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 prostatectomy[2]. 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 it's 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 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 States[28], 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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