

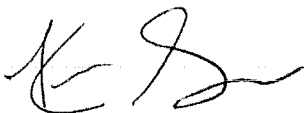
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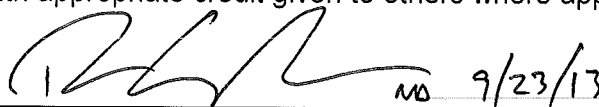
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Acoustic Radiation Force Impulse (ARFI) Prostate Zonal Anatomy: Comparison with Endorectal T2-Weighted MR Imaging (T2WI)

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ABSTRACT

Prostate cancer (PCa) is the most common non-cutaneous malignancy among men in the United States and the second leading cause of cancer related death. Non-invasive imaging could lead to improved diagnosis, risk-stratification, and PCa management. Magnetic resonance imaging (MRI) has been available for use in the workup of patients with PCa since the early 1980s, and recent advances with functional parameters has greatly improved its clinical diagnostic utility. Acoustic Radiation Force Impulse (ARFI) imaging is an ultrasound-based modality that evaluates the mechanical properties of soft tissues. ARFI imaging has the potential to aid in PCa diagnosis and management by evaluating the structural composition of prostate zones and tumors based on their stiffness. In this study, MR and ARFI imaging datasets were compared to one another and with gross pathology measurements made immediately post radical prostatectomy. Imaging datasets were manually segmented to delineate the central gland and prostate capsule, and 3D models were rendered to evaluate zonal anatomy dimensions and volumes. Both imaging modalities showed moderate correlations ($0.39 < R^2 < 0.74$) between estimated organ volume and gross pathologic weights. ARFI and MR total prostate gland volumes were well-correlated ($R^2 = 0.68$), but ARFI images yielded prostate volumes that were, on average, larger ($36\% \pm 28\%$) than MR images, primarily due to over-estimation of the anterior-to-posterior dimension of the prostate total gland ($17.0 \pm 12.1\%$), while over-estimates of the other dimensions were less significant contributors ($8.1 \pm 18.4\%$ and $0.58 \pm 12.9\%$). The central zone volumes of ARFI and MR images were also moderately correlated ($R^2 = 0.41$), with minimal volume bias between the imaging modalities, but significant variability case-to-case ($2.1 \pm 39.1\%$). Central zone volume differences were, again, strongly attributed to over-estimation of the anterior-to-posterior axis ($14.8 \pm 23.1\%$), with a significant underestimation of the apex-to-base dimension ($-10.8 \pm 22.3\%$) and no mean bias in the lateral-to-lateral measurements ($0.006 \pm 17.2\%$). Strong variability in central gland volumes is believed to be related to the extent of benign prostatic hyperplasia (BPH) for select cases. Overall, ARFI imaging of the prostate yielded prostate volumes and dimensions that were correlated with MR T2WI estimates, with biases in the anterior-to-posterior dimension, most likely related to poor displacement SNR in the anterior region of the prostate from greater distance from the rectal wall imaging surface. ARFI imaging is a promising low-cost, real-time imaging modality that can compliment MR imaging for diagnosis, treatment planning and management of PCa.

I. INTRODUCTION

Prostate cancer (PCa) is the most common non-cutaneous malignancy among men in the United States and the second leading cause of cancer related death. [1] Screening with prostate specific antigen (PSA) and digital rectal examination (DRE) has led to earlier PCa detection, but performance of these measures is not optimal, leading to imprecise risk assessment. Additionally, the random nature of transrectal ultrasound (TRUS)-guided biopsies can miss or underestimate the burden of cancer. [2] Earlier disease diagnosis leads to challenges in deciding optimal management strategies for patients presenting with less disease burden, whereas missed tumors on TRUS-guided biopsies can result in inappropriate diagnoses.

The use of non-invasive prostate imaging could lead to improved PCa diagnosis, risk-stratification, and management. Magnetic resonance imaging (MRI) has been available for use in the workup of patients with PCa since the early 1980s, but early studies on its diagnostic accuracy were heterogeneous. However, the more recent ability to include functional parameters in PCa MRI analysis has yielded promising results. [2], [3] Among the MRI modalities currently used in the study of PCa, it is well established that T2-Weighted Imaging (T2WI) offers the best assessment of prostate anatomy due to its ability to delineate prostatic margins, distinguish internal structures and differentiate among the glandular zones.

Acoustic Radiation Force Impulse (ARFI) imaging is an ultrasound-based modality that evaluates the mechanical properties of tissues. [4] ARFI imaging has the potential to aid in PCa diagnosis and management by evaluating the structural composition of prostate zones and tumors based on their stiffness contrast. Zhai *et al.* were able to visualize prostatic anatomy by utilizing

ARFI imaging in freshly-excised prostates. In a second study, Zhai *et al.* demonstrated the feasibility of ARFI prostate imaging *in vivo*. [5]; however, to the authors best knowledge, there have been no studies to date that compare *in vivo* ARFI prostate imaging to other imaging modalities. [6]

The goal of this study is to evaluate the ability of ARFI imaging to delineate prostate zonal anatomy, specifically central gland and total prostate gland, *in vivo* as compared to endorectal MR T2WI. Section II provides an overview of MR and ARFI imaging in the prostate and an overall clinical motivation for prostate imaging. Section III describes the methods used to experimentally-acquire our imaging data, process of gross pathological specimens post radical prostatectomy, and image process our datasets. The results of our analysis, including gross pathology and imaging prostate axis and volume estimates, are presented in Section IV, along with a statistical analysis of the bias and variability associated with each imaging modalities measurements, all of which is discussed in Section V.

II. BACKGROUND

A. Prostate Anatomy

The prostate gland sits below the urinary bladder and surrounds the urethra. Its superior borders include the bladder and seminal vesicles, and the urogenital diaphragm delineates its inferior boundary. The gland is bordered anteriorly by the pubic symphysis and posteriorly by the rectum. The prostate is separated from the rectum by a 2–3 mm fascial layer, [7] and it can be easily palpated on rectal examination.

The prostate gland can be divided from superior-to-inferior into the base, mid-gland and apex. The urethra enters the prostate proximally at the base and extends to the mid-gland, at which point the ejaculatory ducts open into the urethra at the verumontanum. [7] The urethra then continues past the apex and travels through the penis. The prostate can be divided into glandular and non-glandular components. The glandular components include the transitional zone (TZ), central zone (CZ) and peripheral zone (PZ). In the healthy prostate, each zone contains approximately 5%, 20% and 70–80% of glandular tissue, respectively. [8] The non-glandular components include the anterior fibromuscular stroma (AFS) and the urethra. In some imaging modalities, the central and transition zones cannot be visualized as discrete entities, and they are collectively identified as the central gland (CG). This CG was one of the prostate structures manually segmented in MR and ARFI images in this study.

Although not a true capsule, an outer band of fibromuscular tissue surrounds the prostate. [8] This “capsule” is important when assessing the extraprostatic extension of cancer as tumor can spread by disrupting this tissue. Two neurovascular bundles course posterior and lateral to the prostate, which can also be invaded by malignant cells. The prostate capsule is another structure that was manually segmented in both MR and ARFI images in this study, and its overall extent was used to delineate the total prostate gland.

B. Clinical Background and Significance

PCa is the most common non-cutaneous malignancy among men in the United States. Approximately 1 in every 6 men will develop PCa during their lifetime, with the median age of diagnosis at 67 years old. [1] PCa is also the second leading cause of cancer-related death, with 1 in 36 men dying from the disease. The National Cancer Institute (NCI) estimates that 238,590 men will be diagnosed with PCa in 2013 and 29,720 will die from the disease. [1]

PCa diagnosis usually begins by screening with prostate specific antigen (PSA) and digital rectal examination (DRE). Definitive diagnosis is made by random transrectal ultrasound (TRUS)-guided biopsies, which are then used to provide the clinician with the proper Gleason score. The combination of these factors, as well as staging, determines the appropriate therapy and prognosis.

PCa screening has led to earlier diagnosis of smaller tumors and more localized disease; however, it is well known that the sensitivity and specificity of PSA and DRE are not optimal. In addition, DRE has a low predictive value at lower PSA ranges, and PSA yields many false positives. [9], [2], [3] As such, a theoretical risk of over-diagnosis and treatment of low-grade, and possibly clinically insignificant, disease exists. Moreover, due to the random nature of biopsies, PCa located outside the routine sampling sites can be missed and the extent of the cancer might be underestimated. [2], [10] For example, in a study by Mufarrij *et al.*, 45.9–47.2% of patients who were candidates for active surveillance, but underwent radical prostatectomy, had a higher Gleason score on final histopathology than after TRUS biopsy. [11] These inaccuracies may lead to inappropriate diagnosis, imprecise risk assessment and potentially avoidable morbidity.

C. MR Imaging in Prostate Diagnostics

MR imaging has been available for use in the workup of patients with PCa since the early 1980s, but the early work on its diagnostic accuracy is heterogeneous due to heavy reliance on morphology via T1 and T2-weighted imaging (T2WI). More recent abilities to include not only anatomic, but also biologic and functional dynamic parameters, into MR analysis via diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE) imaging or MR spectroscopic imaging (MRSI) is promising in the future diagnosis and management of PCa.

Currently prostate MR focuses on a multiparametric approach, where two-or-more imaging sequences, including anatomic and functional data, are used together to make a diagnosis. [12] As MR technology continues to evolve and improve, its role in PCa diagnosis, staging, treatment planning and follow-up has gained much attention.

1) *T2-Weighted Imaging and Prostate Anatomy*: T2WI sequences are crucial components of prostate MR imaging. T2WI is particularly useful in prostate analysis due to its excellent soft tissue contrast resolution, which can be maximized by using thin sections of 3–4 mm and a small field of view of approximately 14 cm. [2], [8] T2 sequences are the most helpful for tumor localization, as they can clearly show overall prostate morphology, internal structures and prostatic margins. [2]

The prostate can be divided into glandular and non-glandular components. The glandular components include the peripheral zone (PZ) and the central gland, which are typically easily distinguishable on T2WI. The central gland includes the central zone, transition zone and the periurethral glandular tissue. [7] Other anatomical markers such as the urethra, verumontanum and ejaculatory are also often seen on T2WI.

Approximately 70% of the prostatic tissue is found in the PZ, which is high in water content, and thus has higher signal intensity in T2WI. [7] Seventy-five percent of prostatic tumors are found in the PZ and normally show hypointense T2 signal when compared to the higher intensity PZ. [3], [13]; however, tumors can sometimes have similar intensity as the surrounding tissue and false positives can occur secondary to post-biopsy changes/hemorrhage, hyperplasia or prostatitis, making diagnosis more challenging. [13]

2) *Functional MR Sequences*: Even though T2WI is the mainstay of prostate MR, its overall performance in prostate cancer diagnosis is not optimal. The incorporation of two or more functional sequences in multiparametric MR imaging (mpMRI) has been shown to significantly improve the performance of MRI in cancer diagnosis. [14] The European Society of Urogenital Radiology (ESUR) prostate MR guidelines recommend at least 2 functional imaging techniques, in addition to T2WI, to better characterize prostate tumors. [12] In a study by Turkbey *et al.*, researchers found that mpMRI had a PCa detection positive predictive value of 98%. [14] Functional sequences include diffusion-weighted imaging (DWI), dynamic contrast enhanced imaging (DCE-MRI) and MR spectroscopic imaging (MRSI). While mpMRI is critical in improving PCa detection, T2WI is mainstay of delineating prostate anatomy, and for the purposes of comparing prostate anatomy between ARFI and MR images, T2WI were used exclusively in this study.

D. Acoustic Radiation Force Impulse (ARFI) Imaging

Acoustic radiation force-based elasticity imaging has recently been developed for investigation of mechanical properties of human soft tissues, including liver, arteries, heart, prostate, and breast [15], [16], [17], [18], [19], [20], [21], [22], [23]. and it provides a unique tool to use to characterize the cervix during pregnancy. The acoustic radiation force \vec{F} generated in soft tissues by focused ultrasound can be described by [24], [25]:

$$\vec{F} = \frac{2\alpha\vec{I}}{c}, \quad (1)$$

where α is the acoustic attenuation coefficient of the tissue, c is the tissue's sound speed, and \vec{I} is the acoustic intensity at a given point in space. The acoustic radiation force is generated by a transfer of momentum from the propagating acoustic wave to the propagation medium through attenuation mechanisms, such as absorption and scattering of the ultrasonic wave. In these studies, the acoustic attenuation and sound speed of the prostate tissue were assumed to be constant and not vary as a function of the zonal anatomy, meaning that all displacement differences seen in the prostate would be assumed to be stiffness-related after normalizing for depth-dependent focal gain.

III. METHODS

A. Study Inclusion Criteria

Patients undergoing radical prostatectomy for biopsy-proven PCa treatment were enrolled as study subjects in this IRB-approved (Duke IRB# Pro00006458), HIPAA-compliant study. A total of 16 patients were recruited and enrolled in this study. Inclusion criteria were undergoing complete pelvic MRI with endorectal coil for detection of prostate cancer, including multiplanar T2-weighted anatomic imaging, as well as pre-operative ARFI imaging and radical prostatectomy. Patients with previous treatments of PCa or benign prostatic hyperplasia (BPH), or anatomic anomalies of the rectum, were excluded from this study. All patients enrolled in this study provided written informed consent.

B. Pathology Processing

After excision, the prostates were weighed and tri-axially measured, formalin fixed for at least 24 hours without being cut, and then processed for whole mount histology. While tri-axial measurements of the gross prostate were not necessarily anatomically aligned, rough estimates of the prostate volume were made using a tri-axial, ellipsoidal organ volume assumption, where the volume could be estimated as:

$$V = \frac{4}{3}\pi\sqrt{\det A^{-1}}, \quad (2)$$

where A represents the eigenvector matrix of the tri-axial pathology measurements.

C. MR Imaging

All MR imaging was performed on one of two 3.0 Tesla MR scanners (General Electric HDx, GE Healthcare, Waukesha, WI; Siemens Skyra, Siemens Healthcare, Erlangen, Germany) using a single channel Medrad eCoil endorectal coil (Medrad, Indianola, PA), as well as multi-channel surface coils. Imaging sequences included thin-section (3 mm section thickness) fast spin echo T2-weighted images in the coronal, axial and sagittal planes. Diffusion weighted images were obtained using multiple b-values and calculation of ADC maps was also performed. Dynamic contrast enhanced MR sequences were obtained after administration of a weight-based dose of extracellular MR contrast agent with 4-5 second temporal resolution for 5-6 minutes. (If we need it, can put in table with full MR parameters) Prostates were radically removed using a da Vinci Surgical System (Intuitive Surgical®, Inc., Sunnyvale, CA).

D. ARFI Imaging

Experimental ARFI imaging data were acquired using a modified Siemens Acuson SC2000™ ultrasound scanner (Siemens Healthcare, Ultrasound Business Unit, Mountain View, CA, USA) and the longitudinal array of an Acuson ER7B transducer. The ARFI imaging sequence was comprised of standard B-mode ultrasonic imaging, or tracking beams, and pushing beams. For each lateral location, two pre-push reference images were acquired, then three 300 cycle pushing pulses were transmitted in rapid succession, focused at 30 mm, 22.5 mm, and 15 mm, respectively, and finally the response of the tissue was tracked for up to 6ms at a PRF of 8kHz. This pushing strategy is similar to what has been published by Bercoff *et al.* [26]. The 30 mm and 22.5 mm foci pushing pulses were transmitted at 4.6 MHz with a F/2 geometry and the 15 mm focus pushing pulse was transmitted at 5.4 MHz with a F/2.35 geometry to maintain the same beamwidth (0.67 mm) throughout the region of excitation. A total of 82 lateral locations were interrogated to cover the 55 mm field of view, translating 0.67 mm laterally per location.

For the tracking pulses, 16 parallel receive lines at 5.0 MHz were spaced to observe both the on and off-axis response of the tissue to the pushing pulses. Specifically, four lines were dedicated to tracking the on-axis displacement, with all 4 beams located inside the beamwidth of the pushing pulses such that the beam spacing was 0.17 mm.

Displacement estimation was performed using a phase-shift estimator on the beamformed in-phase and quadrature (IQ) data [27], [28]. The ARFI data were then normalized as a function of depth to account for attenuation and focal gain effects. This normalization was performed using a displacement profile measured in a homogeneous tissue-mimicking phantom, which was applied to all displacements in the entire data set at each time step, and then low-pass filtered with a cutoff-frequency of 0.8 mm^{-1} .

E. Image Zonal Anatomy Segmentation and 3D Model Rendering

Axial MR T2WI images were manually segmented using the smooth polygon tool in ITK-SNAP [29], using unique labels for the PZ, CG and AFS. The gland was segmented from base to apex. The base was identified below the bladder, and subsequent images were segmented until the last slice with visible prostatic tissue was identified caudally. The CG, PZ and AFS were segmented independently according to their well-established anatomical characteristics on T2WI. [12], [7], [30], [3], [8] The PZ was identified by its homogenous high signal intensity on T2WI, which is usually similar to that of the nearby periprostatic fat. The CG was visualized and delineated based on its heterogeneous and lower signal intensity as well as its location (Figure 1). Although not readily visible on every case, the AFS was identified by its low T2 signal intensity and its location anterior to the central gland.

Figure 1 shows the anatomic zones and some anatomic orientation labels in the prostate of a representative study subject MR T2WI. The zonal anatomy of the prostate was manually segmented (Figure 2, bottom left) across the image stack, and 3D models of the zonal anatomy volumes were rendered (Figure 2, top).

ARFI images were segmented using a similar procedure to the MR images. B-mode images were used to segment the prostate capsules since contrast between the peripheral zone and the periprostatic fat can be low, and poor displacement SNR can be present along the anterior aspect of the prostate in ARFI images, making it difficult to delineate that boundary. The central gland was segmented as a stiffer region, relative to the peripheral zone, in the center of the prostate.

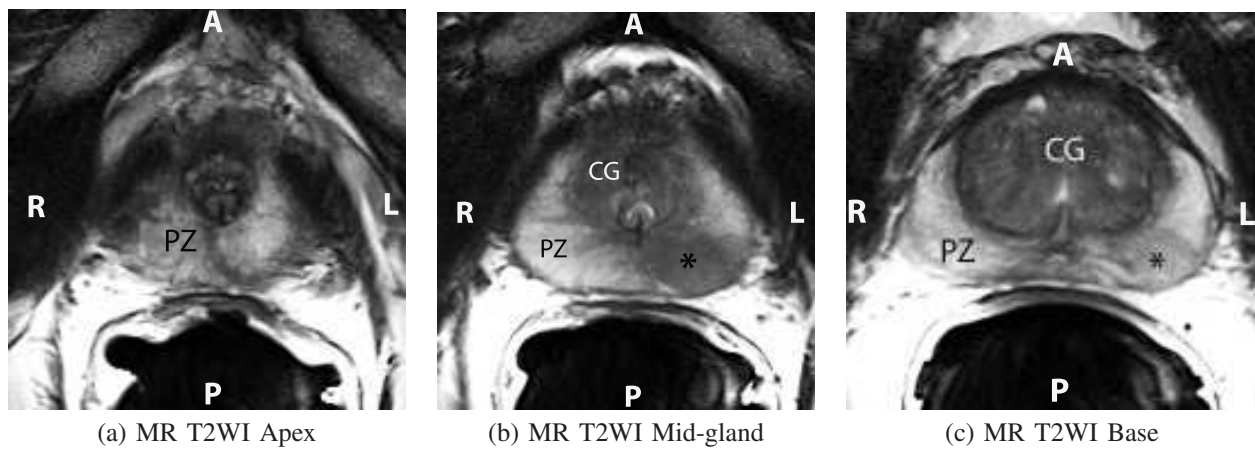


Fig. 1. Axial T2-weighted MR images of the prostate show the apex (a), mid-gland (b), and base (c). The peripheral zone (PZ) is of higher signal intensity than the central gland (CG), the latter which is composed of the central zone and the transitional zone. The apex (A) is composed mostly of PZ glandular tissue and the urethra is seen at the level of the midgland as an inverted “U” (b). Note the area of hypointense signal in the peripheral zone at the midgland and base (asterisk, b and c), which represents a prostatic tumor. The posterior (P) aspect of the prostate is adjacent to the endorectal coil, and the right (R)-to-left (L) extent of the prostate is referred to as the lateral-to-lateral axis in the subsequent analysis.

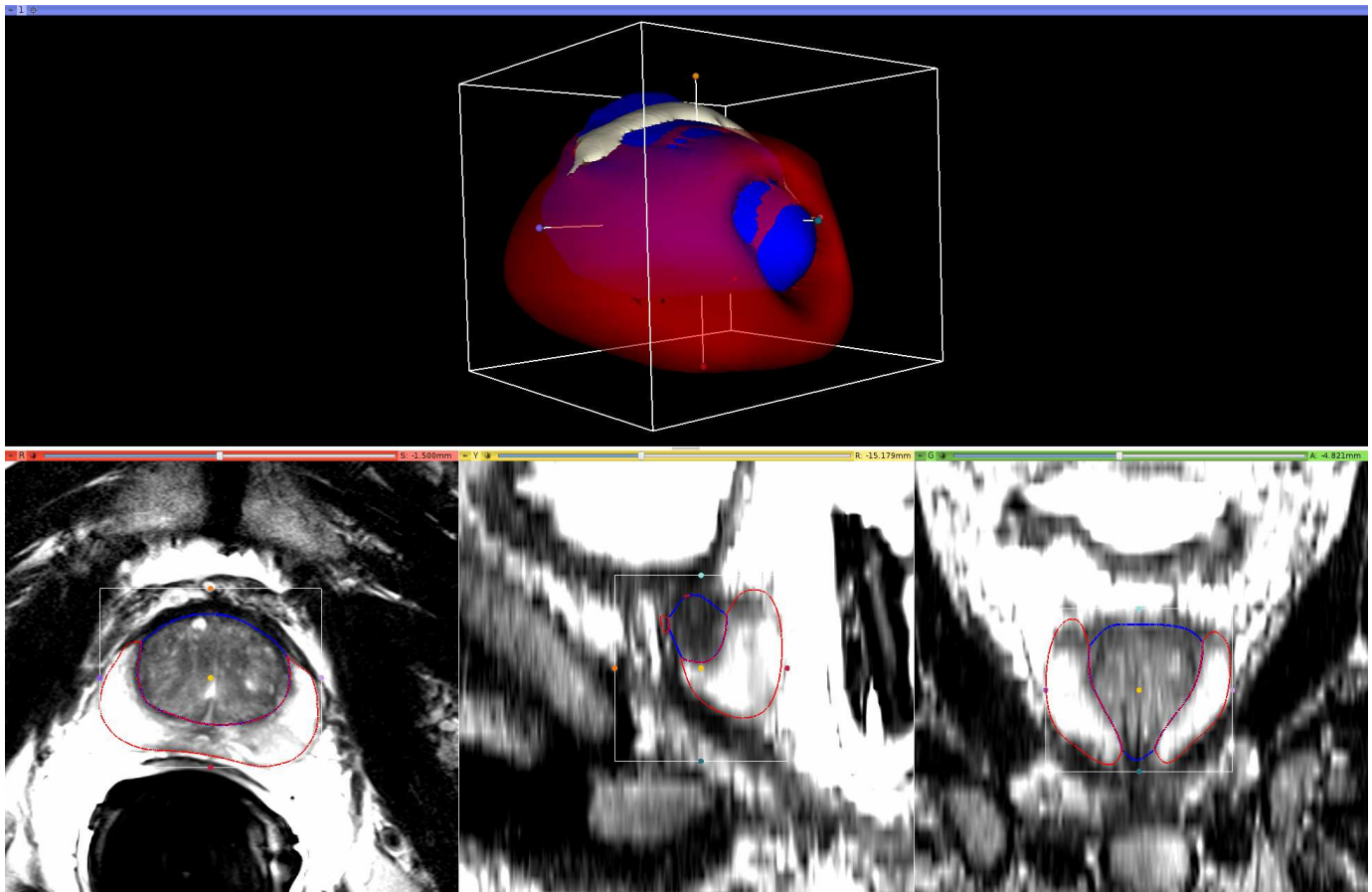


Fig. 2. Representative MR T2WI segmentations and rendered volume performed in 3D Slicer, with the peripheral zone (PZ) being delineated in red, the central gland (CG) being delineated in blue, and the anterior fibromuscular stroma (AFS) being shown in gray. The AFS was combined with the PZ for quantitative analyses shown herein. The native imaging plane for segmentation is the axial view, shown in the bottom left image. The bottom middle and right images show the projections of the rendered model segment outlines in the sagittal and coronal views, respectively.

Segmented image stacks were imported into 3D Slicer (v4.3.0) and 3D models were rendered using the following parameters (Table I):

The 3D slicer models were used to render volume estimates of the PZ and CG, with the sum of PZ and CG representing the total prostate gland volume. AFS volume estimates in select MR cases were included in the total prostate gland volume estimates. Orthogonal tri-axial measurements in the lateral-to-lateral, apex-to-base, and anterior-to-posterior dimensions were

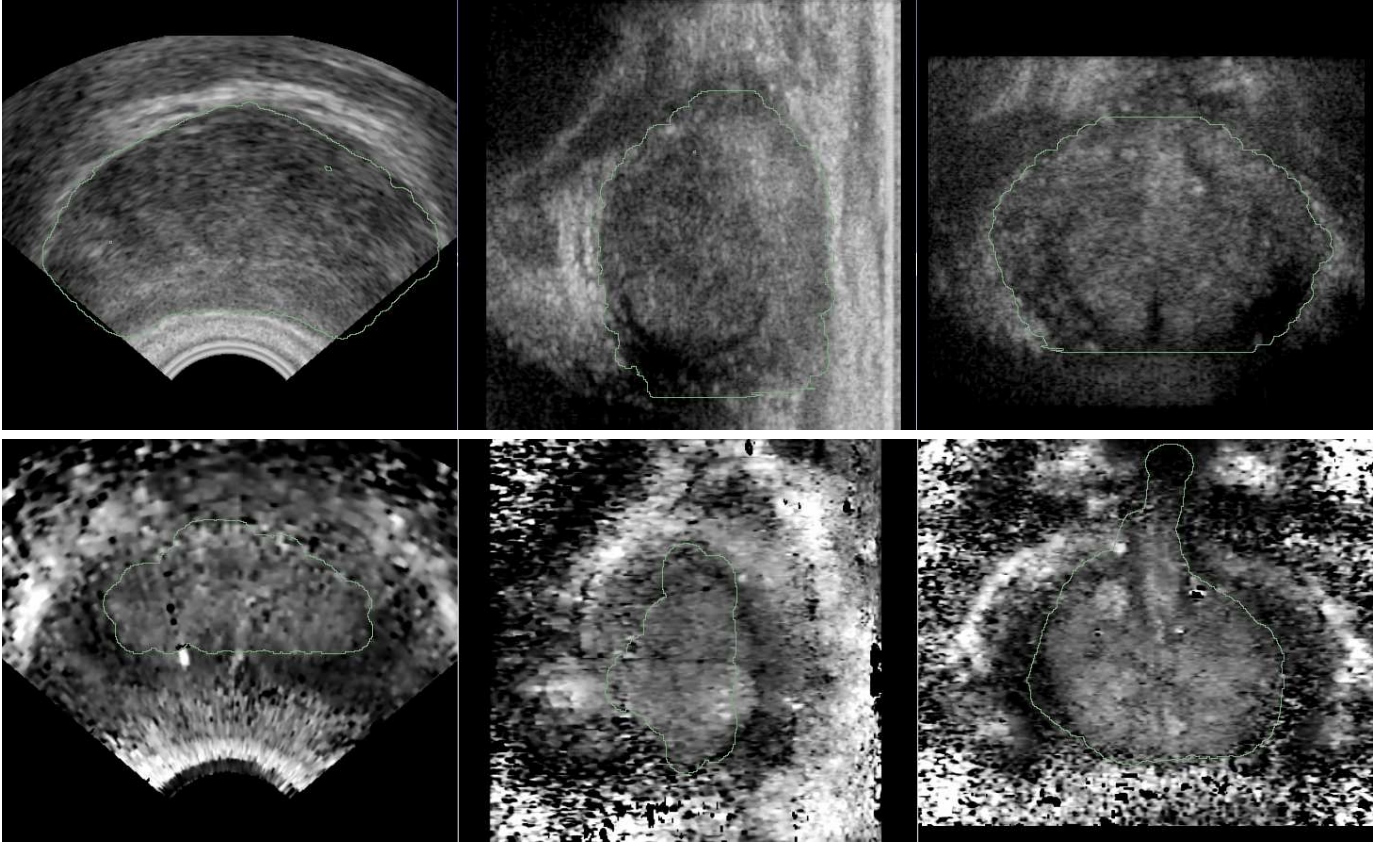


Fig. 3. Representative B-mode (top row) and ARFI images (bottom row), with superimposed segmentation outlines of the capsule and CG, respectively, for the same study subject shown in Figure 2. The B-mode images were segmented in the axial view, using the hypoechoic border of the capsule. Notice that for large prostates, like the one shown in this figure, that the edges of the organ were not always captured in the imaging field-of-view. The CG in the ARFI images was typically segmented using the coronal view, which, especially in the presence of extensive BPH, can have a very characteristic, heterogeneous appearance. It should be noted that the coronal views in these ultrasound images are flipped 180° relative to the same images in Figure 2.

TABLE I
3D MODEL VOLUME RENDERING PARAMETERS

Parameter	Value
Decimation	0.1
Smoothing Algorithm	Laplacian
Smoothing	70.0
Joint Smoothing	Enabled

made in 3D slicer.

IV. RESULTS

The subvolumes associated with the zonal anatomy in each imaging modality were measured (Figure 4(a)), with moderate correlation between the ARFI and MR total prostate gland volumes ($R^2 = 0.68$), with a mean overestimation of $36.7 \pm 27.9\%$ by ARFI imaging compared to MR volumes (Figure 4(b)). Central gland volumes were slightly less correlated between ARFI and MR images ($R^2 = 0.41$) with no significant mean over/under-estimation ($2.1 \pm 39.1\%$), but significant variability between the cases (Figure 4(c)). Table IV has the individually-measured volumes for MR and ARFI imaging for each study subject.

Weights and axis measurements from the gross pathology processing of the excised prostates were collected (Table III), and using the axis measurements (lateral-to-lateral, anterior-to-posterior, and apex-to-base), the prostate volume was approximated as a tri-axial ellipsoid, and its volume was estimated (2). Prostate weights were moderately correlated with estimated pathology ellipsoidal prostate volumes (Figure 5(a), $R^2 = 0.68$). There was moderate correlation between the prostate weight and the image-reconstructed prostate volumes (Figure 5(b), $R^2 = 0.44$ (MR) and 0.21 (ARFI)), though there was weaker correlation with the ellipsoidal approximation of the measurement prostate volume and the image-reconstructed volumes (Figure 5(c), $R^2 = 0.08$ (MR) and 0.01 (ARFI)). Study subject #4 had a very large prostate, which could not be completely captured in MR or

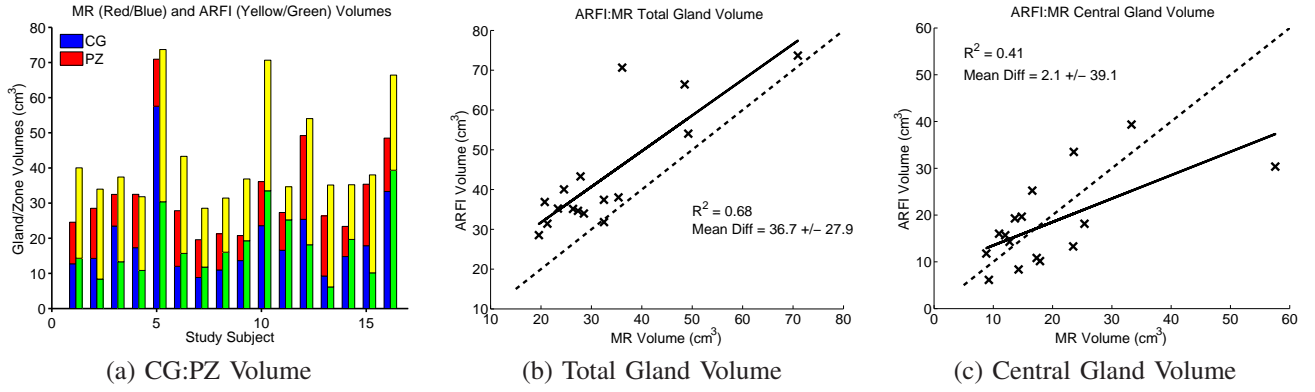


Fig. 4. Comparison of MR and ARFI zonal anatomy volume estimates from manually-segmented images. Total prostate gland volumes ranged from 19.6–71.0 cm³ based on MR image models (a), with a moderate correlation between MR and ARFI imaging for both the total gland volume ($R^2 = 0.68$, (b)) and the central gland ($R^2 = 0.41$, (c)). The ARFI total gland volumes had a positive bias compared with the MR volumes ($36.7 \pm 27.9\%$ (b)), while the ARFI central zone volumes were on average more similar ($2.1 \pm 39.0\%$, (c)), but with some significant variability between study subjects. Table IV contains the individual volume estimates for the total prostate and central glands.

ARFI imaging in the anterior region, so the same analyses were performed with that study subject excluded (Figure 5(d-e)), improving correlations for MR and ARFI to the prostate weights ($R^2 = 0.74$ and 0.60 , respectively), and prostate volumes ($R^2 = 0.39$ for both imaging modalities).

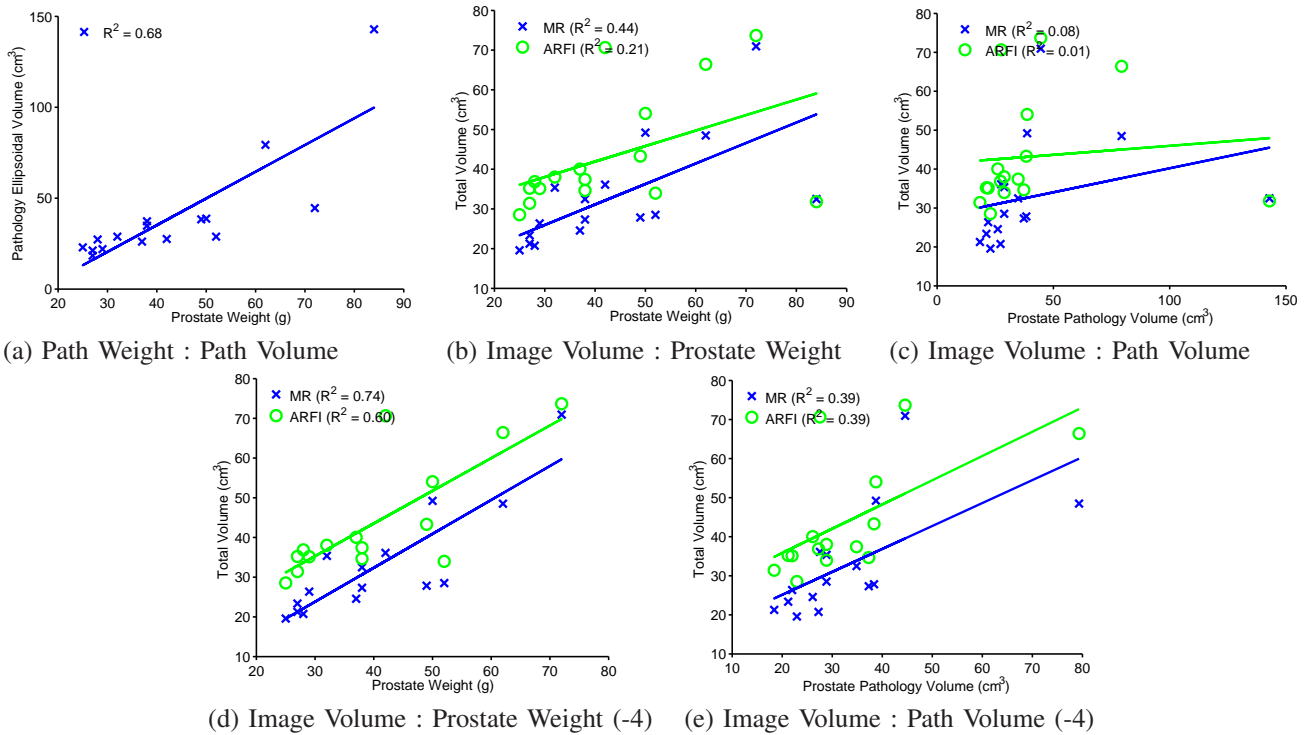


Fig. 5. Tri-axial pathology measurements were used to make an ellipsoidal prostate volume approximation based on gross pathology axis measurements, which was moderately well-correlated with the excised prostates weights (a, $R^2 = 0.68$). T2WI MR (blue, X) showed a moderate correlation between the reconstructed volumes and prostate weight ($R^2 = 0.44$), while volumes reconstructed from ARFI images (green, O) showed weaker correlation ($R^2 = 0.21$) (b). Even weaker correlations existed between both T2WI MR and ARFI image volumes and approximated ellipsoidal prostate pathology volumes ($R^2 = 0.08$ and 0.01 , respectively) (c). It should be noted in these figures that study subject 4 had an excessively large prostate that was difficult to fully capture in imaging, especially in its anterior region, and was therefore grossly underestimated in size. We retrospectively excluded that study subject from the analysis and re-calculated the coefficients of determination, showing that MR and ARFI imaging improved to $R^2 = 0.74$ and 0.60 , respectively, for prostate weight (d), and $R^2 = 0.39$ for both imaging modalities relative to pathology gross volume (e).

Measurements of the prostate total and central gland dimensions along the three standard anatomic axes (apex-to-base, lateral-to-lateral, and anterior-to-posterior) were made (Table V), and the correlation between the imaging axis measurements was analyzed (Figure 6). ARFI was most correlated to MR in the lateral-to-lateral axis in both the total and central glands ($R^2 = 0.47$ and 0.44 , respectively), with mean overestimates of $8.1 \pm 18.4\%$ and $0.06 \pm 17.2\%$, respectively (Table II). ARFI had very good correlation with the total prostate gland axis in the anterior-to-posterior dimension ($R^2 = 0.58$), but poor correlation

in the central gland ($R^2 = 0.00$), with overestimates of 17.0 ± 12.1 and $14.8 \pm 23.1\%$. ARFI imaging had weak correlation with MR images in the apex-to-base dimension ($R^2 = 0.15$, total gland and $R^2 = 0.20$, central gland), with differences of 0.58 ± 12.9 and $-10.8 \pm 22.3\%$, respectively.

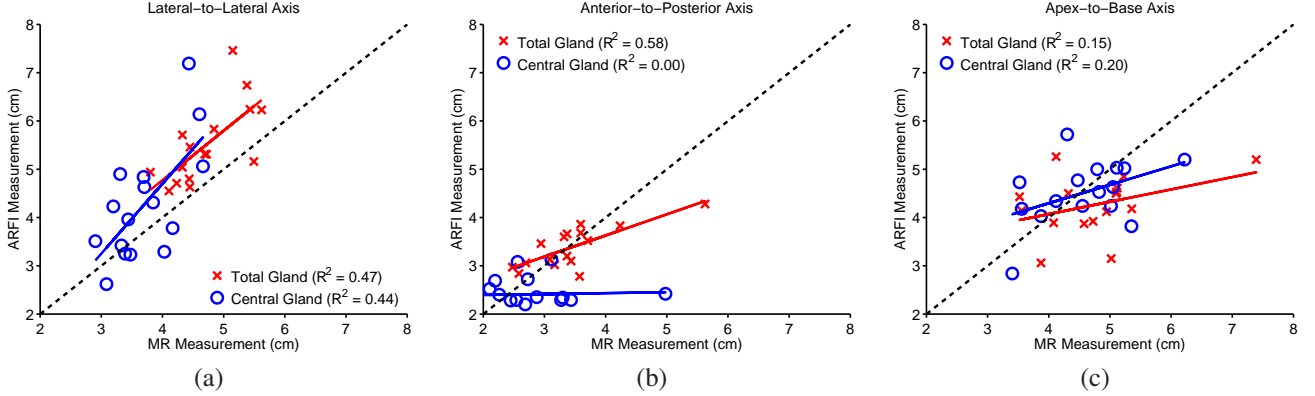


Fig. 6. Measurements of the prostate dimensions along the three standard anatomic axes: lateral-to-lateral (a), anterior-to-posterior (b) and apex-to-base (c). The correlation between the MR and ARFI imaging axis measurements was performed in each orientation for the total gland (red crosses) and central gland (blue circles). The black dashed-line represents the projection of perfectly-correlated measurements between imaging and pathology. The over-/under-estimation of each imaging modality relative to gross pathology and each other is summarized in Table II.

TABLE II
DIFFERENCE IN ARFI IMAGING AXIS MEASUREMENTS RELATIVE TO MR T2WI MEASUREMENTS.

	ARFI:MR Total Gland (%)	ARFI:MR Central Gland (%)
Lateral-to-Lateral	8.1 ± 18.4	0.06 ± 17.2
Anterior-to-Posterior	17.0 ± 12.1	14.8 ± 23.1
Apex-to-Base	0.58 ± 12.9	-10.8 ± 22.3

V. DISCUSSION

This study was designed to compare the zonal anatomy of the prostate in patients with biopsy-proven PCa as seen in ARFI imaging and MR T2WI. Overall, ARFI imaging performed well when compared with MR estimates of total and central gland volume (Figure 4), though ARFI tended to overestimate prostate total gland volume, most commonly due to over-estimation of the anterior-to-posterior dimension of the prostate. As seen in Figure XX, clear delineation of the anterior aspect of the prostate can be challenging in ARFI and B-mode images due to poor SNR, since this is the deepest aspect of the prostate relative to the rectal wall imaging surface. MR T2WI can also have difficulties visualizing and diagnosing lesions in the anterior region of the prostate, [2], which is thought to be secondary to the heterogeneity of the gland in that area, especially in the presence of BPH. This was evident in imaging study subject 4, with a ~ 143 g prostate (Figure 5), which was an outlier in terms of weight and volume. With study subject 4 excluded, MR and ARFI imaging volumes and the ellipsoidal prostate volume estimates had similar correlation with prostate weights (Figure 5(d)).

The most accurate measurements for both the total prostate gland and central gland were in the lateral-to-lateral dimension (Figure 6(a), Table II), with ARFI imaging exhibiting a slight overestimate in both glands. ARFI imaging had weaker correlations with MR imaging in the apex-to-base dimension (Figure 6(c)), though it should be noted that the MR images are limited in spatial resolution by slice thickness and volume averaging in this dimension (~ 3 mm). Finally, as expected from qualitative image evaluation, the anterior-to-posterior dimension had the weakest correlations, especially in the central gland, most likely related to the inability to clearly resolve an anterior border for both the prostate total and central glands. Of note, a slight overestimation of anatomic borders can result in a large relative difference from the true values (by histology) as the gland is small in size.

This study has several limitations that should be considered when interpreting these results. Gross pathology weight and axis measurements could both be affected by the presence of periprostatic tissue that was excised during radical prostatectomy, especially in cases where more aggressive margins may have been necessary. For this reason, unlike the image-to-image measurement comparisons, all of the image metrics presented relative to pathology metrics (Figure 5) were not characterized for absolute accuracy, but instead, relative correlations were evaluated. Additionally, the volumes of the prostate from gross pathologic measurements were approximated as ellipsoids, which also introduced error, most likely an over-estimation of volume. Interestingly, all pathology estimates were thought to have positive biases, but both imaging modalities tended to overestimate relative to the pathology measurements.

It should also be noted that all of the prostates in this study contained varying amounts of PCa, BPH and atrophy, all of which can distort the zonal anatomy, especially in the case of BPH and central gland morphology. While younger, healthier prostates could have been targeted, these healthy organs would not have been excised for pathology characterization, and the zonal anatomy of a healthy (young) prostate is expected to be different from the prostate of a middle-age man, who is the target demographic for PCa screening imaging and PCa characterization; therefore, it was felt that performing this analysis in the presence of these confounding factors was appropriate.

Future directions for our research include deeper analysis of our findings, especially the lateral-to-lateral overestimation, in order to improve our anatomic delineation and assess further its clinical impact. Although work remains to be done, the fact that one can view the different prostatic zones on ARFI images in addition to MRI is encouraging and could lead to targeted diagnostic biopsies and therapies with real-time imaging for men with PCa.

VI. CONCLUSIONS

The delineation of prostate zonal anatomy in ARFI images has been compared with the established methods for identifying zonal anatomy using MR T2W images. Both imaging modalities showed moderate correlations ($0.39 < R^2 < 0.74$) between estimated organ volume and gross pathologic weights. ARFI and MR total prostate gland volumes were well-correlated ($R^2 = 0.68$), but ARFI images yielded prostate volumes that were, on average, larger ($36\% \pm 28\%$) than MR images, primarily due to over-estimation of the anterior-to-posterior dimension of the prostate total gland ($17.0 \pm 12.1\%$), while over-estimates of the other dimensions were less significant contributors ($8.1 \pm 18.4\%$ and $0.58 \pm 12.9\%$). The central zone volumes of ARFI and MR images were also moderately correlated ($R^2 = 0.41$), with minimal volume bias between the imaging modalities, but significant variability case-to-case ($2.1 \pm 39.1\%$). Central zone volume differences were, again, strongly attributed to over-estimation of the anterior-to-posterior axis ($14.8 \pm 23.1\%$), with a significant underestimation of the apex-to-base dimension ($-10.8 \pm 22.3\%$) and no mean bias in the lateral-to-lateral measurements ($0.006 \pm 17.2\%$). Strong variability in central gland volumes is believed to be related to the extent of benign prostatic hyperplasia (BPH) for select cases. Overall, ARFI imaging of the prostate yielded prostate volumes and dimensions that were correlated with MR T2WI estimates, with biases in the anterior-to-posterior dimension, most likely related to poor displacement SNR in the anterior region of the prostate from greater distance from the rectal wall imaging surface. ARFI imaging is a promising low-cost, real-time imaging modality that can compliment MR imaging for diagnosis, treatment planning and management of PCa.

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DISCLOSURES

Some of the authors on this manuscript hold intellectual property related to ARFI imaging, and commercial licenses of this technology with Duke University exist. There are no personal financial disclosures for the authors.

VII. APPENDIX

Tables III–V contain the raw measurements in gross pathology, MR T2W imaging, and ARFI iamging.

TABLE III
PATHOLOGY PROSTATE GROSS SPECIMEN METRICS

Study Subject	Weight (g)	Lat-Lat (cm)	Anterior-Posterior (cm)	Apex-Base (cm)	Ellipsoidal Volume (cm ³)
1	37.	4.3	4.0	2.9	26.10
2	52.	4.5	3.5	3.5	28.85
3	38.	4.5	4.0	3.7	34.85
4	84.	7.0	6.5	6.0	142.87
5	72.	6.6	4.3	3.0	44.56
6	49.	4.9	4.4	3.4	38.36
7	25.	3.7	3.7	3.2	22.93
8	27.	4.2	3.1	2.7	18.40
9	28.	4.4	3.7	3.2	27.26
10	42.	4.7	3.5	3.2	27.55
11	38.	5.4	4.0	3.3	37.30
12	50.	5.0	4.0	3.7	38.73
13	29.	4.0	3.5	3.0	21.98
14	27.	4.5	3.0	3.0	21.20
15	32.	4.5	3.5	3.5	28.85
16	62.	5.5	5.3	5.2	79.33

TABLE IV
COMPARISON OF CENTRAL GLAND / ZONE AND TOTAL PROSTATE VOLUMES IN MR T2WI AND ARFI IMAGING

Study Subject	MR Central Gland Volume (cm ³)	MR Total Volume (cm ³)	ARFI Central Zone Volume (cm ³)	ARFI Total Volume (cm ³)
1	12.74	24.57	14.30	40.03
2	14.26	28.51	8.37	33.98
3	23.47	32.48	13.29	37.42
4	17.32	32.49	10.83	31.82
5	57.56	70.95	30.37	73.68
6	12.01	27.84	15.68	43.30
7	8.82	19.59	11.78	28.55
8	10.97	21.28	16.02	31.42
9	13.63	20.75	19.28	36.88
10	23.58	36.11	33.50	70.65
11	16.57	27.33	25.22	34.66
12	25.38	49.21	18.14	54.04
13	9.25	26.36	6.14	35.14
14	14.79	23.36	19.65	35.21
15	17.87	35.37	10.15	38.03
16	33.32	48.50	39.35	66.42

TABLE V

COMPARISON OF CENTRAL GLAND / ZONE (C) AND TOTAL (T) PROSTATE AXES IN MR T2WI AND ARFI IMAGING. AXES ARE APPROXIMATED IN ORIENTATION TO MATCH THOSE SPECIFIED IN GROSS PATHOLOGY: LATERAL-TO-LATERAL (LL), ANTERIOR-TO-POSTERIOR (AP) AND APEX-TO-BASE (AB).

Study Subject	MR C-AB (cm)	ARFI C-AB (cm)	MR C-LL (cm)	ARFI C-LL (cm)	MR C-AP (cm)	ARFI C-AP (cm)	MR T-AB (cm)	ARFI T-AB (cm)	MR T-LL (cm)	ARFI T-LL (cm)	MR T-AP (cm)	ARFI T-AP (cm)
1	4.12	4.34	2.90	3.51	2.45	2.28	4.12	5.26	3.80	4.94	3.09	3.14
2	3.87	4.03	3.39	3.25	2.80	1.66	3.87	3.06	4.45	5.46	3.59	3.86
3	4.82	4.53	3.48	3.23	3.27	2.29	5.11	4.53	4.11	4.55	3.59	3.68
4	5.35	3.82	3.08	2.62	2.87	2.35	5.36	4.18	4.45	4.63	3.37	3.66
5	6.22	5.20	4.66	5.06	4.98	2.42	7.39	5.20	5.43	6.24	5.63	4.28
6	5.05	4.63	3.44	3.96	3.44	2.29	5.10	4.50	4.84	5.83	3.44	3.10
7	4.47	4.77	3.33	3.42	2.26	2.40	4.72	3.92	4.44	4.80	2.58	2.84
8	4.30	5.72	3.20	4.23	2.10	2.52	4.32	4.50	4.23	4.71	2.48	2.97
9	3.52	4.73	3.31	4.90	2.19	2.69	3.52	4.43	4.33	5.71	2.70	3.06
10	5.24	5.02	4.43	7.19	2.69	2.20	5.23	4.85	5.15	7.46	3.37	3.20
11	5.02	4.24	3.85	4.31	2.73	2.72	5.02	3.15	5.50	5.16	3.57	2.78
12	4.55	4.24	3.70	4.63	3.30	2.34	4.58	3.87	5.38	6.74	4.24	3.83
13	3.40	2.84	4.03	3.29	2.01	1.91	4.08	3.89	4.72	5.31	2.94	3.46
14	3.56	4.18	3.69	4.84	2.54	2.29	3.56	4.14	4.33	5.04	3.17	3.02
15	4.79	5.00	4.17	3.78	2.56	3.08	4.95	4.12	4.69	5.31	3.32	3.60
16	5.11	5.03	4.60	6.14	3.11	3.13	5.12	4.61	5.62	6.23	3.71	3.52

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Manuscript Addendum

1. Statement of the role of the student

When I decided to work with Dr. Rajan T. Gupta from the Department of Radiology in order to further explore my interest in the field, he asked me to attend a prostate-imaging meeting to see if I would like to pursue research in that topic. Although I was not completely convinced about spending my third year studying prostate imaging, once I realized the multidisciplinary nature of the work I wanted to be part of the research team. The team consisted of radiologists, urologists, pathologists and biomedical engineers and each person was essential and thoroughly involved in the discussion.

The most exciting aspect of this multidisciplinary project is that I fortunately ended up working on a couple of different imaging perspectives during the year, namely prostate MRI and ARFI imaging. For instance, I was thoroughly involved on the radiology side by segmenting MRI images; specifically, I segmented the capsule, central gland, peripheral zone and anterior fibromuscular stroma on the ~60 patients we have thus far. I then corroborated my segmentations with Dr. Gupta and adjusted them accordingly. I also segmented all of our histology cases that had been previously delineated by the pathologists on our team. Working with Dr. Mark Palmeri and everyone at the Nightingale lab, I learned about ARFI, participated in image acquisition in the operating room prior to radical prostatectomies, and segmented the central gland, peripheral zone and capsule on ARFI volumes. Although outside of the scope of this paper, I also worked on image registration across different modalities (MR-ARFI, MR-Histology, ARFI-Histology).

For this project, once all our segmentations were complete, Dr. Palmeri and I calculated the volumes of our segmented MR and ARFI images and compared them to the volumes from the pathology reports I retrieved from each patient's hospital chart. We then created our tables and figures to analyze our data. I personally created the MRI figures whereas Dr. Palmeri took charge of rendering the 3D models seen in our paper. We then set out to write our manuscript, which will be shared with the rest of the co-authors across different specialties for further feedback.

I am proud to have had a very productive third year. I was fortunate enough to earn a co-authorship on this manuscript with Dr. Palmeri and am currently working on

my second first author paper with Dr. Gupta on the effect of reader education on prostate cancer MR imaging diagnosis. Much of our ARFI and MRI work has already been presented at several conferences, including a selection to present at our annual AOA Research Symposium. The reason I decided to submit this paper as my thesis requirement is because it shows the multidisciplinary nature of our team's work. It is also the first of many prostate ARFI papers that will come out of our efforts.

2. Comprehensive introduction: additional background and significance, future directions and clinical relevance

Prostate cancer (PCa) is the most common non-skin cancer and the second leading cause of cancer death in American men. The current clinical standard is to perform systematic sampling of the prostate under US guidance. Nonetheless, biopsy cancer detection rates from a first biopsy range from 25-36%^{1,2} and repeat procedures have revealed cancer in 10-35% of cases.¹⁻³ In addition, up to 20% of men require three or more biopsy sessions for diagnosis, a reality that can result in excess morbidity.³

Studies have shown that low tumor burden is not necessarily correlated with low tumor volume and low Gleason score in excised prostates.^{2,4} Men with a small cancer burden on prostate biopsy may have significant disease on histology and a significant risk of PCa recurrence after radical prostatectomy². This finding again highlights the limitations associated with the current, non-targeted, biopsy approach. Further, with the increased concern for prostate infections and associated hospital admissions from transrectal biopsies, the need for more targeted and noninvasive means to characterize prostate disease is high and a potential need imaging could fill.⁵

Multi-parametric MRI (mpMRI) and PCa

As aforementioned, prostate MR imaging has been used since the 1980s but the recent addition of functional parameters to T2W anatomical imaging has greatly improved its accuracy. The European Society of Urogenital Radiology's (ESUR) prostate MR guidelines recommend at least 2 functional imaging techniques in addition to T2WI in order to better characterize prostate tumors.⁶ In a study by Turkbey et al, researchers found that mpMRI had a positive predictive value of 98% in prostate cancer detection.⁷ The mpMRI approach includes diffusion-weighted imaging (DWI), dynamic contrast enhanced imaging (DCE-MRI) and MR spectroscopy (MRSI).

Diffusion-weighted imaging

DWI is based on the free movement of water particles in tissue and measures the degree of motion restriction.⁸ Normal prostatic tissue is very glandular with plenty of water molecule movement. On the other hand, tumors have high cellular density and restricted water movement, which leads to decreased diffusion. Due to this restricted diffusion, tumors seem to be of higher intensity on DWI.⁸

DWI sequences can be processed to obtain apparent diffusion coefficient (ADC) maps. These serve as a more objective measure of diffusivity since they are independent of magnetic field and thus overcome the effects of T2 shine-through.^{8,9} ADC maps are also used to visually assess the tumor, which appears as a focus of decreased signal intensity when compared to normal prostate tissue.⁹

In addition to knowing the location of the cancer within the prostate, being able to identify, which cancers will exhibit more aggressive behavior is important when making clinical management decisions. A number of studies have found that lower ADC values correlate with tumors that have higher Gleason scores.¹⁰⁻¹² This could be explained by the fact that higher-grade lesions are usually of higher cellular density and thus have even more marked restricted diffusion. This inverse correlation suggests that ADC maps might be helpful when characterizing lesions and assessing tumor aggressiveness.¹³

Dynamic contrast enhanced imaging

DCE-MRI has been shown to have a high sensitivity in cancer detection, especially when combined with other MR imaging modalities.¹⁴⁻¹⁷ In a study by Hara et al, this functional modality identified 93% of clinically significant cancers.¹⁸ DCE-MRI provides a measure of tumor vascularity and takes advantage of tumor-induced angiogenesis in PCa.¹⁹ Increased vascularity in PCa results in earlier and higher peak contrast enhancement and a faster washout when compared to normal prostatic tissue. These known characteristics of PCa are helpful when trying to localize lesions.

A variety of different approaches can be used to analyze DCE-MRI and no report has, up to date, described the superiority of one method over the others.²⁰ The approaches include qualitative analysis by visual assessment of the images, semi-quantitative methods that look at kinetic parameters on a voxel-by-voxel basis, or quantitative methods that convert signal intensity into kinetic parameters to determine how much

contrast is being exchanged between the vascular, extravascular and extracellular spaces.²⁰

MR spectroscopy

Like DWI, MRSI can be helpful in lesion characterization as it provides information on the presence of certain metabolites in tissue.⁶ Choline and citrate are especially useful in the setting of PCa. Choline is critical in cell membrane synthesis and is thus usually elevated in cells with cancerous behavior.²⁰ Healthy prostate epithelium synthesizes and secretes large quantities of citrate but levels are decreased in PCa.^{21,22} Therefore, an increase in the choline-to-citrate ratio on MRSI can be used as an indicator of malignancy.²³

Although some data suggests that MRSI increases the accuracy of tumor volume detection and staging when used in addition to anatomic imaging, it is unclear whether it is superior to other modalities.²³ ESUR lists MSRI as an optional modality for the diagnosis of PCa since it significantly lengthens exam time and requires specific technical expertise.⁶ Thus, it is not surprising that many academic centers in the United States do not include MSRI in their mpMRI prostate cancer protocols.²⁰

Acoustic Radiation Force Impulse (ARFI) Imaging

ARFI imaging is an ultrasound technique that evaluates the mechanical properties of tissues by generating short-duration acoustic radiation forces that result in tissue displacement. The response can then be measured for tissue characterization, with displacement being inversely proportional to stiffness.²⁴ This characterization is of particular importance in prostate evaluation due to the gland's complex and heterogeneous composition. Previous studies have shown that the central zone and PCa can be up to 3 times stiffer than peripheral zone (PZ) tissue.²⁵⁻²⁷ This finding can be explained by the PZ's higher water content and is analogous to the higher signal intensity of the PZ on T2WI.

The potential of ARFI imaging to distinguish normal prostatic anatomy from pathologic tissue is promising in the future of PCa diagnosis and image guided therapies. B-mode US, which is currently used for real-time guidance in for more than 1,000,000 annual biopsies performed in the United States²⁸, does not have the ability to clearly visualize PCa or to differentiate it from other normal structures or disease processes such

as benign prostatic hyperplasia (BPH) or prostatitis.²⁵ As stated above, this has resulted in a systematic yet random approach to prostate core biopsies, with 6-12 cores routinely sampled from different anatomical regions.³⁰ The ability to clearly distinguish PCa from other tissues could lead to targeted biopsies with increased sensitivity and resultant decreased morbidity. It could also aid in the development of targeted therapies for those with low burden of disease.

Clinical significance and future directions

The most exciting part of this project is its potential for clinical impact. With our ability to detect earlier cancers comes the possibility of developing directed therapies that lead to less morbidity and not require radical prostatectomy to free men from disease, especially those with localized cancer. We believe that by combining ARFI and mpMR imaging, specific diagnostic procedures and PCa management could shift towards a targeted model.

3. Other related projects

In addition to this manuscript, I am currently writing a second one titled *Detection of Prostate Cancer with Multiparametric MRI: The Effect of Dedicated Reader Education on Accuracy and Confidence of Index Cancer and Anterior Cancer Diagnosis* that I will be first author of and presented at the annual AOA Research Symposium at Duke. Our work this year also led to several presentations and national conferences including the 38th International Symposium on Ultrasonic Imaging and Tissue Characterization Conference where one of our lab members presented on *Non-rigid Registration of Prostate Histology to ARFI and MR Image Volumes* this past June (I was a co-author). In the 6th Image Guided Therapy Workshop, we were able to share some of our findings on ARFI prostate imaging in a poster titled *In vivo Acoustic Radiation Force Impulse (ARFI) Elasticity Imaging of Prostate* (I was a co-author). I will be presenting a poster titled *Registration of Multi-parametric MR and Acoustic Radiation Force Impulse (ARFI) Images for Focal Prostate Cancer Diagnosis and Therapy* for the Coulter Translational Research Partnership in the Pratt School of Engineering this November. We also recently submitted an abstract for the American Roentgen Ray Society's annual meeting titled *Benign prostatic central zone tissue demonstrating diffusion restriction similar to prostate cancer: further investigation of a potential diagnostic pitfall at*

prostate MRI that I was also a co-author for. Finally, this year I also co-authored a chapter on abdominal trauma imaging with Dr. Gupta for Gore and Levine's Textbook of Gastrointestinal Radiology that will be published on 2014.

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