Prediction of Treatment Response and Tumor Recurrence Using MR Elastography

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Target Audience: Clinicians and MR scientists interested in the use of MR for the study of cancer and therapy response.

PURPOSE: It is well known that change in tissue mechanical properties are associated with malignant transformation and is the basis for palpation for the detection of cancerous lesions. Magnetic resonance elastography (MRE) is a promising new methodology for the noninvasive diagnosis, characterization, and monitoring of therapy response in cancer. Recently, MRE-derived estimates of tissue stiffness have been shown to predict response to chemotherapy in certain solid malignancies [1-3]. The *purpose* of this study was to determine if MRE is capable of predicting tumor regrowth following failure of therapy. We *hypothesize* that MRE-derived shear stiffness measurements will reflect the response to chemotherapy observed in the tumors.

METHODS: Tumors were grown in 22 genetically modified mice (6–8 weeks) using a subcutaneous injection of DoHH2 (non-Hodgkin's lymphoma) cells in accordance with institutional animal care and use committee (IACUC) guidelines [1]. Two animals failed to grow tumors and were excluded from the study. Following an initial scan to determine baseline stiffness, 12 animals received a single dose of cyclophosphamide (Sigma Chemical, 160 mg/kg). MRE was performed on every animal using the experimental setup shown in Figure 1 at baseline and every 3 days following treatment until day 18 or until the tumor reached a volume of 2.5 cm^3. In order to investigate the relationship between dose and response to therapy, two animals received an injection of normal saline to serve as controls. The remaining 6 animals were divided into 3 groups to receive different doses of cyclophosphamide: 150, 180, and 210 mg/kg. MRE measurements were obtained for each animal every 24 hours from baseline to 5 days post-treatment, or until the tumor reached a volume of 2.5 cm^3.

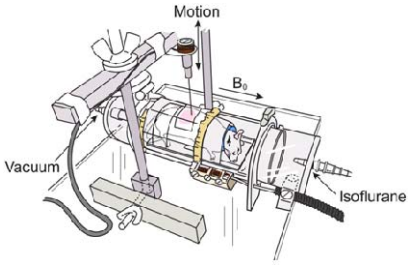

Figure 1: Experimental setup

All imaging experiments were performed on a 3.0T whole-body GE scanner (Signa, GE Healthcare, Milwaukee, WI, USA) using a custom-built, 4cm diameter 8-channel receive only coil. Shear waves were introduced into the tumors at a frequency of 800Hz through an MRI-compatible needle attached to a high-frequency electromechanical driver. The MRE imaging parameters for an EPI-MRE pulse sequence included FOV = 4 cm, coronal image plane, TR/TE = 1100.0/99.3 ms, 4 contiguous slices, 2-mm slice thickness, motion-encoding gradient (MEG) frequency = 800Hz, 60 MEG pairs, through-plane MEG direction, 3 phase offsets, motion-encoding sensitivity = 4.0 μm/(π radians), BW = ±83 kHz. Elastograms (stiffness maps) were calculated using a Multiple Model Direct Inversion (MMDI) algorithm with a directional filter (Butterworth bandpass filter with cutoff frequencies 2-128 cycles/FOV) [5-6]. All mice were allowed to breathe freely and were kept under general anesthesia using a steady flow of isoflurane during the image acquisition. Volumetric measurements were obtained using both a caliper (GENERAL, 6" Dial Caliper) to confirm tumor response to the treatment. Response was defined as a 20% reduction in tumor volume.

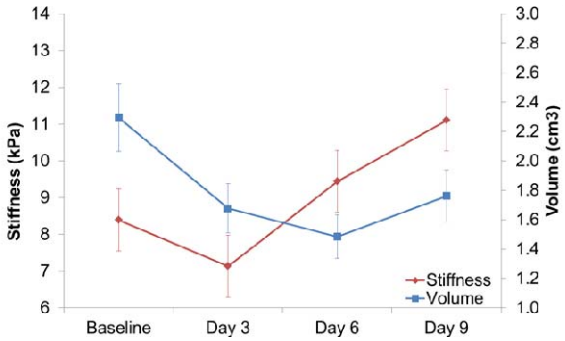

Figure 2: Change in tumor stiffness (red) and volume (blue) with time following a single dose of chemotherapy (n = 2).

RESULTS: In the initial group of 12 animals, 2 had a 20% reduction in tumor volume following chemotherapy. Tumor shear stiffness and volume decreased from baseline at day 3 (Figure 2). Shear stiffness increased at day 6, and this change preceded an increase in tumor volume. Figure 3 shows the percent change in tumor stiffness from baseline for different doses of chemotherapy. Shear stiffness increased in the control group (+8%), and decreased for the treatment groups (-14.5%for the low dose, -14.8% for medium dose, and -22% for high dose).

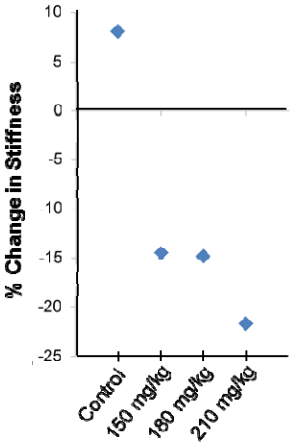

Figure 3: % change in tumor stiffness from baseline to day 3

DISCUSSION: In this study, tumor shear stiffness decreased within 3 days following chemotherapy treatment. Change in tumor mechanical properties are well correlated with decrease in tumor volume, the current clinical criteria for response to therapy. Following failure of therapy, tumor shear stiffness increased at day 6 before an increase in tumor volume, suggesting an earlier indication of tumor regrowth than current clinical criteria would suggest. Change in tumor stiffness also corresponded to change in chemotherapy dose; the higher the dose the greater the decrease in tumor stiffness.

CONCLUSION: Previous work has demonstrated the potential of MRE-derived tumor shear stiffness as a biomarker of response to chemotherapy. This study has demonstrated that MRE-derived tumor shear stiffness is a predictor of tumor regrowth prior to an increase in tumor volume. Tumor response to therapy as determined by MRE also demonstrates a dose-dependence, suggesting that change in tumor stiffness is sensitive to change in therapy. Therefore, these results further demonstrate that MRE-derived shear stiffness may be a sensitive biomarker of tumor response to chemotherapy.

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References: [1] Pepin, K.M., et al. MRM, 2014. [2] Juge, L et al. [3] Li, J. BJC, 2014. 1-6.[4] Ansell, S.M.,et al Leukemia, 2004. 18(3). [5] Manduca, A., et al. Med Image Anal, 2001. 5(4). [6] Manduca, A., et al. Med Image Anal, 2003. 7(7).