Biomechanical Property Quantification of Prostate Cancer by Quasi-static MR Elastography at 7 Telsa of Radical Prostatectomy, and Correlation with Whole Mount Histology

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INTRODUCTION Magnetic resonance elastography (MRE) is a powerful tool for the detection and localization of cancer, as has been well demonstrated in organs such as liver (1) and breast (2). Application to the prostate is in development (3), and holds enormous potential for MRI-guided prostate intervention for cancer, such as targeted radiation therapy, MRI-guided biopsy or high dose rate (HDR) brachytherapy (4). MRE parameters could potentially replace or complement currently used MRI parameters for prostate cancer localization, i.e., T2-weighted (T2w) signal, apparent diffusion coefficient (ADC), dynamic contrast enhanced MRI (DCE-MRI) parameters (5) and MR spectroscopic imaging (MRSI) (6). To inform development, quantitative data on the relative increase in biomechanical stiffness of prostate cancer above that of normal tissue is required. Some initial work using ex vivo tissue has been carried out using dynamic MRE (7). However, these methods are hampered by poor spatial resolution, difficulties in achieving uniform mechanical wave excitation across the sample, and dependency of the results on the wave frequency. To obtain high spatial resolution quantitative data of the whole prostate, an initial investigation has been made applying a quasi-static MRI method at high magnetic field strength (7 tesla) to radical prostatectomy tissue, for which the disease burden was assessed via whole-mount histopathology. Correlation was determined of the MRE-measured tissue stiffness with histopathology-identified disease, and with prostate anatomical structure. MRE was also used to measure the increase in tissue stiffness caused by pathology processing in fixative solution.

METHODOLOGY A whole prostate specimen was received from a patient with biopsy-confirmed reoccurrence of cancer in the peripheral zone, after earlier treatment with targeted radiation therapy. The tissue (~4 cm diameter) was embedded in a cube (7×7×7 cm3) of gel prior to imaging (8). The quasi-static MRE method (8) employed a compression device consisting of a sample holder, a compression plate and mechanical piston, connected via an eccentric disk to a non-magnetic ultrasonic piezoelectric transducer (USR60-E3N, Shinsei, Japan), providing compression at 1 Hz with maximum amplitude of 1.5 mm. The device was placed in the bore of a 7-T preclinical MRI scanner (70/30 BioSpec, Bruker, Ettingen, Germany), where a quadrature volume resonator (15.5 cm inner diameter) was used for transmission and reception. A Stimulated Echo (STEAM) sequence was used. Inversion time (T1) was 1 ms and Echoplanar (E) readout was used: TE = 16 ms, NEX = 7, segments = 17, requiring ~1 hr for the total acquisition. To assist the correlation of MRE with histopathology, a high resolution 3D T2w RARE (Rapid Acquisition with Relaxation Enhancement) acquisition was also made, with isotropic voxel dimensions = 0.3×0.3×0.3 mm3 (matrix=233×233×233, TE=8.5 ms, TR=2400 ms, echo train length=16). On scan completion the gel was removed from the gel and submerged in 10% neutral buffer formalin for pathology fixation over a period of ~60 h. The fixed sample was re-embedded in gel and the MRE scan repeated. Next the specimen was sectioned at 3 mm slice thickness in a cutting plane approximately perpendicular to the axis of the urethra. The sectioned specimens were imaged for three different plane orientations: 1) transverse plane (perpendicular to the axis of the urethra; 2) muscular tissue; 3) histology-defined tumor regions; and the histology-defined tumor areas.

RESULTS The T2w MRI, histology images and MRE E maps of the four central slices are displayed in Figure 1. To verify disease margins, segments of attached extra-prostatic tissue were excised with the prostate (see T2w images); these areas were masked out of the MRE E maps. Pathology identified adenocarcinoma, which was found predominantly in the peripheral zone. Only some portions of disease are detectable as low T2w signal in the peripheral zone; however all tumors have corresponding areas of increase in MRE E (although T2w contrast for disease is likely to be reduced post radiation therapy). Table 1 provides summary data for MRE. The mean E of pre-fixation prostate (excluding muscular tissue and tumor) of 37 kPa corresponds with ~36 kPa (12 kPa shear modulus) reported for normal prostate in (7). Tumor areas defined by histology were significantly stiffer (3-fold, p<0.0001, 2-sample t-test) than the region excluding tumor and muscular tissue. However, the muscular tissue was also significantly stiffer (2-fold, p<0.0001). The comparison of histograms (Figure 2) indicates that muscular tissue should be neglected if MRE is used to automatically identify disease. Furthermore, the highest Dice-similarity index (DIC) of 0.85 was obtained at a threshold of 55 kPa, which agrees with a threshold of ~54 kPa (18 kPa shear modulus) identified by (7). The Gleason scores ranged 7-9; however no correlation was measured with E. Fixation caused an 8-fold increase in mean E for the four slices. Figure 3 shows an example post-fixation E map (corresponding to pre-fixation slice 4) showing increased stiffness in a non-uniform pattern.

DISCUSSION AND CONCLUSION Quasi-static MRE at 7 T provides fine spatial resolution coverage of the entire sample and demonstrates sensitivity to disease. Furthermore, it reveals the variability of stiffness in normal prostate; information not obtained using dynamic MRE. This data could inform a strategy for MRI-guided tumor detection. Although this sample was obtained post radiation therapy, the glandular tissue stiffness is comparable to that in vivo, suggesting that the tissue stiffness should be made pre-fixation, and this data will be used to inform biomechanical model based registration strategies for improved correlation of histopathology with imaging (8). The technique will be applied to further prostatectomy specimens to allow calculation of population-wise data.
