Utilizing a reference material for assessing absolute tumor mechanical properties in modality independent elastography

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ABSTRACT

There is currently no reliable method for early characterization of breast cancer response to neoadjuvant chemotherapy (NAC) [1,2]. Given that disruption of normal structural architecture occurs in cancer-bearing tissue, we hypothesize that further structural changes occur in response to NAC. Consequently, we are investigating the use of modality-independent elastography (MIE) [3-8] as a method for monitoring mechanical integrity to predict long term outcomes in NAC. Recently, we have utilized a Demons non-rigid image registration method that allows 3D elasticity reconstruction in abnormal tissue geometries, making it particularly amenable to the evaluation of breast cancer mechanical properties. While past work has reflected relative elasticity contrast ratios [3], this study improves upon that work by utilizing a known stiffness reference material within the reconstruction framework such that a stiffness map becomes an absolute measure. To test, a polyvinyl alcohol (PVA) cryogel phantom and a silicone rubber mock mouse tumor phantom were constructed with varying mechanical stiffness. Results showed that an absolute measure of stiffness could be obtained based on a reference value. This reference technique demonstrates the ability to generate accurate measurements of absolute stiffness to characterize response to NAC. These results support that 'referenced MIE' has the potential to reliably differentiate absolute tumor stiffness with significant contrast from that of surrounding tissue. The use of referenced MIE to obtain absolute quantification of biomarkers is also translatable across length scales such that the characterization method is mechanics-consistent at the small animal and human application.

Keywords: breast cancer, mechanical properties, elastography, parameter reconstruction, mechanical model

1. INTRODUCTION

Pathological phenomena such as the presence of scirrhous carcinoma in the breast can be detected through changes in tissue elasticity [9]. Elastic moduli of malignant breast carcinoma samples have been reported to be 5 to 20 times higher compared to adipose-glandular tissue and fibroadenoma specimens [9]. Tumors appear as hard nodules which result in increased stromal density. Diseases that deposit fats and collagen can also increase or decrease tissue elasticity. Fluid filled cysts that are invisible to ultrasound examinations are often softer than the embedding tissue. In many cases, small pathological lesions preclude ultrasonic detection due to lack of acoustic backscatter properties [10]. For similar reasons, standard methods like palpation and mammography are also unable to detect certain tumors or lesions [9].

Elastography is an emerging imaging tool that can be used to identify potential pathologies that elude standard detection. Further, we hypothesize that elastography may be an important tool to monitor and track therapy-induced structural changes to breast cancer tissue architecture. Many current quasi-static elastography methods used in breast cancer imaging, such as modality-independent elastography (MIE) [3-8] and strain imaging [11-13], assess relative differences in tissue stiffness between the tumor and layers of surrounding tissue. This is generally achieved through a combination of image and signal processing, and numerical methods to evaluate the relative tissue stiffness at every point within the imaging domain [14]. A fundamental limitation of such quasi-static elastography methods is the inability to reconstruct absolute measurements of elasticity due to the indeterminate nature of displacement based boundary conditions. Consequently, the actual value of tissue stiffness for the tumor and neighboring tissue remains unknown. This limits our understanding of the biomechanical properties of tumors in breast cancer and hinders longitudinal assessment and monitoring of tissue stiffness.

The goal of this work is to describe a technique for accurate and reliable absolute quantification of mechanical properties in cancer therapeutic systems through direct comparisons against a known fixed reference material. This so called 'referenced MIE' approach improves upon previous work [3] in which the elasticity biomarker reported by MIE only provided relative estimates of mechanical properties within the tissue of interest at a single time point. Generating a map of absolute material properties thus facilitates longitudinal comparisons required for dynamic characterization of tumor response during the course of NAC, which we hypothesize may be an imaging biomarker capable of early prediction of response to therapy. Compared to several other proposed characterization methods, the elastography imaging methodology used within this work is: (1) robust and simple to implement, (2) noninvasive, (3) capable of being registered to other assessment modalities, and (4) translatable across length scales.

2. METHODS

2.1 MRI imaging

T_2 weighted image volumes of phantoms were acquired in a pre-deformation state using a Varian 7.0T MRI scanner (Varian, Palo Alto, CA) with a 38-mm quadrature coil using a fast spin echo sequence. Phantoms were then deformed using a balloon catheter controlled by a syringe driver and imaged again to obtain a post-deformation image volume (Figure 1).

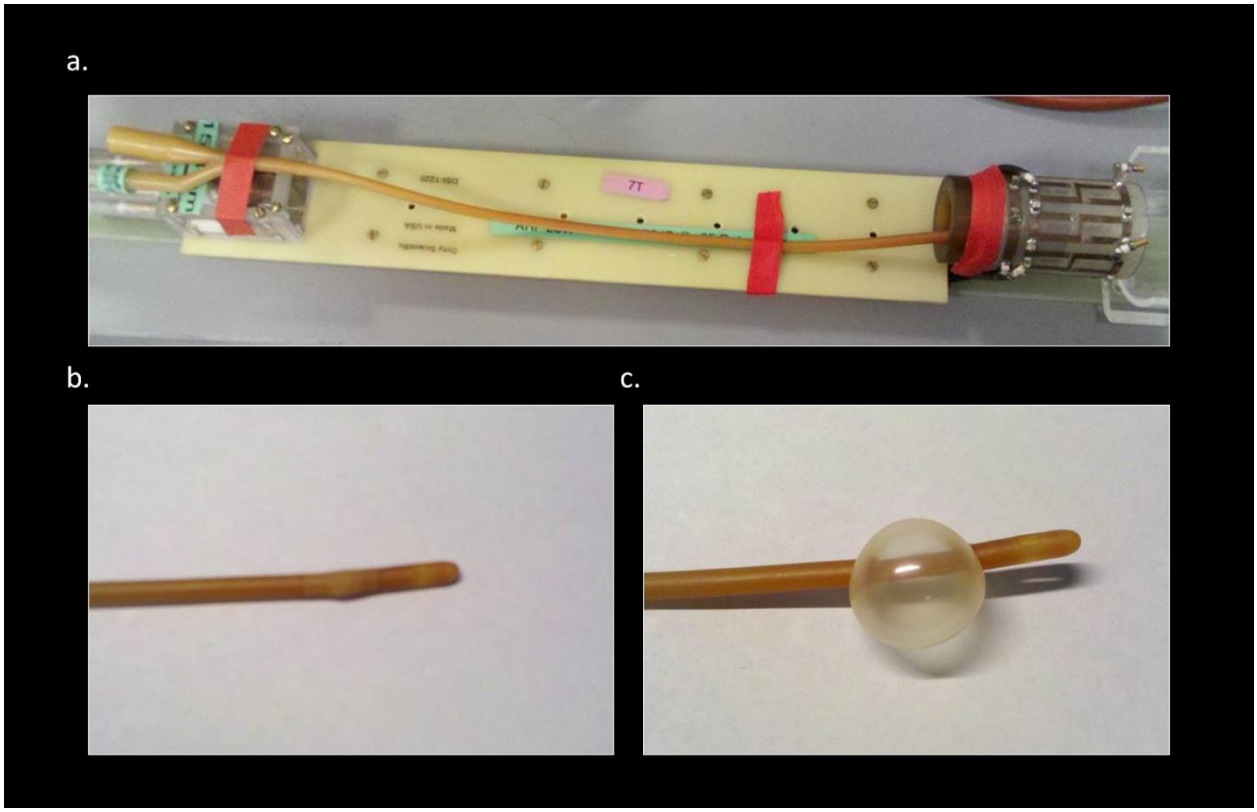

Figure 1. Quadrature coil platform (a). Balloon catheter controlled by a syringe driver in undeformed state (b) and deformed state (c) is used to control the amount of deformation in the phantom.

2.2 Mechanical testing

Mechanical testing was performed on phantom components using a commercial mechanical testing unit (ELF 3100, Bose Corp., Electroforce Systems Division, Eden Prairie, Minnesota) using a 50 gram force transducer (Honeywell, Sensotec, Columbus, Ohio). Samples of each material used in this study for mechanical testing were cast into cylindrical 12-well plates. Testing consisted of a series of seven incremental unconfined compressions from 0.35 to 0.65 mm with a 60 s dwell to eliminate viscoelastic effects. Testing was performed on three separate samples from each set of gels to obtain average absolute measures of Young's modulus for each phantom component.

2.3 Elasticity reconstruction

MIE is a quasi-static model-based elastography methodology that reconstructs a quantitative distribution of mechanical properties through the use of two image volumes acquired under differing deformation states. Computer models are generated from pre-deformation image volumes, and a linear elastic biomechanical finite element model is used to simulate the applied deformation. Spatial priors from *a priori* MR signal intensity information are used to cluster like-intensity image volumes and assign regions for property reconstruction. Boundary conditions representing the application of deformation are automatically generated through the use of a demons non-rigid registration algorithm [15] that registers the pre-deformation image volume to the post-deformation image volume. Mechanical property distributions are iteratively reconstructed through the use of a conjugate gradient method with a Polak-Ribière update [16] and an adjoint-based gradient evaluation [17]. Reconstruction continues until the simulated post-deformation image volume matches the experimental post-deformation image volume using an image volume zone-based correlation coefficient metric. Further details regarding the MIE computational methodology can be found in previous work [4,15].

2.4 PVA cryogel phantom experiment

Phantoms were fabricated from a 8% w/v polyvinyl alcohol (PVA) solution (Flinn Scientific, Batavia, IL). PVA cryogels exhibit increased mechanical stiffness with repeated freeze-thaw cycles, therefore two groups of PVA gels were cast in cylindrical 12-well plates; one set underwent 12 hours of freezing at -20°C and 12 hours of thawing at room temperature (one freeze-thaw cycle) and the other set was doped with 1% gadopentetate dimeglumine, Gd-DTPA (Magnevist, Wayne, NJ) and underwent two freeze-thaw cycles. A bi-layer phantom was then constructed using a non-doped, one freeze-thaw cycle cryogel layered on top of a doped, two freeze-thaw cycle cryogel. In this experiment, the non-doped cryogel on the top of the phantom was used as a reference material to obtain the absolute stiffness of the doped gel, which was then compared to experimental observations from independent mechanical testing.

2.5 Murine phantom experiment

In a separate experiment, we implemented a similar referenced MIE experiment using a mouse/tumor phantom formulated from silicon rubber to validate this technique in a more realistic geometry that replicates a pre-clinical murine subcutaneous xenograft tumor model of breast cancer [18]. ‘Ecoflex’ (Smooth-On, Inc., Easton, PA) was used for the mouse body and a stiffer material, ‘Dragonskin’ (Smooth-On, Inc., Easton, PA), was used for a tumor placed on the right hind flank. Similar to the PVA experiment, Ecoflex was used as a reference material to obtain the absolute stiffness of Dragonskin, which was then compared to experimental observations from independent mechanical testing.

3. RESULTS

Image contrast is required for segmentation of objects of interest for property reconstruction, and a concentration of 1% Magnevist in PVA gel displayed significant contrast in image intensity compared to a non-doped PVA gel (Figure 2a, 2b) for pre- and post-deformation states. Based on image segmentation, intensity-based regions were assigned for each material and reference MIE reconstruction was performed as described (Figure 2c). Using the reference material Young's modulus of non-doped, one freeze-thaw cycle PVA as 1 kPa, as determined by mechanical testing, and the traditional MIE reconstructed ratio of stiffness between doped and non-doped PVA of 5.70 (Figure 2d), we find an absolute Young's modulus, as determined by referenced MIE, of 5.70 kPa for the doped, two freeze-thaw PVA. Mechanical testing of doped, two freeze-that cycle PVA reveals a gold standard Young's modulus of 5.21 kPa, representing a 9.4% error in our referenced MIE reconstruction.

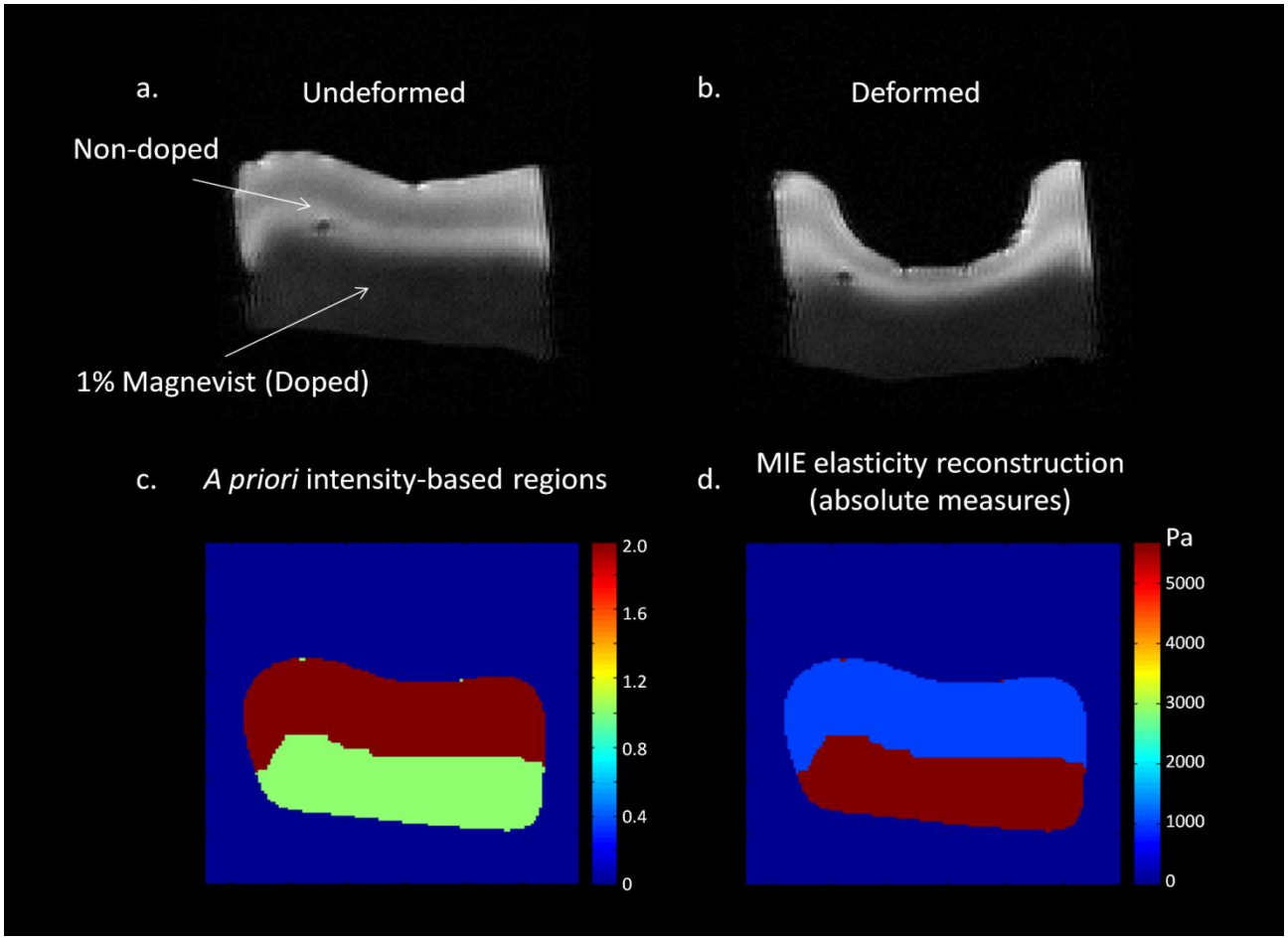

Figure 2. Pre-post deformation images of PVA gels (a,b) with corresponding intensity regions (c) and MIE elasticity reconstruction (d). A combination of mechanical testing, image intensity assessment, and MIE reconstruction was used to obtain absolute stiffness of the doped gel using the non-doped gel as a reference material.

The post-deformation PVA phantom image volume (Figure 2b) depicts significant indentation in the non-doped gel (on top) compared to the doped gel (on bottom) indicating that the doped-gel is much stiffer relative to the non-doped gel. MIE elasticity reconstruction confirms this by showing that absolute measures of stiffness (Figure 2d) are much higher for the doped gel. The results suggest that MIE reconstruction on *a priori* intensity-based regions is a promising approach for taking advantage of existing image heterogeneity (potential anatomic differences) to identify stiffness reconstruction targets. The colorbar for the intensity-based regions map in Figure 2c shows the arbitrary index values assigned to distinguish the top from the bottom gel. For the elasticity reconstruction, the colorbar displays absolute measures of Young's modulus for the PVA phantom calculated from the referenced MIE approach (in this case, using the known modulus of the non-doped gel as a reference).

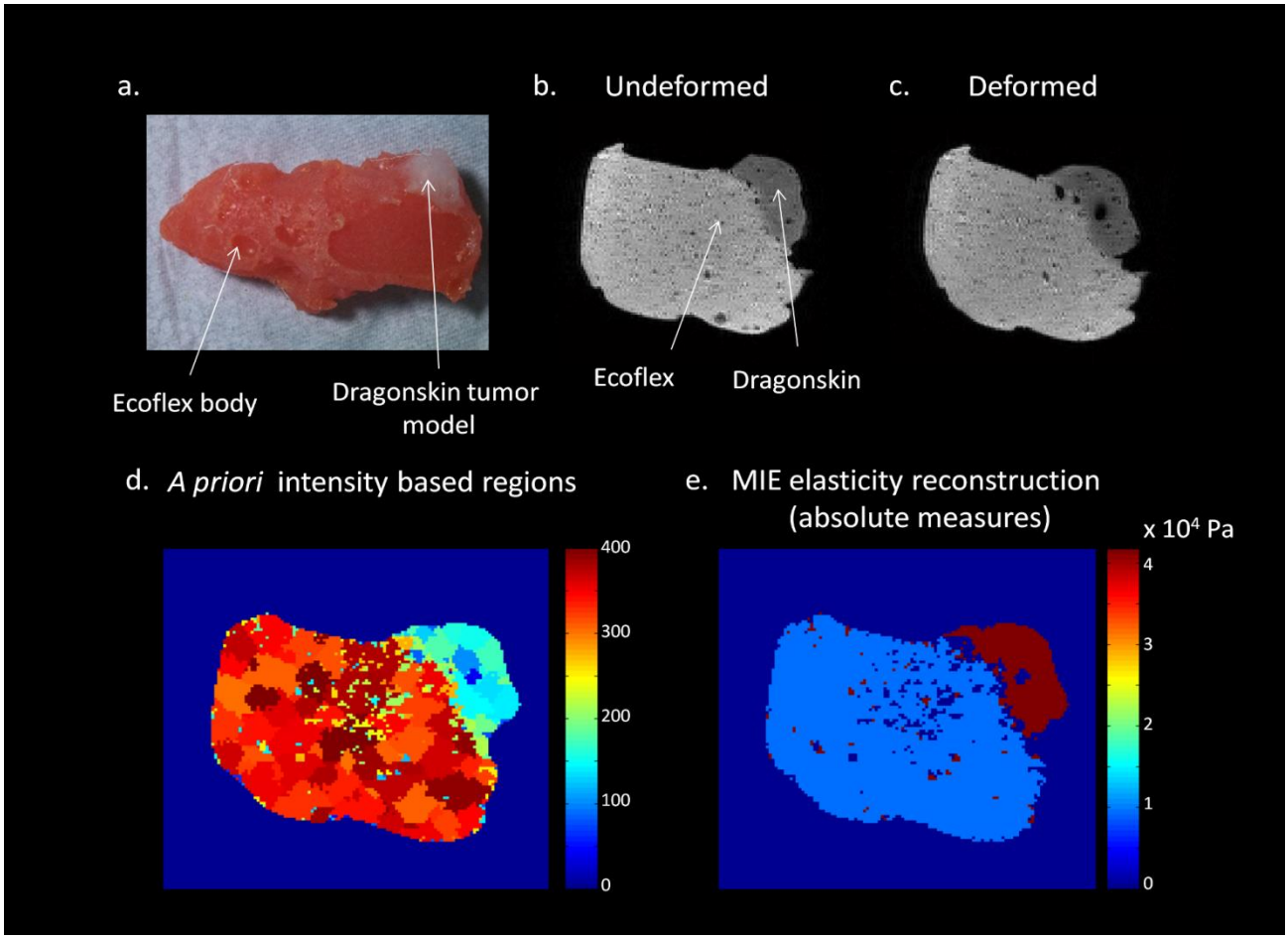

Figure 3. Silicone mouse phantom (a), pre-post deformation axial cross sections (b,c) with corresponding intensity regions (d) and MIE elasticity reconstruction (e). The Ecoflex body is used as the reference material for obtaining the stiffness of the Dragonskin tumor model placed on the right hind flank. The MIE reconstruction shows the absolute measures of stiffness for the Dragonskin (light-blue) and Ecoflex (dark red).

Similar results were seen in the murine phantom experiment (Figure 3a). MR axial cross sections across the hind flank demonstrate sufficient image contrast between the Ecoflex/Dragonskin mouse tumor phantom (Figure 3b, 3c). Here, Ecoflex is used as a reference material to obtain absolute stiffness in the Dragonskin 'tumor'. The *a priori* intensity-based regions used for reconstruction and the associated MIE reconstruction (Figure 3d, 3e) highlight the process of extracting measures of Young's modulus from spatial priors. Using the mechanical testing validated modulus of Ecoflex as 9.65 kPa we find an absolute Young's modulus, as determined by referenced MIE, of 41.78 kPa for the Dragonskin tumor model (Figure 3e). Independent mechanical testing of the Dragonskin tumor phantom material reveals a gold standard Young's modulus of 46.14 kPa, representing 9.4% error in our referenced MIE reconstruction.

	MIE Reconstructed Ratio	Mechanical Testing Ratio	MIE Reconstructed Target Modulus	Mechanical Testing Target Modulus	Percent error
PVA Phantom	5.69 : 1	5.20 : 1	5.70 kPa	5.21 kPa	9.4%
Murine Phantom	4.33 : 1	4.78 : 1	41.78 kPa	46.14 kPa	9.4%

Table 1. Comparison between relative and absolute measures of stiffness for MIE reconstruction and mechanical testing. Results are compiled for PVA phantom and murine phantom models.

Table 1 shows the compiled comparisons of referenced MIE and mechanical testing for both PVA and silicone rubber murine phantoms. Doped/non-doped PVA referenced MIE reconstruction was performed with the doped gel as the target for reconstruction. Absolute values of Young's modulus were calculated for the entire phantom based on normalization to the reference material stiffness of the non-doped gel. Mechanical testing validation shows the absolute measure of stiffness for the doped PVA target differs from the MIE reconstructed value by 9.4%. Similarly, referenced MIE reconstruction was also used to determine absolute stiffness for a silicone rubber murine tumor phantom. The Dragonskin tumor used was the target for referenced MIE reconstruction, and mechanical testing validation shows an error of 9.4%. From the PVA and Ecoflex/Dragonskin phantoms, we see that referenced MIE demonstrates a high degree of accuracy and shows initial promise as a method to measure absolute Young's modulus from relative MIE reconstructions.

4. CONCLUSIONS

This study demonstrates the use of a known fixed reference material in determining absolute measures of stiffness with MIE. This work improves upon previous MIE studies where only relative elasticity contrast ratios could be obtained. Phantom validation in both simple and complex geometries reflecting pre-clinical experimental systems confirms that accurate measures of absolute stiffness can be obtained from our novel referenced MIE approach. We hypothesize that longitudinal monitoring of the mechanical integrity of breast cancer through use of referenced MIE during the course of therapy may prove invaluable in both characterization and prediction of treatment response.

Our lab has been investigating MIE for several years [3,4,7,8] having been first introduced in [5,6]. We have previously demonstrated that MIE is capable of reconstructing relative elasticity contrast ratios in pre-clinical and clinical breast cancer systems [3]. This work demonstrates that use of a known reference stiffness can be used to generate a map of absolute stiffness in geometrically complex systems, thus potentially providing quantitative insight into mechanical properties of both tumor and internal tissue. These preliminary results are encouraging for employing a referenced MIE approach to obtain absolute measures of material properties for clinical characterization of tumor stiffness in NAC.

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