Correlation of Ultrasound Tomography to MRI and Pathology for the Detection of Prostate Cancer

Reza Seifabadi1, Alexis Cheng1, Bilal Malik3, Shun Kishimoto1, James Wiskin1, Jeeva Munasinghe1, Ayele H. Negussie1, Ivane Bakhutashvili1, Murali C. Krishna1, Peter Choyke1, Peter Pinto3, Arman Rahmim1, Maria Merino1, Mark Lenox2, Baris Turkbey1, and Bradford J. Wood1

1National Institutes of Health, Bethesda, MD, USA
2John Hopkins University, Baltimore, MD, USA
3QT Ultrasound LLC, Novato, CA, USA
4University of British Columbia, Vancouver, BC, Canada

ABSTRACT

Purpose: This study aims to investigate correlation of speed of sound (SoS) map with T2-weighted (T2w) MRI and pathology in an ex vivo human prostate tissue with cancer, as an early proof of concept towards cost effective augmented ultrasound diagnosis of prostate cancer. Method: A commercial breast full angle ultrasound tomography scanner was used to generate US tomography images. Prostate-specific Echolucent mold was fabricated to allow MRI and UST to be spatially correlated. Similarly, a 3D printed mold was developed to align the histology slices with the UST and MRI. The resulting slices of prostate tissue were H&E stained. A radiologist with 10 years of experience in using multi parametric MRI for prostate cancer diagnosis labeled and contoured the suspicious ROIs in both MRI and UST. For all tissue blocks (N=10 slices with 6 mm thickness), H&E slides were prepared and labeled by an expert pathologist. Results: The radiologist found two slices with prominent cancer in each modality (i.e. MR and UST) in the peripheral zone. These two pairs of slices correlated with each other and with slices #6 and #7 in pathology. The cancer ROIs were found at similar locations in all modalities, although MR and UST underestimated the size of lesions (Sørensen–Dice coefficients, with respect to pathology, for T2w and UST were 0.11 and 0.20 respectively for first ROI, and 0.33 and 0.27 for second ROI). The SoS was 1580.4±17.7 m/s and 1571.4±9.2 m/s for normal and cancer tissues in first ROI, and 1577.7±17.7 m/s and 1574.5±10.1 m/s for second ROI. Conclusions: SoS map can correlate with MRI and pathology findings in prostate cancer. Further ex vivo validation with fresh prostate tissue is warranted.

Keywords: Transmission ultrasound, full angle ultrasound tomography, limited angle tomography, prostate cancer

1. INTRODUCTION

Prostate cancer (PCa) is the most common cancer, and second leading cause of death in men in the US. Early detection and accurate tissue characterization may avoid over-treatment and minimize morbidity and mortality [2]. TRUS guided prostate biopsy has been the standard technique in PCa detection for almost 3 decades [3]. TRUS is real-time, relatively low cost, and shows the prostate capsule and boundaries. However, it suffers from poor spatial resolution, subjectivity, and a relatively low sensitivity for cancer detection (40-60% [4]).

MRI is a superior imaging modality for visualizing the clinically-relevant cancer. With multi parametric MRI (mpMRI) or MRI/US fusion guided biopsy, the sensitivity of cancer detection can go as high as 80% [5]. However, real-time MRI is challenging, requires specialized and costly equipment, and in-gantry prostate biopsy is time and resource intensive and impractical to apply across a broad population. Even though US-MRI fusion guided biopsy has been shown to be highly sensitive to detect higher-grade cancer, it still suffers from a high rate of false positives for lower-grade cancers resulting in unnecessary biopsies.

Some US-based technologies have been proposed to address this clinical need in addition to MRI/US fusion, including elastography [6], Doppler, US contrast, and US time series analysis [7]. Although several studies reported substantial enhancement in prostate cancer identification with quasi-static elastography, there are still some limitations in reproducibility, subjectivity, and the inability of this method to differentiate cancer from chronic prostatitis [6]. Time series analysis [7] is a machine-learning approach to perform the tissue characterization and has recently shown promising results for labeling prostate cancer using the US RF image [7]. This method is currently based on a post-processing of reflection data.
Ultrasound tomography is based on transmission data rather than the reflection data used in the conventional B-mode US, and generates images based on acoustic properties such as speed of sound (SoS) and acoustic attenuation. Both full angle and limited angle ultrasound tomography have been extensively studied, particularly in the context of breast imaging and have shown promising results in breast tissue classifications [8-9].

The current transmission US systems (e.g. [7,8]) are full angle tomographic systems where the organ of interest is placed into a water tank and imaged by a transducer that can rotate around it a full turn or by using a ring transducer. However, for applications such as prostate, a full angle system cannot be used. Previously, we proposed a limited angle tomography system and technique for prostate cancer screening in [10] enabled by robotic technology. In this concept, an endorectal TRUS probe resides in the rectum, and a linear or curved array transducer images through the bladder, with the prostate in between two probes (Fig. 1).

![Figure 1](https://www.spiedigitallibrary.org/conference-proceedings-of-spie)

**Figure 1.** Limited angle UST tomography concept for prostate cancer screening: a) co-robotic ultrasound tomography concept for prostate screening, b) limited angle image reconstruction concept, c) and d) sagittal imaging concept, e) and f) axial imaging concept of prostate [14].

The abdominal probe is then aligned with the TRUS probe using a co-robotic setup similar to the one we proposed in our prior work [11]. We previously demonstrated the feasibility of a co-robotic ultrasound alignment setup [11, 15]. The endo-rectal probe can be manually manipulated [15] or by a second robot [11]. Figure 1c shows the sagittal imaging concept where the linear array of an endorectal probe is used. Fig.1d shows simulation study for such configuration [14]. Fig. 1e shows the axial imaging configuration where the curved array of an endorectal probe is used. Fig. 1f shows simulation results for such configuration [14]. We have shown preliminary results in a phantom with different materials including water and plastisol where a limited angle system similar to what shown in Fig.1b can generate accurate SoS map [10]; however, the variation of SoS among different prostatic tissues are expected to be considerably smaller than that model [12], making it challenging for the reconstruction algorithm to generate SoS map.

In this study, we aim to demonstrate feasibility of using SoS for prostate cancer detection using a full angle system. An ex vivo study with a full angle system allows us to find the SoS variation in different prostate tissue without the burden of dealing with patient anatomy, robotic alignment, and most importantly, image reconstruction algorithms given that limited angle tomography is an under-determined and numerically ill-conditioned problem.

## 2. METHOD

In this study, we compare UST images with MRI as a superior imaging modality and pathology as the ground-truth in detecting prostate cancer. We propose a method to spatially correlate these three modalities. Fig. 2 shows the workflow. First, multi parametric MRI is taken from the ex vivo tissue. Then, an exholucent mold is made using the MR image in order to orient the prostate while UST scan is conducted. Then, the prostate is placed inside the cavity of the echoluent mold. The mold is then placed inside the water tank of a full angle UST scanner. Next, the prostate is removed and placed into a 3D printed mold that orients prostate similar to the echoluent mold with some groves for passing pathology knife
for slicing. Then, tissue blocks and H&E staining slides are produced. UST and MRI are interpreted and labeled by an expert radiologist and pathology slides are interpreted by an expert pathologist. Finally, labeled SoS map, T2w MRI, and H&E staining slides are compared.

**Figure 1.** Workflow of correlating UST images with MRI and pathology for an *ex vivo* prostate tissue.

Below, we provide details of different steps described above.

2.1 *Ex vivo* prostate tissue

Five whole prostate glands (Science Care Inc, Philadelphia, PA) from donors with prostate cancer were screened and the most ideal specimen was selected for the least treatment effect by medical record. The specimen was from a pre-deidentified 63 year old Caucasian donor who died of prostate cancer, with a BMI = 21.8. The subject was reported to have metastatic prostate cancer. The gland was taken out within 5 days of postmortem, formalin fixed, and shipped with seminal vesicles to help with anatomic orientation. Extra cleaning of tissue was performed in house by an experienced urologist, to remove unnecessary surrounding tissues such as the bladder wall, rectal wall, and penis muscular tissue.

2.2 MRI scan

After cleaning, the whole prostate specimen position inside a 60 × 60 × 80 mm plastic box (with the rectal wall touching the base of the box). Then, acrylamide tissue mimicking gel phantom was made, using a previously reported method [12] and poured into the box to fixate the prostate thus eliminating potential motion artifact during MRI scanning. To avoid heating of the prostate tissue as the phantom gel set, the casting process was done by immersing the box into ice water. Originally, the box was scanned with a Philips Achieva 3T scanner (Amster-dam, Netherland). An mpMRI prostate scan (including T1w and T2w and ADC map) with 3mm slice thickness was acquired. Although it was possible to identify a tumor, a higher resolution 9.4T BioSpec 94/30 USR small animal MRI scanner (Berker, Billerica, MA) was later used to increase the confidence in finding and defining malignant lesions. T1w and T2w images were acquired and the slice thickness was set to 300 micron. Given that each scan took about 70 hours, 10% formalin was used in making acrylamide gel instead of water, so that the tissue was preserved while being scanned.

2.3 UST-MRI-Pathology correlation

In order to correlate MRI and UST images, the whole tissue volume from the 9.4T MRI scan was segmented using DynaCAD Prostate software (Invivo, Gainesville, FL) and a *stl* file was generated. Then, the *stl* file was imported into a CAD software (Solidworks, Dassault Systèmes, France) to design a casting mold that positioned the prostate specimen during UST scan. Two rods were used to position the 3D printed prostate relative to the casting box (Figure 2-a). Then, the prostate, the echolucent casting box, and the rods were 3D printed (UPrint Plus, Stratasys, Eden Prairie, MN).

Similar acrylamide gel was made for the echolucent mold. 10% formalin was used since the UST scanner was in a different geographical location, and the specimen had to be shipped with 24 hours delivery time. For UST, the formalin was degassed for one hour before being used in acrylamide gel, to minimize bubble formation. Iced water was used again to keep the tissue cool during polymerization. Once the mold was polymerized, it was cut in half using a histology knife and the 3D printed prostate and rods were removed. Next, the real prostate was placed into the cavity and slight glue was applied to the corners of each half to hold the mold fixed. Then, the mold-specimen was shipped for remote but blinded acquisition on UST.
Figure 2. (a) The prostate-specific casting mold setup to make the echolucent mold, (b) The 3D printed prostate, echolucent mold, and the specimen, (c) The slicing mold used for pathology assessment. The prostate is oriented similar to (a) such that pathology can be correlated later with MRI and UST images.

Figure 1-c shows the slicing mold for pathology. The prostate was in similar orientation to the mold showed in (a) making it possible to correlate pathology slides with MRI and UST images. The pathology slice thickness was 6 mm and the slices were parallel to MRI/UST slices.

2.4. UST scan
In this study, the latest generation QT Ultrasound Breast Scanner 2000 (Fig. 2-a) was used (QT Ultrasound LLC, Novato, CA), which is an FDA-cleared device for breast imaging. Technical details of this system are described previously [13]. Briefly, Quantitative Transmission (QT) ultrasound is a tomographic ultrasound modality that can produce 3D maps of SoS of and reflection from objects within the field of view. It performs this measurement by propagating a plane wave through the medium from a transmitter on one side of a water tank to a high-resolution receiver on the opposite side. This information is then used via an inverse scattering algorithm to compute a speed of sound map [14]. Reflection transducers allow the creation of a high resolution, spatially compounded reflection map that is naturally co-registered to the SoS map [13].

Figure 3. (a) QT Ultrasound System, (b) QT scan-head [13].

The specimen with the echolucent mold was placed in a temperature controlled water bath for 30 min until it reached 31 degrees Celsius. The specimen along with the mold was then placed in the scan tank of the QT scanner and the scan was initiated. The raw data was processed using the same algorithm as used for breast tissue, resulting in generation of both SoS and reflection image volumes. The same radiologist blindly interpreted the UST images 3 months after the MRI interpretation (with > 100 clinical MRI patient interpretations in the interval). Areas diagnostic for cancer were annotated and contoured.
2.5 Pathology

Once the tissue was UST scanned, the acrylamide gel was removed and the tissue was placed into the slicing mold. A pathologist sliced the tissue using a histology knife. The slices were then placed separately in small bags, numbered with the orientation (i.e. base or apex). The bags were then placed in formalin and sent to a histopathology laboratory (American Histo Labs, Gaithersburg, MD). The whole-mount slices were fixed in paraffin blocks and H & E stained on 2x3 inches slides (10 slides altogether). Digital images of the slices were then acquired using the Leica Aperio ScanScope (Leica Biosystems, Germany) with x20 magnification. An expert genitourinary pathologist then interpreted the H&E slides and annotated and contoured the area of interest in the diagnosed cancer tissue.

3. RESULTS

Figure 3 shows T1w and T2w images of two slices (we call them x and y) in which a radiologist with 10 years of experience in reading mpMRI of prostate interpretation could confidently find prominent malignant lesions.

![Figure 3](https://www.spiedigitallibrary.org/conference-proceedings-of-spie)

The radiologist was then given 3 month interval (>100 mpMRI reading in the middle) to read the UST images. He could then identify two slices with prominent suspicious lesions (slices c and d as demonstrated in Fig. 4). The radiologist reported to benefit using the reflection image in finding the orientation of the prostate as well as differentiating the prostatic tissue from surrounding tissue (Figure 4-b and 4-d).

After UST image acquisition, the prostate was cut into 10 slices using a prostate specific mold (Fig. 2c), formalin fixed, and sent for H&E staining. Next, slides were interpreted and labeled by an expert prostate pathologist with >25 years of experiences under microscope. The pathologist however could not grade the cancer (apparently related to 5 days postmortem time before formalin fixation and prior to H&E staining).
Figure 4. UST images corresponding to 2 slices containing 2 suspicious lesions found by radiologist in SoS images (prior to annotation). (a) SoS map of suspicious lesion 1, (b) reflection image of suspicious lesion 1, (c) SoS map of suspicious lesion 2, and (d) reflection image of suspicious lesion 2. The red contour shows the tumor while the gray dashed contour shows the prostate.

Figure 5. Correlation of MRI, SoS map, and pathology for cancer 1 and 2 with diagnostic regions found in MRI and UST.

Slices x and z were matched best with slice #5 in pathology while slices y and w were matched with slice #7. Figure 5 shows gross correlation among MRI, SoS, and pathology. Although both MRI and UST underestimated the size of cancer,
they were able to detect the malignant region location (and corresponding slice location). In slice $x$ ($z$), the prominent lesion was found in left apical-mid peripheral zone in both MR and UST. In slice $y$ ($w$), the prominent suspicious lesion was found in left mid-base peripheral zone in both MR and UST. Reflection UST (and T1w MRI) were not diagnostic, but were helpful for orientation.

To more quantitatively demonstrate the correlation between MRI and UST with pathology as the ground-truth, we use Sørensen–Dice coefficient which can be defined as follows:

$$DSC = \frac{2|X \cap Y|}{|X + Y|}$$

where $X$ and $Y$ are the contour of MRI (or UST) and pathology, respectively. Table 1 summarizes the $DSC$. Each row compares the $DSC$ in MRI and UST for the corresponding slices.

<table>
<thead>
<tr>
<th>Slice #</th>
<th>MRI (T2w)</th>
<th>UST (SoS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#6</td>
<td>0.1054</td>
<td>0.1992</td>
</tr>
<tr>
<td>#7</td>
<td>0.3272</td>
<td>0.2678</td>
</tr>
</tbody>
</table>

We segmented the normal and cancer contours from pathology and mapped them on corresponding SoS images. For slice $z$, the SoS was 1580.4±17.7 m/s for prostate tissue and 1571.4±9.2 m/s for the lesion. For slice $w$, the SoS was 1577.7±17.7 m/s and 1574.5±10.1 m/s for prostatic and cancer tissue, respectively. Figure 6 shows the histograms for the slices $z$ and $w$.

![Histograms](https://example.com/histograms.png)

Figure 6. Histograms of the distribution of normal and cancer pixels in the image. a) slice $z$ and b) slice $w$.

Table 2 and 3 summarizes the SoS, kurtosis and skewness for the normal and cancer tissues in slice $z$ and $w$. Although speculative given the scarcity of data, it seems that kurtosis and skewness are more indicative of normal versus cancer tissue than SoS.

<table>
<thead>
<tr>
<th>Slice 6</th>
<th>SoS (m/s)</th>
<th>Kurtosis</th>
<th>Skewness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1580.4±17.7</td>
<td>9.56</td>
<td>-1.69</td>
</tr>
<tr>
<td>Caner</td>
<td>1571.4±9.2</td>
<td>2.74</td>
<td>0.48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Slice 7</th>
<th>SoS (m/s)</th>
<th>Kurtosis</th>
<th>Skewness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1577.7±17.7</td>
<td>8.26</td>
<td>-1.54</td>
</tr>
<tr>
<td>Caner</td>
<td>1574.5±10.1</td>
<td>2.77</td>
<td>0.31</td>
</tr>
</tbody>
</table>
4. DISCUSSIONS

This study has several key limitations; First, we report results of human cadaver prostate rather than fresh dissected prostate from a radical prostatectomy procedure. This imposes number of limitations: 1) since the prostate tissue is usually taken out after a few days postmortem (5 days in this case), the tissue may lose water content leading to suboptimal T2w images. Also, the DWI-ADC maps may not be useful, which is critical in high grade cancer detection. 2) Due to the postmortem fixation, the pathologist could not make the Gleason grading determination for the cancer aggressivity. 3) Since there is little control over the subject’s tissue, the donor may have gone through different treatments, making it difficult to find the lesion in both MRI and UST. 4) We speculate that the SoS image of a formalin fixed prostate tissue with over 5 days postmortem is not representative of fresh tissue. 5) Our results are very scarce. We will perform a larger cohort of cadaveric studies with different radiologists to study inter and intra-observer variabilities.

5. NEW WORK

This study demonstrates very preliminary but exciting results that ultrasound tomography may be further studied toward the goal of cost-effective ultrasound-based prostate cancer detection that may not require MRI.

6. CONCLUSIONS

Ultrasound tomography has the potential to localize and diagnose prostate cancer in ex vivo human specimens, with MRI and pathology validation. Future plans include analysis in immediate post-surgical specimens using a similar approach. Even though this study is focused on full angle tomography for the detection of prostate cancer, it provides the foundation and may support further development of a limited angle system, which would be requisite for future consideration of translation for prostate cancer screening.

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REFERENCES


