Predicting Location and Extent of Prostate Cancer using Micro-Ultrasound Imaging

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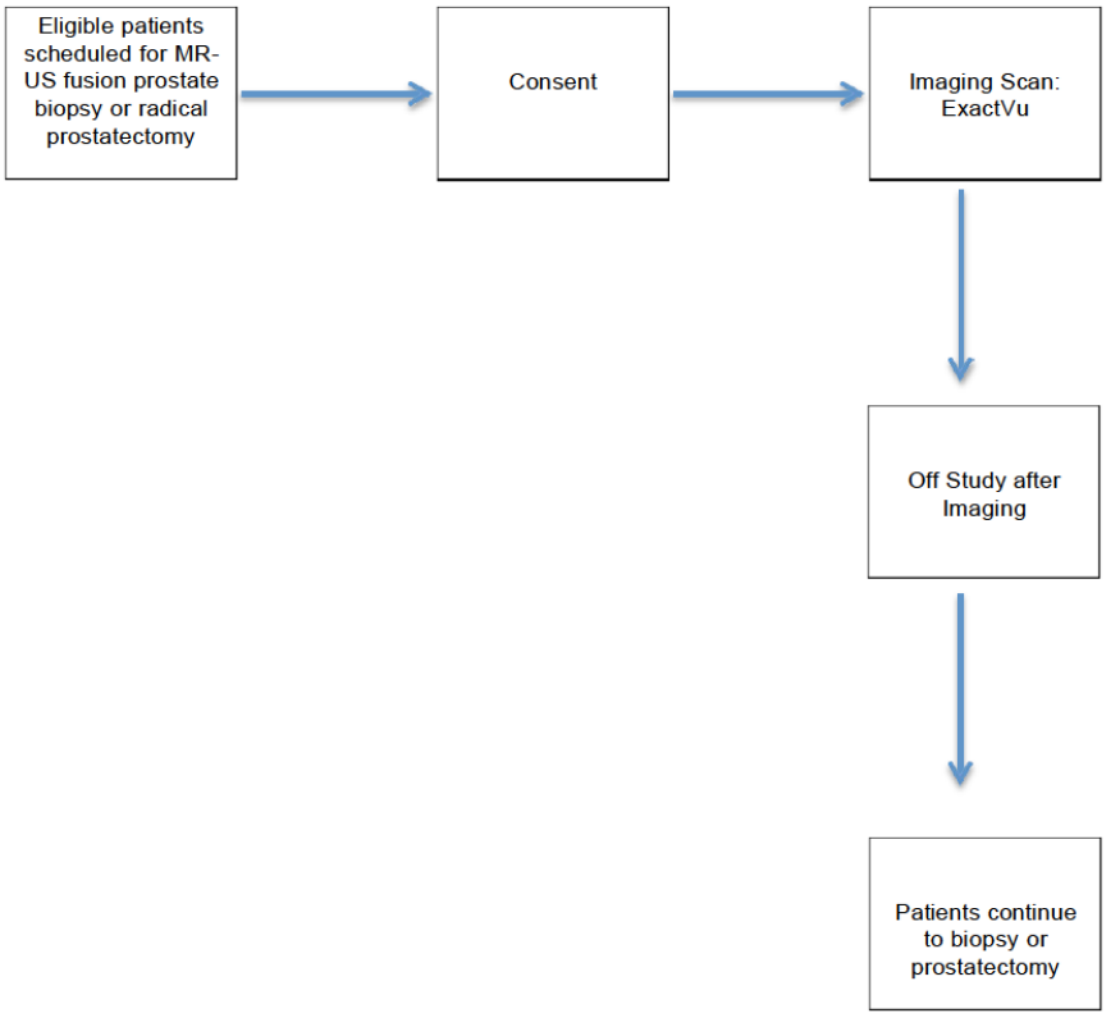
SCHEMA

This study is to use the ExactVu device, a clinical micro-ultrasound to systematically image the prostate before biopsy or surgery. This is an open, non-randomized, single arm trial. All subjects will know that they will be scanned using the ExactVu device.

SCHEMATIC DIAGRAM



LIST OF ABBREVIATIONS AND DEFINITION OF TERMS (Example)

Include additional abbreviations as needed. Remove any unnecessary abbreviations.

CRF	Case report/Record form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
IRB	Institutional Review Board
IV	Intravenous
PD	Progressive diseased
RR	Response rate
SAE	Serious adverse event

1. OBJECTIVES

1.1. Primary Objective

The goal of this study is to use a clinical micro-ultrasound to systematically image the prostate before biopsy or surgery. The images from the ultrasound system will be saved and compared to other imaging modalities and pathology in order to develop better tools for prostate cancer detection using micro-ultrasound. We hope that through the analysis of ultrasound images and comparison to standard of care pathology, we are able to determine the sensitivity of this new platform in our initial cohort.

2. BACKGROUND

2.1. Study Disease

This is an approved clinical ultrasound machine. The goals are to use the device at Stanford for the first time, in correlation with pathology and other imaging modalities. In prior work, our team has developed a database of MRI and pathology data that has been correlated to build predictive models for cancer detection using the MR images. Now, we plan to apply similar methodology using micro-ultrasound instead of MRI. The goal is to improve prostate cancer detection on micro-ultrasound images.

2.2. Study Device – ExactVu is an IDE Exempt Device that will be used according to label

2.3. This study will be register on Clinicaltrials.gov

2.4. Rationale

There are no adequate models for prostate cancer. Since we are hoping to find ultrasound imaging biomarkers that correlate with prostate cancer, human subjects must be used for this project. Because of the established safety of ultrasound, this study is best accomplished on human subjects.

2.5. Preliminary results

2.6. Study Design

- The interventional model:
  - Single Group
- 1 Arm
- The study will not be masked (the party is unaware of the treatment)
  - Open: no masking is used
- The study will not be randomized.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1. Inclusion Criteria

3.1.1. Patient scheduled for MR-US fusion prostate biopsy or radical prostatectomy

3.1.2. Ability to understand and the willingness to sign a written informed consent document.

3.2. Exclusion Criteria

3.2.1.1. Does not agree to consent

3.3. Informed Consent Process

All participants will be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4. Study Completion: This will be a one time imaging scan.

4. IMAGING AGENT/DEVICE/PROCEDURE INFORMATION

4.1. Device/Imaging Procedure: ExactVu

The following diagnostic procedures:

- In the operating room after time-out and anesthesia induction and immediately before radical prostatectomy or in the clinic immediately before biopsy, the EV29L transducer will be inserted in the subject's rectum. Cine sweeps will be performed to save images of:

1. The entire prostate from posterior to anterior (may require 2 sweeps to cover base and apex)
2. The peripheral zone using the highest zoom setting (30mm depth) on the system (may require 2 sweeps to cover base and apex).

Analysis of these images will be performed after surgery but before prostatectomy or biopsy pathology is available. Reviewers will be blinded to prior biopsy pathology and imaging reports at time of analysis.

4.2 Procedure Details for Pre-Biopsy Patients

In subjects undergoing pre-biopsy ExactVu micro-ultrasound imaging of the prostate, the imaging will occur immediately before biopsy. Prior to imaging, risks and benefits will be discussed with patient and informed consent will be obtained. He will be placed in a left lateral decubitus position for imaging. The imaging protocol will be identical to that listed above for the pre-surgery micro-ultrasound imaging. After images are complete, the micro-ultrasound probe will be removed and the prostate biopsy will proceed. Apart from the micro-ultrasound imaging, the biopsy will proceed as normal including administration of a single dose antibiotics, a pre-procedure cleansing enema, imaging with a Hitachi Noblus Ultrasound Unit featuring a 7 mHz probe, peri-prostatic anesthetic block, and biopsy core acquisition.

At the close of the procedure, the patient will be reminded of the signs and symptoms of urinary sepsis, urinary retention, and excessive bleeding. These risks are a result of the biopsy and are unchanged by the micro-ultrasound imaging.

5. STUDY PROCEDURES

5.1 Criteria for Removal from Study – participation is voluntary and the patients have the right to withdraw consent or discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled.

6. STUDY CALENDAR

	Screening	Treatment	Off Study after Treatment
Informed consent	X		
Pre-Op	X		
Imaging Scan: ExactVu		X	
Scheduled for MR-US fusion prostate biopsy or radical prostatectomy		X	X
Adverse event evaluation		X	X

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1. Potential Adverse Events
This protocol involves little to no risk to participants. Transrectal ultrasound has a long track record of safety. No contrast material will be administered. There is no radiation exposure.

7.2. Adverse Event Reporting

For guidance on reporting adverse events, refer to the Adverse Event SOP. Please modify the below template language as needed.

Adverse events will be graded according to CTCAE v4.0. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochures, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution and 30 days after the last dose of the study treatment.

8. REGULATORY CONSIDERATIONS

8.1. Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB and SRC prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

8.2. Data Management Plan

The study team will develop paper CRF's tracking patient identifiers, prostate cancer history including the most PSA lab value, results of any U/S or MR imaging, results of prior biopsy, results of genomic or other laboratory tests. Date of micro-ultrasound will be stored, along with pathology (either biopsy or prostatectomy final pathology). Data will then be transcribed into OnCore and REDCAP for use of research analysis. All paper CRFs will be stored in a locked filing cabinet and retained until study conclusion. After data is entered into REDCAP, and validated by the research team, each data record will be locked to reduce risk of inadvertent deletion or error. As further described in the Data and Safety Monitoring plan, routine data reviews will occur at 8 week intervals. In future work, data may be transferred or receive to/from collaborators to pool data from various sites. In this case, all data extracted will be de-identified, as per IRB and appropriate data sharing agreements, as applicable.

8.3. Data and Safety Monitoring Plan

During the clinical investigation, the Protocol Director will evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome. Monitoring of the trial will occur every 8 weeks and a record of monitoring activities will be maintained by the study team. As part of this routine data review, if there are any discrepancies in the data values stored in REDCAP, the research team will manually audit paper CRFs and clinical notes from the EMR will be done to ensure data validity.

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will audit study related activities at least annually in accordance with the DSMC SOP to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of DSMC audits will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

9. MEASUREMENTS/ STATISTICAL CONSIDERATIONS

9.1. Primary outcome will be the prospective data collection of a consecutive series of biopsy and prostatectomy patients.

- PRIMARY OUTCOMES:
  - Evaluate the ability of micro-ultrasound to identify high grade prostate cancer foci (Gleason score ≥7) in comparison to final surgical pathology result (prostatectomy or biopsy)

9.2 Secondary outcomes will be an analysis of this data to identify or develop features that form a cancer prediction model

- SECONDARY OUTCOMES:
  - Evaluate the ability of micro-ultrasound to identify the borders of prostate cancer foci in comparison to final surgical pathology result in men after prostatectomy.
  - Evaluate the ability of micro-ultrasound to detect low grade prostate cancer foci (Gleason score 6)
  - Comparison of prostate cancer detection between micro-ultrasound and multiparametric magnetic resonance imaging (mpMRI).
  - Perform a detailed pathologic and imaging correlation between findings on micro-ultrasound, MRI and final surgical histopathology in men who undergo prostatectomy

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Design

This study is primarily exploratory, with the goal of collecting the initial correlative data between micro-ultrasound, conventional imaging, and pathology gold standard. As such, we are not intending to directly compare this imaging modality with standard of care, but rather to rigorously and prospectively collect this data in order to plan for larger, multi-institutional studies.

10.2. Randomization - There is no randomization in this study

10.3. Descriptive Statistics and Exploratory Data Analysis

Initial analysis will include characterizing our consecutive patient cohort among prostate cancer risk factors including, age, PSA, race/ethnicity, prostate volume and scoring of MRI lesions. These this data will be summarized and compared to our typical clinical cohort to examine biases.

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10.4. Primary Analysis

A prospective collection of correlative data including micro-ultrasound, MR imaging U/S, PSA and pathology data.

10.4.1. Analysis Population

The entire cohort

10.5. Secondary Analysis

Goal will be to quantitatively co-register the micro-ultrasound data with MRI and pathology data, and apply advanced processing techniques such as machine learning or deep learning. Once an initial model is built to identify prostate cancer from micro-ultrasound, we will be able to design future studies.

10.5.1. Analysis Population

The entire consecutive series will be analyzed

10.6. Sample Size

Statistical Power for N=68:

Primary outcome: We seek to characterize the sensitivity of micro-ultrasound at detecting significant cancer, especially in comparison to the sensitivity of standard of care multiparametric MRI. With earlier published data with a sensitivity of 90%, we project to

detect significant cancer at a sensitivity of 77% by PIRADS 4 and 5 at Stanford. Therefore, we propose a single micro-ultrasound cohort with a sample size of 68 subjected recruited to reach 80% power at alpha level of 0.05.

10.7. Accrual estimates

This research study is looking for 100 participants and is only being conducted at Stanford.

10.8. Criteria for future studies

If data can be effectively co-registered, and initial models are promising, as evaluated by visual feedback from overlaid images and initial ROC analysis

11. REFERENCES

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Eur Urol. Focus October 14, 2020

11.2 Evolution of Targeted Prostate Biopsy by Adding Micro-Ultrasound to the Magnetic Resonance Imaging Pathway
Laura Wiemer, Markus Hollenbach, Robin Heckmann, Beatrice Kittner, Henning Plage, Max Reimann ,Patrick Asbach
Eur Urol. July 09, 2020

11.3 Prostate Mapping for Cancer Diagnosis: The Madrid Protocol. Transperineal Prostate Biopsies Using mpMRI Fusion and Micro-ultrasound Guided Biopsies
Rodríguez Socarrás ME1, Gomez Rivas J1, Cuadros Rivera V1, Reinoso Elbers J1, Llanes González L1, Michel Mercado I1, Fernandez Del Alamo J1, Juarez Del Dago P1, Gomez Sancha F1
J Urol. 2020 Apr 21:101097JU0000000000001083

11.4 Can high resolution micro-ultrasound replace MRI in the diagnosis of prostate cancer?
Laurence Klotz CM1
Eur Urol Focus. 2020 Mar 15;6(2):419-423

11.5 Assessing Cancer Risk on Novel 29 MHz Micro-Ultrasound Images of the Prostate: Creation of the Micro-Ultrasound Protocol for Prostate Risk Identification
Ghai S, Eure G, Fradet V, Hyndman ME, McGrath T, Wodlinger B, Pavlovich CP.
J Urol. 2016 Aug;196(2):562-9.

Appendix A: Inclusion/Exclusion Criteria Checklist

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

Inclusion Criteria (From IRB approved protocol)	Yes	No	Supporting Documentation*
1. -Scheduled for MR-US fusion prostate biopsy or radical prostatectomy	☐	☐	
2. -Agree to consent to the study	☐	☐	
Exclusion Criteria (From IRB approved protocol)			
1. -Does not agree to consent	☐	☐	

IV. Statement of Eligibility

This subject is [☐ eligible / ☐ ineligible] for participation in the study.

Signature:	Date:
Printed Name:	