

Assessment of Early Tumor Response to Chemotherapy Using MR Elastography (MRE)

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Introduction: In the treatment of cancer with chemotherapy, a key strategy is to identify as early as possible the response of tumors to the therapeutic agent. Traditionally, therapeutic response is based on volumetric measurements obtained using imaging based methods, which typically requires a significant period of time before a tumor response can be detected [1-4]. We are investigating tumor stiffness as a new biomarker to evaluate the response of tumors to chemotherapy, as early as several hours after drug administration. The *purpose* of this study is to test the feasibility of using magnetic resonance elastography (MRE) to assess the early response of tumors to chemotherapy in an immune-deficient mouse model. Our *hypothesis* is that chemotherapy treated tumor stiffness is significantly different from those tumors treated with saline.

Methods and Materials: Following institutional animal care and use committee (IACUC) approval 11 tumors were grown in genetically modified mice (6-8 weeks) using a subcutaneous injection of DoHH2 cells [5]. The mice were divided into two groups, the first considered the "control" (N=6) and the second the chemotherapy or "chemo" (N=5) group. The saline group received an injection of normal saline while the chemo group received 4mg of cyclophosphamide (160mg/kg). Four hours after administration, the mice were sacrificed by inhalation of CO₂ gas following which the tumors were excised in preparation for imaging (Figure 1(a)) while MRE was performed using the experimental setup shown in Figure 1(b). A high-frequency shear driver was developed to vibrate the tumor at 1 kHz while an in-house 6-cm diameter transmit-receive RF coil was used for imaging. All experiments were performed on a 1.5T scanner (14.0 EXCITE twinspace, GE Healthcare, Waukesha WI) using a spin echo MRE sequence. MRE imaging parameters included FOV = 5 cm; TR/TE = 500/71 msec; motion encoding gradient (MEG) frequency = 1kHz; through-plane MEG direction; motion encoding sensitivity = 7.77 $\mu\text{m}/(\pi \text{ radians})$; BW = 15.63 kHz. After MRE data acquisition elastograms (stiffness maps) were calculated using a phase gradient algorithm with directional filters (Butterworth band pass filter cutoff frequencies 1-80 waves/FOV) [6, 7].

Results: The shear wave displacement field and reconstructed elastograms for a control and chemo treated tumor are shown in Figure 2. In these data, the chemotherapy treated tumor is qualitatively stiffer than the control tumor. A one-sided t-test (JMP Statistics Package, Raleigh NC) was applied to the individual stiffness values for all data and indicated that the difference in shear stiffness between the two groups at four hours post administration was statistically significantly different ($p = 0.034$) with chemotherapy tumors being the stiffer of the two (Figure 3).

Conclusions: This study indicates that MRE has the potential to detect change in tumor stiffness in response to chemotherapy at time points significantly shorter than those derived from imaging-based assessment of treatment response. Overall, the results provide motivation for investigating the potential for MRE as an early predictor of tumor response to chemotherapy and suggest that MRE-based shear stiffness is a highly sensitive biomarker in this regard. Ongoing work involves the testing of the above hypothesis *in vivo* within the same mouse tumor model under conditions of general anesthesia (Figure 4).

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References:

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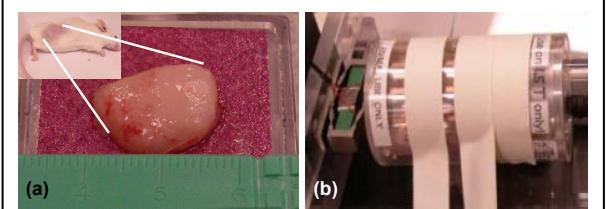


Figure 1: Experimental set up for mouse tumor MRE. (a) Excised flank tumor. (b) MRE driver RF coil.

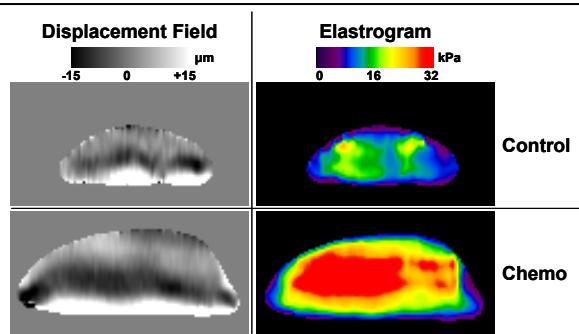


Figure 2: Shear wave displacement field & elastogram images for a saline (control) and chemotherapy (chemo) treated tumors.

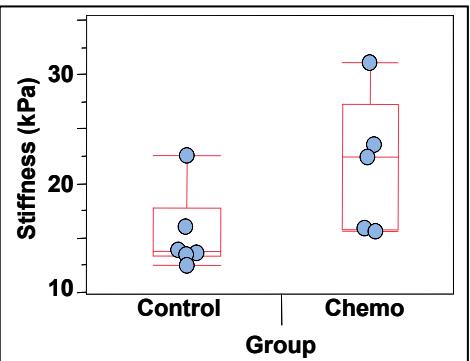


Figure 3: Tumor shear stiffness four hours post administration of saline (control) and chemotherapy (chemo). The chemo group is statistically significantly stiffer than the control ($p=0.034$).

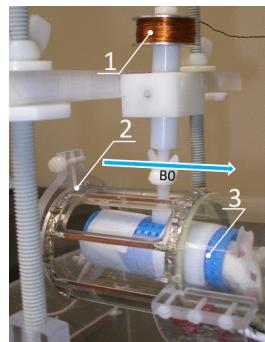


Figure 4: In vivo whole mouse MRE experimental set up showing electro-mechanic coil (1), 6 cm RF coil (2) and whole body shear driver (3).