

# A New Biomarker for the Assessment of Early Tumor Response to Chemotherapy Using MR Elastography (MRE)

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**Introduction:** Chemotherapy is considered an effective option in the treatment of cancer either alone or as an adjuvant therapy. Due to the nonspecific normal tissue toxicity of most chemotherapeutic agents, early identification of therapeutic response is essential so as to minimize treatment-induced complications and allow for alteration of the chemotherapy agent to improve treatment efficacy. Clinically, reduction in tumor size by metabolic (i.e. PET) or anatomical (MRI & CT) imaging is the primary metric for assessment of therapeutic response. However, it is generally appreciated that a significant time delay exists between initiation of therapy and when the tumor becomes visibly or measurably smaller [1-3]. The *purpose* of this study is to determine if magnetic resonance elastography (MRE) is capable of detecting an early change in the stiffness of tumors that have been treated with chemotherapy. We therefore *hypothesize* that chemotherapy treated tumor stiffness is significantly different from tumors treated with a placebo (i.e. saline).

**Methods and Materials:** Following institutional animal care and use committee (IACUC) approval, 20 tumors were grown in genetically modified mice (6–8 weeks) using a subcutaneous injection of DoHH2 (non-Hodgkin's lymphoma) cells [4]. The mice were divided into two groups, the first considered the "control" (N=7) and the second the chemotherapy or "chemo" (N=8) group. Four mice failed to grow tumors and were excluded from the study. Following an initial scan to determine baseline stiffness, the control group received an injection of normal saline while the chemo group received 4mg of cyclophosphamide (160mg/kg). MRE was performed on each mouse using the experimental setup shown in Figure 1 at 5 different time points (baseline to 4 days post-injection). A high-frequency electromechanical driver was developed to produce localized vibrations in the tumor at 800Hz through an acupuncture needle inserted into the tumor. All experiments were performed on a 3.0-T whole-body GE scanner (Signa, GE Healthcare, Milwaukee, WI, USA) using a custom-built, 6-cm diameter, transmit-receive RF coil and an EPI MRE sequence. The MRE imaging parameters included FOV = 5 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  $\mu\text{m}/(\pi \text{ radians})$ , BW = 83 kHz. 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) and measurements from a T2-weighted image to confirm a tumor response to the treatment. 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].

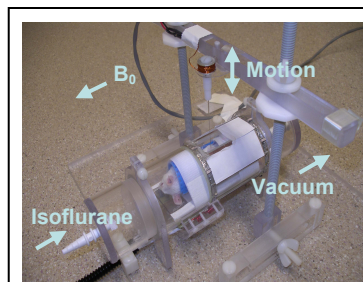
**Results:** Elastograms at baseline and day 4 for both a saline- and a chemotherapy-treated mouse tumor are shown in Figure 2. In the saline-treated mice (N=7), the average shear stiffness from baseline to day 4 increased by 1.4 kPa ( $9.7 \pm 1.1$  to  $11.1 \pm 0.94$  kPa). Alternatively, the average change in stiffness in the chemo mice (N=8) was a decrease of 1.7 kPa ( $9.9 \pm 1.7$  to  $8.2 \pm 1.9$  kPa). The large standard deviation is mainly due to heterogeneities within the tumors. A multiple-comparison Tukey HSD test was performed and the results are shown in Figure 3. In the chemo group, there was a significant change in stiffness from baseline at day 3 ( $p = 0.04$ ) and day 4 ( $p = 0.02$ ). No significant change in stiffness was observed in mouse tumors following administration of saline. Similarly, no statistically significant change in volume was observed in either the control or chemo group, however the tumors in the control group tended to become larger ( $p=0.53$ ) and tumors in the chemo group remained the same or decreased slightly ( $p=0.59$ ). A previous ex vivo mouse tumor study suggested that stiffness increased in the chemo group 4 hours after drug administration [7]. No changes in stiffness were observed in vivo at time points before three days after injection. Histological analysis will be performed on the tumors excised immediately following the day 4 scan to determine if there is a difference on the cellular level between the control and chemo groups.

**Conclusions:** These initial data confirm the hypothesis that MRE is capable of detecting a change in tumor stiffness within 3-4 days of drug administration. Changes in tumor stiffness may be an early predictive biomarker for the effectiveness of a chemotherapy treatment, which may improve the individualized response-adaptive chemotherapy to reduce both short- and long-term side effects. Ongoing efforts involve additional animal models and preliminary in vivo testing.

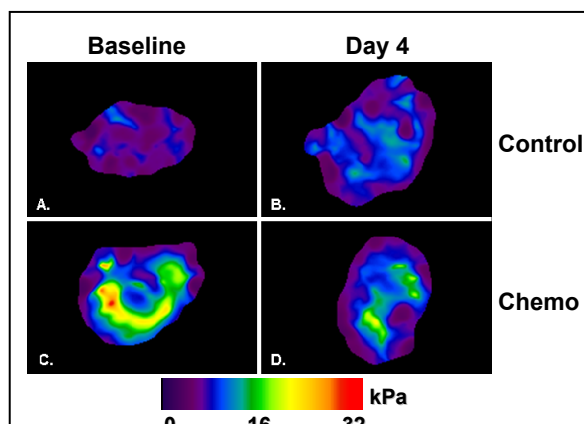
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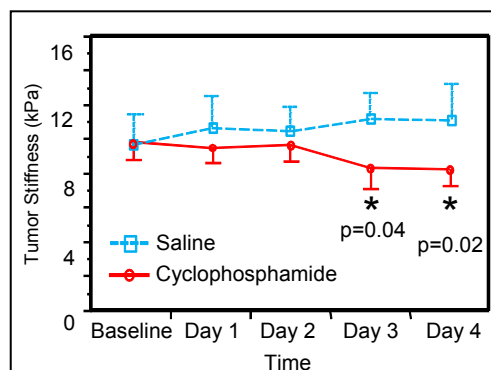
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**Figure 1:** Experimental setup for mouse tumor MRE.



**Figure 2:** Reconstructed elastograms for a saline- (control) and a chemotherapy-treated (chemo) mouse tumor at baseline (A,C) and day 4 (B,D).



**Figure 3:** Measured change in tumor stiffness after administration of chemo (red circle, N=8) and saline (blue square, N=8). Asterisk: statistically significant.