was scanned in 3 mm spiral pattern. Temperature elevation was spatially mapped. **(d)** Subset of phase images acquired over 3 minutes before, during and after insonation applied starting in frame 3 above, insonation ended in frame 9. **(e)** Representative MR slice from a 3-minute 20-slice scan mapping location of tumor and surrounding structures to plan acoustic therapy in live Met-1 tumor mouse. Scan used 200 mm gradient set, circularly polarized 15.4 cm transmit coil in quadrature mode, rat brain 4-element phased array coil on receive with fat and motion suppression applied and the following parameters: TR 450 ms, TE 7.1 ms, FOV 4.32/3.2 cm, 0.17 x 0.25 x 0.65 mm^3 voxels. Red scale bar 5 mm, yellow arrow indicates Met-1 tumor implanted within mammary fat pad. **(f)** PET images acquired from Met-1 mouse after injection with ^{64}Cu-labeled particles and tumor insonation (red arrow indicates insonified tumor).