COMBINING DCE-MRI AND DCE-ULTRASOUND: A NOVEL PRE-CLINICAL IMAGING PROTOCOL FOR ASSESSING CANCER TREATMENT EFFICACY

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Introduction

The use of complementary non-invasive imaging modalities has been proposed to track disease progression, particularly cancer [1], while simultaneously evaluating therapeutic efficacy. The applicability of these techniques spans a wide spectrum of disease processes. However, a major obstacle presents itself if it is necessary to compare images between modalities if care is not taken to image the same region. One potential solution is to engineer dual scanners that allow for (near) simultaneous imaging (e.g., PET-MR). However, in certain circumstances (such as MRI and Ultrasound), it is nearly impossible to design a scanner without making significant engineering compromises or making cost-prohibitive choices. Multi-modality imaging is also hampered by a limited ability to compare parameters obtained from different modalities, especially those from exogenous contrast agents or tracers. With the proposed imaging protocol, a number of challenges can be bypassed with *a priori* image registration between MR and Ultrasound (US) data, accurate to within 0.25mm in-plane and 0.5mm through-plane. We hypothesize that using DCE-MRI (extravascular contrast agent) in combination with DCE-US (intravascular contrast agent) will extend non-invasive characterization of tumours and facilitate a more complete analysis of the tumour microenvironment following treatment.

Materials and Methods

Imaging Apparatus: To enable co-planar MR and US imaging, a physical co-registration apparatus was designed for mouse tumour imaging. Acoustic waves transmitted from a transducer located above the apparatus are coupled to a water tank placed between the mouse and the transducer. A 1-mm thin fiducial marker is fixed in the water tank and provides a reference plane (Fig. 1).

Mice: Six (6) nude SCID mice from Charles River were injected with Lewis Lung Carcinoma cells subcutaneously in the hind limb and allowed to grow to a diameter of 1cm. Mice were anaesthetized with an injectable anaesthetic cocktail and imaged sequentially first with US and then MR. Immediately following the baseline scan, four of the six tumours were irradiated with 8Gy, delivered as a single fraction and imaged 24 hours later. Mice were then sacrificed and the tumours excised and sectioned in planes parallel to the US/MR imaging planes.

MRI: Imaging was performed using a 7T (Bruker Biospin, Germany) scanner with an 86cm coil for both transmit and receive. A high contrast anatomic image with high spatial resolution (0.2 x 0.2 x 0.5 mm) was taken with a 2D spin echo sequence (TR/TE = 3200ms/11.6ms with an acceleration factor of 8 at 15 NEX). For DCE-MRI, a 3D spoiled gradient echo sequence was used (TR/TE= 7.8/3.8 ms, flip angle = 15, spatial resolution of 0.2 x 0.2 x 1.0 mm). A 0.2 mL bolus of Gd-DTPA-BMA (Omniscan, GE Healthcare, Milwaukee, WI) diluted to 0.05 mM/mL was injected manually and data acquired at a temporal resolution of 8.7s with full tumour coverage. A semi-quantitative parameter map was constructed by taking the difference of voxel intensities pre and post injection, and then dividing by the signal intensity before agent administration ($\Delta S/S_0$).

Ultrasound: US imaging was performed using the Vevo 2100 scanner (VisualSonics) operating at a centre frequency of 21 MHz. Anaesthetized mice were continuously infused with commercially available (MicroMarker; VisualSonics, Toronto, Canada) gas filled lipid shells (microbubbles) and DCE-US data was acquired at a temporal resolution of 0.2s. A high mechanical index ultrasound pulse (burst) can destroy all bubbles in plane creating a negative bolus, followed by the circulating microbubbles re-perfusing the tissue. A parameter map of relative contrast agent concentration was constructed by taking the difference of voxel intensities just after a burst and after ~90s of reperfusion. The fiducial marker was used to align the US transducer and acquire three sagittal slices, parallel to the reference plane, 1 mm apart.

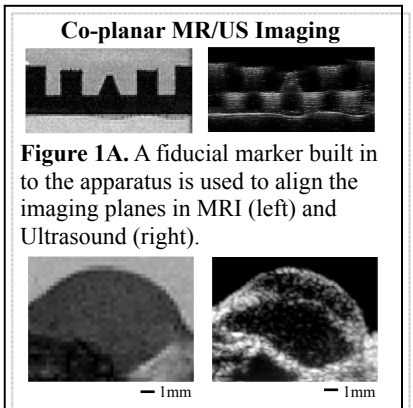

Figure 1A. A fiducial marker built in to the apparatus is used to align the imaging planes in MRI (left) and Ultrasound (right).

Figure 1B. Using the fiducial markers in 1B, MR (left, Spin Echo) and US (right, B-mode) anatomic images of a mouse tumour can be acquired in a very similar plane.

Results and Discussion

High doses of radiation (> 8Gy) have been demonstrated to cause severe vascular destruction within hours after irradiation [2] followed by secondary tumour cell death. Contrast agents used in DCE-MRI typically extravasate from abnormal and tortuous tumour vasculature. Following a vascular disrupting treatment such as radiation, these contrast agents, through a combination of extravasation and diffusion, have a larger accessible volume and as indicated in Fig.2, this leads to increased signal intensity. In DCE-US, these same regions (circles) show a reduced distribution of microbubbles due to vascular disruption and overall poor perfusion. Preliminary results suggest that effects of an 8Gy radiation dose delivered in a single fraction manifests in tumour microenvironment changes as early as 24 hours following treatment (Fig. 2). The combination of intravascular (US, microbubbles) and extravascular (MR, Gd-DTPA-BMA) contrast agents in the same animal with similar imaging planes provides a novel pre-clinical platform for improved characterization of the tumour microenvironment. Several applications of this protocol arise such as studying the effects of novel anti-angiogenic agents including theories of vascular normalization, metronomic dosing and synergistic combinations of existing drugs.

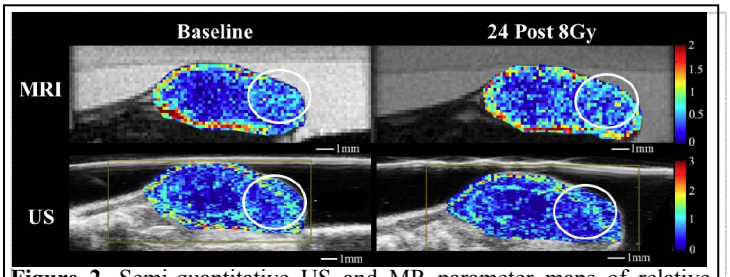

Figure 2. Semi-quantitative US and MR parameter maps of relative contrast agent concentration in the same slice of a representative mouse. The colour bars for MR (linear) and US (log-compressed) are shown representing signal intensity increase. Effects of radiation 24h after treatment are evident, especially in the marked areas (circle).

References: [1] Laking, G.R. et al., *Critical Reviews in Oncology Hematology*, 2006. **58** (2): 95-113.
[2] Garcia-Barros M et al., Science, May 16 2003;300(5622):1155-9