Acoustic Radiation Force Impulse (ARFI) Imaging for Targeted Prostate Biopsy

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Purpose of the Study

The objective of the proposed study is to evaluate the feasibility of a new ultrasonic acoustic radiation force impulse (ARFI) elasticity imaging system with a custom-designed transducer and biopsy guide to provide imaging guidance and targeting during prostate needle biopsy. This study will be conducted in two parts. Part 1 will evaluate a new, custom designed ultrasound transducer and needle guide in performing systematic transrectal ultrasound-guided prostate biopsies, as is the current standard-of-care. In addition to standard imaging, the new probe will be capable of ARFI measurements of tissue stiffness. Part 2 will evaluate the feasibility of targeted prostate biopsy guidance using ultrasound ARFI targeting as compared to ultrasound-MR fusion targeting in subjects electing to have ultrasound fusion-MR targeted biopsy procedures.

Background & Significance

Prostate cancer is the most common cancer and the second leading cause of cancer death for American men. For men harboring occult aggressive cancers, early diagnosis is essential for better treatment and increasing survival rate. Although the current screening techniques (prostate-specific antigen (PSA) blood testing and digital rectal examination (DRE)) are moderately sensitive but lack specificity for cancer screening, resulting diagnostic biopsies have significant shortcomings. Transrectal ultrasound is currently used to provide biopsy guidance only; however, it has poor sensitivity and specificity for prostate cancer. Without a good imaging technique to guide the needle biopsy in prostate glands, only about 25% of tests are positive for cancer in more than 1 million prostate biopsies performed each year; the false negative rates range from 25-45% based on the first-time biopsy. Although studies have shown more biopsy cores can increase diagnostic accuracy, prostate needle biopsy is an invasive procedure for the patient associated with both pain and risks, such as infection, hematuria (blood in the urine), urinary retention, hematochezia (blood during bowel movement), and hematospermia (blood in the semen). More biopsy cores mean higher risk for the patient. Thus, improved needle biopsy procedures guided by ARFI imaging would be of great clinical benefit.

Design & Procedures

PART 1: The new ultrasound probe will be used in the same manner as current probes for standard-of-care prostate biopsy using systematic sampling with transrectal ultrasound (TRUS) guidance. In addition to B-mode images during the procedure, ARFI images will be acquired immediately before each needle insertion, after needle insertion, and following needle removal in each sampled image plane. The additional time required for ARFI measurements will be approximately 5-10 minutes.

PART 2: Three-dimensional ARFI images of the prostate will be acquired by sweeping the imaging plane through the prostate volume as in our current study of ARFI prostate imaging (Pro00006458), using the custom-designed ARFI-capable ultrasound probes. Image volume acquisition will take approximately 12 minutes, and not more than 20 minutes. Display of these images will be in real-time, and immediately following the volume acquisition, the most suspicious targets (up to 3) in the gland will be identified. The ultrasound probe will be positioned to image the target in plane and two-four biopsy cores will be acquired per target – with ARFI and B-mode image data acquired from each targeting procedure. The

ARFI ultrasound probe will be removed, and the standard ultrasound-MR fusion biopsy procedure will then proceed using the clinical ultrasound fusion-MR system. The additional time required to acquire the ARFI image volume and perform the ARFI-targeted biopsy cores is approximately 25-30 minutes

Selection of Subjects

PART 1: We will enroll patients scheduled for standard TRUS biopsy with suspected PCa.

PART 2: We will enroll patients with suspected PCa who are scheduled to undergo an ultrasound fusion-MR prostate biopsy.

Due to the nature of PCa, this study is open to men only; women and children are excluded. It is open to members of all racial and ethnic groups. Patients will be recruited by the treating physician or a healthcare provider known to the patient at the time of consultation.

Inclusion criteria:

PART 1: Men with suspected PCa based on suspicious PSA or DRE, or abnormal radiological finding scheduled for standard TRUS prostate biopsy;
PART 2: Men who are scheduled to undergo ultrasound fusion-MR prostate biopsy;
Men who are willing to participate in the study;
Subjects must freely sign informed consent to enroll in the study;
18 years or older

Assessing eligibility: eligibility for the study will be assessed, based upon the above criteria, by the participating urologist at the time of consultation.

Exclusion criteria:

Men who have had previous treatment for PCa including radiation, cryoablation, chemotherapy, surgery, high intensity focused ultrasound (HIFU), laser therapy or hormone therapy;
Men who have had previous non-pharmacological invasive or minimally invasive treatment for benign prostatic hypertrophy (BPH) (i.e., TURP, TUMPT, WIT, TUNA, etc); standard pharmacological treatment of BPH is allowable;
Men who are mentally impaired and cannot give written consent;
Men with anomalies of the rectum

Subject Recruitment and Compensation

This study will be open to members of all demographic groups who meet the eligibility criteria. The study will be introduced to potential subjects by a healthcare provider known to them. If interested, someone from the research team will discuss the study with the potential subject. Potential subjects will be identified from the pool of adult male urology patients at clinic 1G, the Duke Cancer Center, the Duke Raleigh Urology clinic or referred from an outside facility which will provide sampling from a diverse

patient population spanning all demographics in order to support equitable subject selection. Subjects will not receive any compensation. We will need to review protected health information such as name, history number, appointment date and physician, past cancer history, other past medical history and other protected health information (PHI) to determine study eligibility. This activity is used only to identify subjects, and information resulting from this activity will be used only to assess eligibility of subject. Once the subject has been assigned to the study and consent has been obtained, documentation of eligibility will be recorded.

PART 1: Ten patients will be recruited for the first part of the study, which will evaluate the performance of a new, custom designed ultrasound probe and biopsy guide for systematic transrectal ultrasound guided prostate biopsies.

PART 2: Up to 60 patients will be recruited per our existing NIH grant.

Study Interventions

PART 1: Participation will not affect the subjects' standard clinical treatment in any way.

PART 2: Two-four additional biopsy cores per target lesion will be acquired at suspicious positions identified by ARFI targeting.

Risk/Benefit Assessment

PART 1: If, as we expect, the B-mode image quality and biopsy guide performance of the new transducer and system are comparable or better than the current clinical TRUS system, there should be no increased risk to the patient from using the prototype system for standard systematic TRUS biopsy. If the imaging capabilities of the new ultrasound probe are insufficient as compared to the clinical ultrasound system, the attending physician will remove the new probe and use the clinical system to perform the required measurements and TRUS-guided biopsy. If necessary, this change would require approximately 5 minutes. Per our current IRB protocol, the additional ARFI images that will be acquired in each image plane where a biopsy is taken are of minimal risk. The primary risk associated with ARFI measurements using the new ultrasound probe is slightly increased tissue heating that is within the FDA limits for ultrasound, and a theoretical risk of cavitation. There will be no direct benefit to the patients enrolled in this part of the study.

PART 2: The primary risk associated with the second part of the study is the acquisition of two-four additional biopsy cores per target as compared to the number obtained during the standard-of-care ultrasound fusion-MR biopsy acquisitions. Actually, subjects may require fewer overall numbers of biopsy cores as abnormal areas of imaging (ARFI and MRI) will be targeted compared to standard, blind, non-targeted prostate biopsy. Per our current IRB protocol (Pro00006458), while minimal, the primary risk associated with ARFI imaging is tissue heating, though temperature increases are below FDA limits for ultrasound measurements. There is also a theoretical risk of acoustic cavitation associated with the ARFI pulses, however, this is unexpected based upon the pulse MI and duration (Nightingale et. al, JUM, 2015), and has not been observed in the over 200 ARFI/SWE imaging studies we have performed to

date. The additional time required for the ARFI measurements and targeted biopsy procedure will extend the time the patient will receive anesthesia. Additionally, this study will require a separate insertion of the ARFI probe in addition to the standard TRUS probe used for MRI targeted biopsy. The subject will benefit directly from the acquisition of two-four additional biopsy cores per ARFI target at suspicious positions identified by ARFI imaging.

We consider the risks identified to be minimal, and we hypothesize that the ARFI technology has significant potential for improving the diagnostic accuracy of TRUS prostate biopsy. Thus, we consider this study to have a favorable benefit/risk ratio.

Data Analysis & Statistical Considerations

For the first part of the study, images acquired with the new ultrasound transducer will be evaluated qualitatively by the attending physician to determine if they are adequate for ultrasonic systematic biopsy sampling of the prostate. ARFI images will also be obtained and will be analyzed off-line using existing methods to assess tissue stiffness, needle visualization, and changes in tissue stiffness following needle removal. We expect b-mode ultrasound imaging and ARFI imaging capabilities to be comparable or superior to those we have obtained with the transducer/system we have been using under our current imaging protocol. We plan to include up to 10 patients in this Part 1 study. We do not plan to perform statistical analyses for this part because our goal is primarily to verify the functionality of the probe/system prior to initiating part 2.

For the second part of the study, we will test the hypothesis that ARFI guided targeted biopsy provides a higher PCa detection rate than that reported for systematic TRUS biopsy. We will also compare ARFI-targeted biopsy performance to that of MR-ultrasound fusion targeting by evaluating the biopsy cores obtained using each method with standard statistical tests to compare the length and grade of cancerous tissue in the cores. Biopsies will be scored for clinically significant disease (CSD) using the same clinical standard as for TRUS biopsy (e.g., percent PCa per/core, Gleason score, Gleason Grade Group) and yield of CSD (i.e., number of cores containing CSD/total number of cores) for each biopsy method. In addition, the spatial location of the targeted cores within the prostate will be compared between ARFI and Ultrasound-MR fusion. Assuming an ARFI imaging specificity for CSD of 70% (our preliminary data from Protocol Pro00006458 in patients receiving radical prostatectomy yielded 79% CSD from ARFI suspicious regions, and, 71% detection of all CSD present in the gland), and comparing to the systematic sampling TRUS PCa mean detection rate of 30% that has been well-established in the literature, inclusion of 35, 45, and 50 patients would achieve study powers of 80%, 90%, and 95%, respectively through a one-mean, one-sample equivalence test with a 30% testing margin and a standard deviation of up to 20% of the target ARFI imaging specificity. We plan to include 50 patients in this Part 2 study, plus 10 initial patients for early phase development and workflow integration (60 total in part 2).

Direct personal identifiers in study records will not be disclosed outside of Duke University Health System. For records disclosed outside of Duke, subjects will be assigned a unique code number.

Data & Safety Monitoring

The Principal Investigator, Dr. Thomas Polascik, will be responsible for monitoring the safety of these studies. As previously described, we do not anticipate any adverse events. However, in the event that adverse events occur, they will be immediately reported in detail in writing to the Duke University Medical Center's Institutional Review Board (IRB) in accordance with the re portable events policy.

Data for this study, including relevant medical records such as prostate-specific antigen (PSA) level, biopsy results, and any available imaging studies (MR, prior ultrasound, etc.) will be analyzed at the completion of study enrollment. A code number will be assigned to each subject, which will be used for data analysis and result reporting. The patient name and history number will be recorded only in the electronic enrollment log, which will also have the unique code number. The patient consent forms will be stored in the office of the primary study coordinator, which is locked when the primary study coordinator is not present and is a restricted access area. The protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study.