Molecular Image-directed, 3D Ultrasound-guided Biopsy System

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1.0. Introduction - Background:

1.1. What is the clinical problem?

Systematic transrectal ultrasound (TRUS)-guided prostate biopsy is considered as the standard method for prostate cancer detection. The current biopsy technique has a significant sampling error and can miss up to 30% of cancers (Hricak 2005). Not only is the volume of the biopsy sample small but the presence of prostate cancer (PCa) is involving only a small part of the prostate in the early stages of the disease. As a result, a patient may be informed of a negative biopsy result but may in fact be harboring an occult early-stage cancer. It is a difficult challenge for physicians to manage patients with false negative biopsies who, in fact, harbor curable PCa as indicated by biochemical measurements such as rising prostate specific antigen (PSA), as well as patients diagnosed with early-stage disease. Another important challenge facing physicians is patients diagnosed on biopsy as having premalignant lesions, i.e., high grade prostatic intraepithelial neoplasia, and, in particular, atypical small acinar proliferation (ASAP). This biopsy result is clinically significant as there is a 40%-80% chance of finding cancer on repeat biopsy if there is ASAP (Iczkowski et al 1998). As there might be coexisting cancer, especially with ASAP, where the pathologist finds only a small amount of histological “atypia” but not enough material to confidently diagnose cancer, such patients require a repeat biopsy soon after the first one. For ASAP patients, it is vital to rebiopsy the same area. Unfortunately, two-dimensional (2D) ultrasound provides only a vague location of the abnormal findings, and it is not possible to be certain that the same area has been sampled by the repeat biopsy. As a negative result does not preclude the possibility of a missed cancer and due to patient anxiety, a third biopsy may be requested, and etc. On the other hand, due to the increasing number of younger men with potentially early and curable PCa who undergo repeated biopsies, it is important not to re-biopsy the same area if the original biopsy was negative. Because of the biopsy sampling error and uncertainty associated with the current approach, both the patient and physician face significant challenges in making treatment decisions.

1.2. What is the potential impact of the research?

As reported by the Prostate Cancer Foundation, this disease affects 1 in 6 American men. In 2008, 186,320 American men were diagnosed with prostate cancer, which accounts for approximately 25% of all cases in men (Jemal et al 2009). Of the newly diagnosed prostate tumors, greater than 75% of the patients present with clinically localized disease. In the United States, more than 1.2 million TRUS-guided prostate biopsies are performed annually and these biopsies exceeds two billion dollars annually (Beck 2009). However, most of the biopsies (70-80%) show negative results including numerous false negatives. Novel biopsy technology is needed in order to reduce those unnecessary biopsies and thus to reduce medical cost and save patient’s time. The proposed research is to develop new “targeted” biopsy technology in order to replace current “blind” biopsy. If successful, the targeted biopsy would improve the cancer detection rate. As many patients would not need repeated biopsies, the total number of prostate biopsies could be reduced by more than 30%; this could save more than half billion dollars annually in just the biopsy costs. Furthermore, it will also reduce the potential morbidities of life-threatening sepsis and transrectal bleeding, both of which are associated with the biopsy procedures. As molecular information from PET/CT will direct the biopsy needle to a suspicious tumor target, the biopsy results will provide vital information for both the physicians and the patients in order to make optimal treatment decisions. For example, a patient may select active surveillance i.e. watchful waiting if the biopsy result shows a low-grade, non-clinically significant tumor. An accurate biopsy can help to reduce their anxiety that often increases due to possible sampling error and the uncertainty associated with the current biopsy technique. As a
false negative result may delay treatment, an accurate biopsy is extremely important for those active surveillance patients because they rely on the biopsy result in order to follow up the disease without any radical treatment.

2.0. Objectives

Every man over the age of 45 is at risk for prostate cancer. Systematic transrectal ultrasound (TRUS)-guided biopsy is the standard method for a definitive diagnosis of prostate cancer. However, a critical problem is its significant sampling error and low sensitivity (39-52%). A negative biopsy does not preclude the possibility of a missed cancer. Due to the increasing number of younger men with potentially early and curable prostate cancer, this problem must be addressed. Two limitations are associated with the current biopsy approach: (1) Two-dimensional (2D) ultrasound imaging does not provide accurate location information in three dimensions; and (2) ultrasound imaging has difficulty to differentiate carcinoma from benign prostate tissue. This "blind" biopsy approach can miss up to 30% of prostate cancers. Nevertheless, more than 1.2 million prostate biopsies are performed in each year; and the biopsy cost is more than two billion dollars. Most (70-80%) biopsies show negative results including numerous false negatives. Those unnecessary biopsies not only increase medical cost national wide but also increase the risk of potential complications associated with the biopsy procedures. As a negative biopsy is not completely reassuring, both the physician and the patient face significant challenges in making treatment decisions. Innovative biopsy technology that can improve cancer detection can have significant impact on the management of this disease that affects 1 in 6 men.

2.1. 3D ultrasound has advantages over conventional 2D ultrasound for biopsy guidance

A 2D ultrasound image represents a thin plane at an arbitrary angle in the body, yet the anatomy is 3D, hence the physician must integrate multiple images in his/her mind. This practice is inefficient during interventional guidance, and may lead to variability and incorrect localization of lesions. Because of manually controlled scanning, it is difficult to localize the same image plane and reproduce it at a later time for follow-up studies. When using 2D transrectal ultrasound for needle guidance, physicians have restricted anatomical reference points for guiding the needle to target sites. Any motion of the probe during the procedure may cause the prostate image to change or deform to a prohibitive extent. These variations make it difficult to establish a consistent frame of reference for needle guidance. On the contrary, 3D ultrasound imaging provides volumetric representation of an object and offers images along any cross sections. The intuitive presentation by 3D ultrasound allows more accurate lesion localization and treatment planning (Fenster et al 2003; Shen et al 2008). Our 3D TRUS-guided system can record and display the 3D locations of biopsy cores, which is not possible with a conventional 2D image-guided system (Bax et al 2008). Existing 3D US-guided prostate biopsy systems include the TargetScan® prostate biopsy system (Envisioneering Medical Technologies, St. Louis, MO); which uses a side-firing TRUS imaging system containing flexible biopsy needles to perform a templated biopsy (Andriole et al 2007), and the Voluson prostate biopsy system (General Electric, Fairfield, CT), which is a 3D hand-held ultrasound imaging system with a 5.9 MHz endorectal probe (Long et al 2007). Unlike the two systems, our system can make use of any manufacturer’s end-fire TRUS probe and thus can be easily adapted by most of current biopsy systems.

2.2. Multiple modality images will be combined to improve cancer detection

Although ultrasound imaging is a preferred method for image-guided biopsy because it is performed in real time and because it is portable and cost effective, current ultrasound imaging technology has
difficulty to differentiate carcinoma from benign prostate tissue. Hence, MR spectroscopic imaging (MRSI) is playing an increasing role in prostate cancer management (Manenti et al 2006; Mueller-Lisse et al 2007). MR spectroscopy metabolite profiles of biopsy tissues can help direct treatment plans by assessing PCa pathologic stage and aggressiveness (Cheng et al 2005). MRSI has been shown to be valuable for depicting locally recurrent PCas after radiotherapy (Coakley et al 2004). Choline MRSI can depict prostate carcinoma with a high degree of sensitivity and specificity (Swindle et al 2003). Combined MRI and MRSI allow metabolic and structural evaluation of prostate cancer and improve the diagnostic accuracy for localizing and detecting the disease (Carlani et al 2008; Hasumi et al 2002; Kurhanewicz et al 2002).

Various PET imaging agents have been developed for prostate cancer detection and staging, these include $^{18}$F-FDG (Schoder et al 2005), $^{11}$C-choline (Hara et al 1998; Schilling et al 2008), $^{18}$F-fluorocholine (DeGrado et al 2001), $^{11}$C-acetate (Oyama et al 2003), $^{11}$C-methionine (Nunez et al 2002), and other PET agents. $^{18}$F-FDG is widely used in cancer applications. However, it has low sensitivity in the primary staging of prostate cancer and poor detection of abdominal-pelvic nodes because of excretion of tracers in the ureters, bladder, and bowel. At our Emory Molecular and Translational Imaging Center, PET imaging with the new molecular imaging tracer FACBC has shown very promising results for detecting and localizing prostate cancer in humans as reported by our group (Schuster et al 2007). Our clinical trials on FACBC are currently supported by the National Cancer Institute (NCI). As shown in our preliminary results, FACBC PET images show focal uptake at the tumor and thus could be ideal information to direct targeted biopsy. One innovation of the proposed research is the combination of FACBC PET images and 3D ultrasound for targeted biopsy. The multimodality imaging approach will combine the high sensitivity from PET and real-time information from ultrasound in order to improve the cancer detection rate.

Specific Aims

We hypothesize that FACBC molecular images can be incorporated into ultrasound-guided biopsy for improved cancer detection. This research is to test a molecular image-directed, 3D ultrasound-guided biopsy system. The specific aims include:

**Aim 1: To test a real-time, mechanically assisted, 3D ultrasound-guided device**

An FDA-approved mechanical device will be used to guide, track, and stabilize the position of an ultrasound probe. The device will be used to acquire 3D TRUS images, reconstruct a 3D model of the prostate, and record the biopsy core locations in three dimensions. Compared to conventional 2D image guidance, 3D images of the prostate will be used to guide the biopsy procedure.

**Aim 2: To develop fast DSAM-based segmentation methods for 3D ultrasound images**

This aim is to develop image processing and analysis methods for ultrasound images. A deformable and statistical appearance model (DSAM) of the prostate will be created from our TRUS image databases. The prior information from our DSAM model will be used to guide automatic segmentation of the prostate on 3D TRUS images. The new model-based segmentation method will improve the speed and accuracy and will save time during biopsy.

**Aim 3: To combine FACBC PET images with 3D ultrasound for targeted biopsy**

This aim is to develop image registration methods for PET/CT and ultrasound images. A new deformable registration method based joint saliency map (JSM) and fuzzy point correspondence (FPC) will be developed in order to combine FACBC PET/CT images with 3D ultrasound. Multimodality image fusion methods will be developed to incorporate FACBC images into ultrasound-guided biopsy in order to better locate suspicious tumors and thus improve needle guidance.

**Aim 4: To test the accuracy of the integrated, molecular image-directed biopsy system**
The accuracy of the integrated, multimodality image-directed biopsy system will be measured in phantoms and animal experiments. As our ongoing FACBC studies are recruiting human patients, the proposed FACBC-directed biopsy system will be tested in a small number of patients in order to lay the groundwork for large clinical trials using the new targeted biopsy technology.

3.0. Patient Selection:

Forty-two (42) patients will be enrolled in this study. Patients who are enrolled in , IRB00061518 (PI: Dr. David Schuster, Title: Transmolecular imaging of Recurrent Prostate carcinoma)and have a positive imaging scan will be scheduled for biopsy. These patients will be offered this study as an option instead of the 2D ultrasound biopsy.

The 3D ultrasound device has received the FDA 510K approval. Because the device can provide 3D ultrasound images as well as fused PET/MRI/ultrasound images, we think that the clinician will be able to better biopsy the tissue at the right location.

3.1. Inclusion Criteria:

(1) Patients must be 18 years of age or older.
(2) Abnormal uptake in prostate necessitating biopsy
(3) Patients must be able to provide written informed consent.

3.2. Exclusion Criteria:

1. Age less than 18.
2. Cannot provide written informed consent.
3. Less than 2 months since any prior prostate biopsy (to decrease false positive uptake from inflammation).
3.3. Flowchart *

The flowchart of the proposed study is shown below. The patients have the option to choose the new biopsy with the 3D image guidance. All the imaging scans will be the same as the IRB-approved study (IRB00061518). We hypothesize that the 3D image-guided biopsy may be able to detect the cancer that was missed by the current biopsy with 2D image guidance.

Patients will undergo the usual clinical and presurgical evaluation with studies deemed necessary by the Urology team including pelvic CT, bone scanning. Note that the PET scan will be part of the IRB-approved study (IRB00061518). Hence, this study will NOT involve radiation from PET scans. Our study will focus on the feasibility test of the 3D image-guided biopsy with the aid from FACBC PET imaging. Six patients will participate in this study. Once the feasibility of the proposed biopsy is validated, the data from this pilot patient study will provide important data for a large study in the next phase.

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4.1. Conventional Imaging Performance and Interpretation
All the conventional imaging performance and interpretation will be the same as those in the IRB-approved study (IRB00061518). Briefly, as part of the standard workup of suspected recurrent prostate cancer, all patients will have undergone standard evaluation which includes bone scan, pelvic CT with oral and IV contrast. These are already obtained as part of our routine evaluation, and will not place an extra financial burden on the proposed study. Details on the imaging methods are described in the approved IRB protocol IRB 00061518.

5.0. Registration/Randomization:
Patients will be registered and consented into the study by one of the research nurses on staff working in the clinical Urology setting. There will be no randomization.

6.0. Therapy
This is not a therapeutic study. Diagnosis only.

3D ultrasound-guided biopsy
In this proposed study, we will test the 3D ultrasound-guided biopsy with the aid of PET images. The steps of the proposed prostate biopsy are as follows. (1) Before biopsy, the patient already has a PET/CT scan with FACBC as described in the IRB-approved study (IRB000061518). The anatomic CT images will be combined with PET images for improved localization of suspicious tumors. (2) During biopsy, 3D ultrasound images will be acquired immediately before the procedure when the patient is on the table. The 3D ultrasound images will be registered with the PET/CT data for biopsy planning. Freshly acquired, real-time, 2D ultrasound images will also be acquired and then registered with the 3D ultrasound and PET/CT images for improved lesion targeting. Three-dimensional visualization tools will guide the biopsy needle to a suspicious lesion. (3) At the end of each core biopsy, the needle tip position will be recorded on the real-time ultrasound images. The location information of biopsy cores can be saved and then restored in the re-biopsy procedure. This allows the physician to either re-biopsy the same area for a follow-up examination or not to re-biopsy the same region if the original biopsy was negative. Either of the two re-biopsy examinations is not possible with the current 2D ultrasound-guided biopsy approach. Furthermore, the FACBC PET images will direct the biopsy to the suspicious tumor for targeted biopsy.

7.0. Pathology:
All pathologic samples will undergo standard analysis to determine if prostate carcinoma cells are present. The majority of tissue will be analyzed from clinically interpreted fixed specimens. Specimens will be fixed in neutral-buffered formalin, embedded in formalin, sectioned at 5-micron thickness and stained with hematoxylin & eosin (H&E) using standard pathology procedures. Board-certified anatomic pathologists from Emory University will perform all diagnosis of prostate carcinoma (and when applicable Gleason grading and staging) using standard criteria. Quantitative RT-PCR and immunohistochemistry will be performed on parallel histologic sections of tissue confirmed to contain prostate carcinoma. The archived histologic sections of tissue will also be used for new staining methods such as quantum-dot (QD) based staining.

8.0. Patient Assessment:
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Patients who are prostate bed positive and extraprostatic negative will get treated with local therapy (radiation, cryoablation, salvage surgery, etc.) These patients will not get hormonal therapy and will be entered into the follow-up group. It is true that some patients with either high Gleason scores, impending or with cord compression and/or pathologic fracture, hydronephrosis, and/or rapid PSA doubling time of less than 3 months will require hormonal therapy, but this is not the majority of patients (approximately 15-20% worst case scenario). The majority of patients (80-85%) will have low to intermediate risk disease and PSA recurrence reflecting the prevalence of low and intermediate risk disease in the United States. Therefore these patients can be followed off hormonal therapy but with local therapy as needed.

9.0. Data Collection:

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10.0. Statistical Considerations:

Although this pilot human study will not be able to provide the statistical power to analyze the sensitivity of the 3D image-guided biopsy, this small number of 6 patient study will be able to test the feasibility of the biopsy system and will provide important data for a large clinical trial later.
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