Targeted Fusion Biopsy of the Prostate

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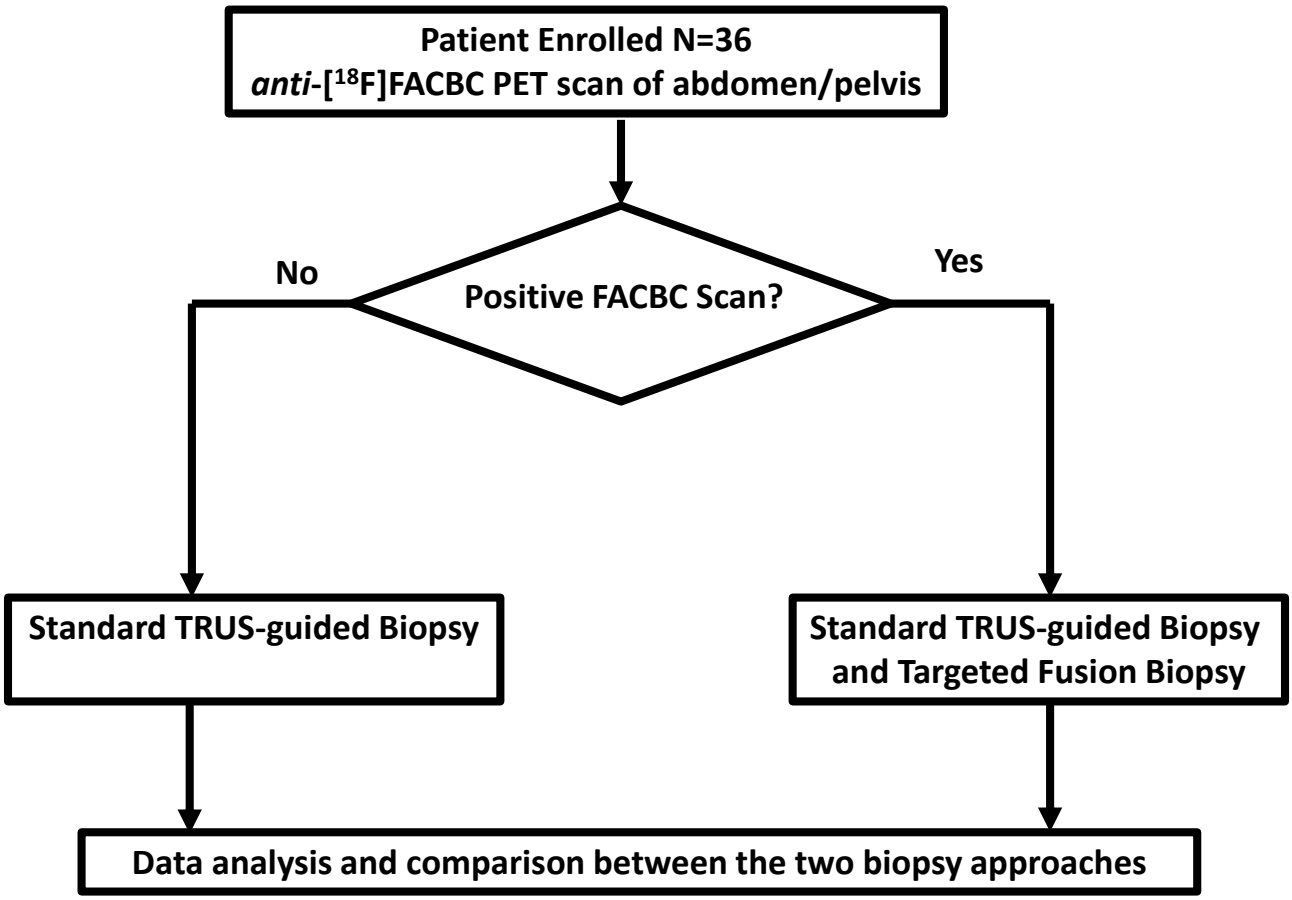
Schema



Precis/Abstract

Every man over the age of 45 is at risk for prostate cancer. Two-dimensional (2D) transrectal ultrasound (TRUS) guided biopsy is the standard method for prostate cancer diagnosis. A critical problem of this TRUS-guided biopsy approach is its significant sampling error and its low sensitivity (24%-52%). Current biopsy approaches may miss up to 30% of prostate cancer. Nevertheless, more than 1.2 million prostate biopsies are performed each year and the biopsy cost is more than two billion dollars. Innovative image-guided, targeted biopsy technology that can improve cancer detection can have a significant impact on the management of this disease that affects one in six men.

The objective of the proposed study is to evaluate a molecular image directed, three-dimensional (3D) ultrasound guided biopsy system in human patients. At our NIH-funded Emory Molecular and Translational Imaging Center, it has been shown that PET/CT imaging with the PET molecular imaging agent i.e., FACBC, is more sensitive than the FDA-approved PSMA SPECT radiotracer in prostate cancer detection. FACBC images showed higher focal uptake in tumor foci than in normal prostate and thus could be ideal information to direct targeted biopsy of the prostate. This targeted biopsy system has a unique feature that FACBC PET/CT images can be registered with 3D ultrasound images, as a result, a suspicious PET lesion is superimposed over the real-time ultrasound data; and the fused image is then used to direct biopsy needles to tumor targets.

The hypothesis of the study is that FACBC PET/ultrasound fusion targeted biopsy can detect more cancer per core than the standard 12-core TRUS guided biopsy. The specific aims include: 1) To perform FACBC PET/CT directed, 3D ultrasound-guided biopsy and determine if fusion targeted biopsy can detect more cancers than 2D TRUS-guided biopsy; and 2) To develop the workflow for performing deformable registration and fusion of FACBC PET/CT and 3D ultrasound images of human patients, Thirty six patients, who have suspicion of recurrent prostate cancer after definitive therapy such as radiotherapy, will be recruited into this study. At least half of the patients will have positive imaging findings and will undergo 2D TRUS-guided biopsy as well as PET/ultrasound fusion biopsy. The proposed study will be the first-in-human trial that uses PET/CT imaging to direct 3D ultrasound-guided biopsy of the prostate. The multimodality imaging approach will combine the high sensitivity from PET and real-time information from ultrasound for improved cancer detection.

This early-phase clinical trial will help transform the field from the current “blind” biopsy to future “targeted” biopsy and result in the change of prostate cancer management. The new biopsy technology can have an immediate impact on patient care by improving the detection and diagnosis of prostate cancer.

1. Background and Significance

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. 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 PCa 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, they have 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.

3. Specific Aims

Central Hypothesis: FACBC PET/ultrasound fusion guided biopsy can detect more cancer per core than the standard 12-core TRUS-guided biopsy. The specific aims include:

Aim 1: To perform FACBC PET/CT directed, 3D ultrasound-guided biopsy and to determine if fusion targeted biopsy can detect more cancer per core than standard TRUS-guided biopsy.

We will recruit 36 patients who have suspicion of recurrent prostate cancer after definitive therapy such as radiotherapy or other non-prostatectomy focal therapy such as cryotherapy. Based on our clinical experience, at least half of the patients ($N \approx 18$) will have positive imaging findings in the prostate bed. These patients will undergo a standard 12-core systematic biopsy followed by PET/ultrasound fusion targeted biopsy at the same setting. Patients with negative scan will undergo the standard biopsy. We will determine (i) whether fusion targeted biopsy can detect more cancer per core than the standard biopsy; (ii) whether the addition of targeted biopsy to systematic biopsy increases the rate of diagnosis of Gleason 7 or greater cancer.

The patient will be in the same setting for the standard TRUS-guided biopsy and the PET/TRUS fusion targeted biopsy. The same setting allows us to directly compare the accuracy of the two biopsy approaches for the same patients. This sequential study is supported by the literatures. For example, the NIH team led by Dr. Peter Pinto is one of the pioneer groups in the field of MRI/TRUS fusion

targeted biopsy. In their study, *"Patients in the trial underwent a standard of care 12-core TRUS biopsy and MRI/US fusion guided biopsy in the same setting."* (P.A. Pinto, P.H. Chung, A.R. Rastinehad, A.A. Baccala, Jr., J. Kruecker, C.J. Benjamin, S. Xu, P. Yan, S. Kadoury, C. Chua, J.K. Locklin, B. Turkbey, J.H. Shih, S.P. Gates, C. Buckner, G. Bratslavsky, W.M. Linehan, N.D. Glossop, P.L. Choyke, B.J. Wood, "Magnetic resonance imaging/ultrasound fusion guided prostate biopsy improves cancer detection following transrectal ultrasound biopsy and correlates with multiparametric magnetic resonance imaging," The Journal of urology 186, 1281-1285, 2011).

The TRUS-guided procedure uses an 18-gauge needle for prostate biopsy. This procedure does not intend to remove the tumor but take a tiny tissue sample for pathological processing and diagnosis of prostate cancer. Based on the well-known Epstein criteria on clinically significant tumors, a tumor with a radius of less than 5 mm is considered insignificant (Epstein,JI; Sanderson,H; Carter,HB; and Scharfstein,DO. Utility of saturation biopsy to predict insignificant cancer at radical prostatectomy. *Urology*. 66:356-360. 2005). Based on the size of the 18-gauge needle and based on the Epstein criteria, the amount of cancer tissue that may be possibly remove by a standard TRUS-guided biopsy core will not affect the evaluation of the targeted biopsy for the diagnosis of clinically significant cancer.

Aim 2: To develop and optimize the workflow for performing deformable registration and fusion of FACBC PET/CT and 3D ultrasound of human patients for fusion targeted biopsy of the prostate

We hypothesize that FACBC PET/CT images can be combined with 3D ultrasound to direct a biopsy needle to a suspicious cancer target as shown on FACBC images. We have developed deformable image registration and fusion software to combine FACBC PET/CT and 3D ultrasound images of human prostate. We have developed a workflow for fusion targeted biopsy and will optimize its efficiency in our clinic setting.

The specific aim 2 is to optimize the clinical workflow for the registration between PET/CT and 3D ultrasound images for the fusion targeted biopsy. We have performed the PET/TRUS fusion targeted biopsy in nine patients based on our currently approved IRB protocols. This new protocol is to combine two IRB-approved protocols into one protocol so we can streamline the recruitment of patients. The study is currently supported by two NIH grants. The feasibility of the specific aim 2 has been demonstrated in our preliminary study. This aim has mostly been achieved and the workflow will be continuously optimized during the whole study.

Milestones for this specific aim: For the first specific aim, there are three milestones. The first milestone is to obtain a complete set of FACBC PET/CT and 3D ultrasound data to test the fusion method. This milestone was achieved after we acquired the PET/CT and 3D ultrasound data from the first patient. The second specific aim is to complete a fusion targeted biopsy plan in a 3D prostate model. This milestone was also achieved when we completed the biopsy procedure in our first patient. The third milestone is to complete the first half patients, i.e. 18 patients, for the NIH-funded early-phase study. This milestone will be achieved when we recruit more patients into the study and when we complete the optimization of the workflow.

4. Research Design and Methods

4.1. Patient Selection:

Thirty-six (N=36) patients will be enrolled in this study. All patients in this study may undergo routine conventional testing and imaging per usual clinical determination. This study will not interfere with routine diagnostic evaluation. All patients will have a FACBC PET-CT scan.

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 believe that the clinician will be able to better biopsy the tissue at the right location.

Inclusion Criteria:

1) Patients must be 18 years of age or older.
2) Patients will have been originally diagnosed with prostate carcinoma and have undergone what was considered definitive non-prostatectomy therapy for localized disease.
3) In the case of cryotherapy, external beam radiation, or HIFU the procedure will have occurred at least one year in the past. In the case of brachytherapy, treatment will have occurred at least 2 years in the past to eliminate patients with so-called “PSA bump.”
4) Patient will have suspicion of recurrent prostate carcinoma as defined by: Older ASTRO criteria of three consecutive rises of PSA or earlier if clinically appropriate, and/or nadir + 2.0 ng/ml (ASTRO-RTOG Phoenix criteria).
5) Patients must be able to provide written informed consent.

Exclusion Criteria:

1) Age less than 18.
2) Less than 1 year since cryotherapy, external beam radiation therapy, or HiFU, or 2 years since brachytherapy. Does not meet above criteria of suspicious PSA elevation.
3) Cannot provide written informed consent.
4) Less than 1 month since any prior prostate biopsy (to decrease false positive from inflammation).
5) Not otherwise eligible for prostate biopsy.

Patients will be required to fast in preparation for PET scan. Verbal consent will be obtained from patient prior to the PET scan day

Written informed consent will be obtained before subject participation in the study. No procedures will be performed before written informed consent is obtained. Participants will be assigned an identification number for screening purposes; data collected during the screening process will be recorded using that number.

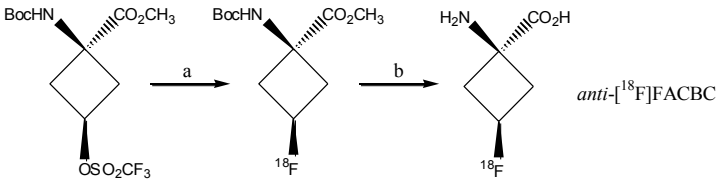
PET Scan Day: The following procedures will be performed:

- Obtain written informed consent
- Inclusion/exclusion criteria review

4.2. Anti-[^{18}F] FACBC radiolabeling

Methods. Production will be accomplished by the GE FastLab cassette system. Alternatively by automated synthesis developed by J. McConathy and M.M. Goodman. The automated radiosynthesis of *anti*-[^{18}F]FACBC will be carried out in a chemical process control unit (CPCU) with a computer interface. The two-step reaction sequence will involve incorporation of no-carrier-added potassium [^{18}F]fluoride into a protected triflate precursor and deprotection using aqueous hydrochloric acid. The crude reaction mix will be passed in series through ion-retardation resin, an alumina-N SepPak®, an HLB cartridge and a 0.22 µm sterile filter, and the resulting aqueous solution will be collected in a dose vial. The radiochemical purity of the product will be determined by TLC. Additional chemical solvent purity will be measured by Gas Chromatography (GC). The total time for synthesis of *anti*-[^{18}F]FACBC after delivery of ^{18}[F]fluoride will be ~70 minutes, and the average decay-corrected yield of *anti*-[^{18}F]FACBC will be 24 ± 4 % (n = 40 runs, average ± standard error) in over 99% radiochemical purity. This procedure will provide 140-200 mCi of *anti*-[^{18}F] FACBC at the end of synthesis. We have prepared greater than 200 batch productions for tumor imaging in volunteer subjects.

Synthesis of *anti*-FACBC



a)K^{18}F, K_{222}, K_2CO_3; 90C b) 4 NHCl, 120 C

4.3. PET-CT imaging protocol to measure amino acid uptake

Methods. PET-CT images will be acquired on a GE Discovery 690 Time of Flight (TOF) 16 slice PET-CT scanner or other PET-CT scanner. All studies will use measured attenuation correction (routinely acquired through the initial CT portion of the scan). All subjects will be required to fast for four hours to normalize their neutral amino acid levels. Non-strict fasting is not an absolute contraindication and may be overridden on a case by case basis since it is unknown if fasting affects FACBC uptake positively or negatively. One hour prior to scanning, the patient will drink 450ml of oral contrast over 1 hour to maximize conspicuity of abdomen and pelvic structures. IV contrast will not be used. Prior to placement in the tomographic gantry, an intravenous catheter will be placed for injection of tracer. The subject will be placed in the tomograph gantry for completion of the CT scan. Ambient conditions will be a quiet, dimly lit room. *anti*-[^{18}F]FACBC (approximately 10 mCi) will be injected into an antecubital vein in a slow bolus infusion over 1-2 minutes. At 5 minutes, 4 consecutive 2.5 minutes per frame acquisitions will be obtained starting from the prostate level of the pelvis and extending superiorly to the diaphragm. At 16 minutes, this process will be repeated. Thus, 4-15.5 minute, and 16-27.5 minute acquisitions from the pelvis extending superiorly to the abdomen at the diaphragm will be obtained. This imaging schema is based on analysis of our data to date in which early and delayed uptake to 30 minutes yields the most diagnostic information. Imaging may be carried out with HD mode and respiratory gating or TOF mode with or without respiratory gating.

Summary of PET-CT Scanning Procedure

1) The patient will be placed in the tomographic gantry for a CT scan of the abdomen-pelvis to be utilized for anatomic imaging and correction of emission data (approximately 1 minute).
2) The patient will then receive a bolus of *anti*-[^{18}F]FACBC injected IV over 1-2 minutes
3) The dosage will be approximately 10.0 mCi (3.70 x 108 Bq).

4) At 5 minutes after initial injection (3 minutes after injection ceases), a 2.5 minute per bed position PET acquisition will start at the pelvis with the inferior aspect of the acquisition to include the entire prostate or prostate bed.
5) 4 bed positions will be obtained which should cover pelvis through abdomen to the diaphragm.
6) This sequence will be repeated once.
7) The entire study including injection of radiotracer should take approximately 30 minutes.

4.4. Image Analysis of *anti*-[^{18}F]FACBC PET-CT

The methods of image analysis to be used for the *anti*-[^{18}F]FACBC PET-CT are as follows:

1) Images will be reconstructed with iterative technique and hardware fused (PET to CT) on a MimVista or similar workstation which enables SUV (mean, maximum, total lesion activity) as well as standard size measurements of lesions. An edge seeking conformational volume of interest tool as appropriate (PET Edge, MIMvista, Cleveland, OH) will typically utilized. If this is not possible due to anatomy an appropriate 2D or 3D ROI will be utilized.
2) Visual inspection of the PET-CT images by a board certified nuclear medicine imager who will be blinded to all history and other imaging.
3) For *anti*-3-[^{18}F]FACBC, uptake will be defined according to the following criteria in relation to background structures: mild (above blood pool but less than marrow), moderate (above or equal to marrow but less than liver), and intense (equal to or above liver). Visual analysis will aided by quantitative criteria of SUV_{max} lesion/SUV_{mean} background. Maximum and mean SUV of each focus of abnormal uptake as well as background structures including liver, marrow at L3, aorta, and bladder will be recorded. For prostate beds as well as extra-prostatic sites such as lymph nodes and bone, abnormal moderate or intense focal uptake over background marrow which persist from early to delayed images will be considered prospectively positive. These criteria were used to analyze data in our study of *anti*-[^{18}F]FACBC in recurrent disease.
4) Confidence in interpretation for disease within the prostate bed and outside the bed will be recorded with the following scale on a per patient basis and any all recordable lymph nodes: 1-defiinitvely negative; 2 -probably negative; 3 - indeterminate; 4 - probably positive; 5 – definitively positive.
5) In summary, we will record both visual and semi-quantitative analysis of the prostate bed, positive lymph nodes (greater than blood pool), and other structures such as skeletal foci on early and delayed time frames. We will use maximum and mean SUV as well as standard bidimensional size measurements. We will also record similar measurements on background structures such that we may derive uptake ratios.

4.5. Clinical and Histological Assessment.

After the *anti*-[^{18}F]FACBC scan has been obtained and interpreted, the following will occur:

1) All patients with identifiable sites of disease on FACBC PET will, if clinically feasible, undergo targeted fusion biopsy followed by the standard TRUS-guided biopsy. The targeted biopsy will be performed before the standard TRUS-guided biopsy because patient motion and movement may affect the accuracy of the targeted biopsy and because the standard TRUS-guided biopsy is a random biopsy and does not have a high requirement on patient motion. If this is not deemed appropriate by the clinical team and referring Urologist or Radiation Oncologist, patients will undergo standard TRUS 12-core biopsy as clinically appropriate.

2) All pathologic samples will undergo standard analysis to determine if prostate carcinoma cells are present as well as (if there is sufficient tissue) provide tissue for Aim 1. 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.

3) As a secondary endpoint, patients with abnormal extraprostatic suspicious findings on *anti*-[^{18}F]FACBC PET-CT may have those suspicious lymph nodes or other extraprostatic sites sampled as clinically appropriate through a combination of percutaneous image guided needle biopsy, laparoscopic techniques, as well as open lymph node dissection when appropriate. With both laparoscopic and open nodal dissections, it is standard practice to also sample adjacent imaging negative nodes. Rare sites of suspect metastases such as the inguinal nodal regions will be evaluated via a combination of physical exam and percutaneous biopsy as appropriate. Due to the high PPV of FACBC for extraprostatic disease, at the least, the referring clinician will discuss the findings with the patient and offer biopsy or other diagnostic investigations (such as advanced bone imaging for suspected skeletal lesions) as deemed clinically appropriate. In the event that the PET/CT demonstrates that the prostate cancer may have spread to areas outside of the prostate, the referring urologist or primary care physician will be notified and the findings will be discussed with the patient.

4.6. Statistical Analysis

The PI consulted with Dr. Nelson Chen at the Winship Statis*tica*l ^{Co}re. The following description was provided by Dr. Chen for the analysis plan and sample size.

Analysis Plan: After we obtain the pathological results for each core from the standard TRUS-guided biopsy and the PET/TRUS fusion targeted biopsy, we will calculate the cancer detection rate per core. For example, we will calculate how many cores are able to detect prostate cancer in the standard TRUS-guided biopsy and how cores will detect cancers in the PET/TRUS-guided biopsy. Based on the total numbers of cores for each biopsy approach, we can calculate the cancer detection rate per core for each biopsy approach. In order to compare the detection rates between the PET positive and negative groups, Chi-square test will be used to compare the detection rates with standard biopsy between the two arms with FACBC scan positive and negative, respectively. Logistics will be further employed to test their adjusted effect after adjusting for other factors in the multivariate analysis. In the first specific aim, the goal is to determine if the PET/TRUS fusion targeted b**i**opsy can detect more prostate cancer than the standard TRUS-guided biopsy. Therefore, among the FACBC positive arm, Kappa coefficient will be calculated to measure the correlation of the paired diagnostic results between the standard biopsy and the fusion targeted biopsy. McNemar's test will be further used to test on its significance.

Sample Size: We will recruit a total of 36 patients for this study. According to the inclusion criteria, approximately half of patients will have positive imaging scans and the other half negative. We determine the sample size in order to compare the performance of standard biopsy with the fusion targeted biopsy. We will expect to have 18 patients with FACBC positive, therefore, with McNemar's test, the sample size of 18 paired samples will achieve a power of at least 80% to detect a Kappa coefficient of 0.62 or higher between the two methods at the significant level of 0.05, assuming equal probability of positive or negative diagnosis outcome. We also like to determine the power to compare the detection rates of standard TRUS-guided biopsy between the PET positive and negative groups. With 18 FACBC positive patients and 18 FACBC negative patients, this study will have a power of at

least 80% to detect a difference in detection rates of 41% or higher between the two groups at the significant level of 0.05.

5. Registration/Randomization

Patients will be registered and consented into the study by one of the research nurses on staff working in the clinical Urology or Radiology setting. There will be no randomization. Patients are referred to the study by an Emory physician and or Co-I via email or telephone. Patient is seen at next appointment or at FACBC PET scan visit. Patient is then consented, registered into ERMS and eligibility criteria completed.

6. Intervention

This is not a therapeutic study. Diagnosis only.

Standard transrectal ultrasound (TRUS) guided biopsy: An ultrasound probe about 2.5 cm in diameter is gently inserted into the rectum. This ultrasound probe allows visualization of the prostate on two-dimensional (2D) images and allows for the placement of a biopsy needle that collects samples of the prostate. Usually, a total of 12 biopsy specimens are usually collected. The procedure takes about 20 minutes. This TRUS-guided biopsy is considered as the standard method for prostate cancer diagnosis. However, this biopsy procedure randomly takes tissue specimens from the prostate. Because of sampling errors, this standard TRUS-guided biopsy may miss the tumor in the prostate. In this proposed study, we will use three-dimensional (3D) ultrasound imaging to guide the biopsy in order to improve the location of the biopsy needle and will also use PET imaging to direct the biopsy to a suspicious target. The 3D ultrasound guided biopsy procedure is outlined in the next paragraph.

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. 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. 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.

8. Data Collection:

As noted above and per routine IRB requirements.

9. Adverse Event Reporting

An adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug-related

A significant shift from baseline which can be attributable to the radiotracer injection and not the patient's medical condition will be considered an unexpected AE. An event greater than 7 days post scan will not be considered an AE since 95% of ligand is eliminated by 7days.

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (June 14, 2010) will be used as a guide address potential AEs subject to limitations above and medical and scientific judgment as to plausibility of such criteria in a diagnostic radiotracer study.

Adverse Event Reporting

Any patient death that may be due to the study procedure (i.e. severe radiotracer reaction), unanticipated problem, would be promptly reported to the Emory IRB office. Additionally any patient death not associated with the study procedure or serious unanticipated event(s) (i.e. radiotracer allergy) will be reported to the Emory IRB and FDA upon continuing review. Protocol deviation/non-compliance will be reported according to IRB Policies & Procedures. This radiotracer is studied under IND 72437 and monitoring will be performed per already agreed upon FDA guidance. Over 900 patients in multiple centers have been studied without attributable serious adverse events.

A serious adverse event is any medical occurrence which is fatal, is immediately life threatening, requires hospitalization (or prolongs an existing hospitalization), results in persistent significant disability or incapacity, is a congenital abnormality or a birth defect, or is considered medically significant by a physician.
Serious adverse events will be communicated by the PI to the Emory IRB and FDA using standard adverse event reporting forms. Yearly safety reporting will also be forwarded to the FDA. Blue Earth Diagnostics, Ltd,(BED). BED is involved in the development and commercialization of FACBC for diagnostic purposes and will supply the FACBC cassettes for FACBC production. BED will receive data on safety since they supply the FACBC cassettes.

The Investigator will report all Serious Adverse Events occurring in a subject on the day of or within 28 days following the Agent administration to Pharsafer® Associates Ltd ("**Pharsafer**") by telephone (+44 1483 212151), FAX (+44 1483 212178) or e mail (drugsafety@pharsafer.com). Pharsafer is the clinical research organization (CRO) that functions as the safety oversight on behalf of BED Events should be reported to Pharsafer within 24 hours of the investigator becoming aware of the events occurrence.

10. Safety Monitoring

This study is being performed under the auspices of FDA IND 72,437. Patients will be monitored by the technologists and study nurse before and after the studies for any adverse events/reactions.

They will be given contact phone numbers to call if they experience any problems (i.e. problems with the IV site, any allergic reaction symptoms). They will be followed routinely by their referring physician with clinical exams, and the PI will work with the co-investigators and referring physicians to ensure that the patients continue to follow up as scheduled.

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will also oversee the conduct of this study (every 6 months or annually – depending on the risk level of the protocol). This committee will review pertinent aspects of study conduct including patient safety, compliance with protocol, data collection and efficacy. The committee will review the charts of 10% of patients enrolled to the study and two of the first 5 patients entered to the study. The Committee reserves the right to conduct additional audits if necessary. The Principal Investigator (PI) or designee is responsible for notifying the DSMC about the accrual of patients when the first 5 have been entered to the study. The PI or designee will also notify the DSMC of study status within 2 months before the next scheduled review is due.

Reference

Andriole,GL; Bullock,TL; Belani,JS; Traxel,E; Yan,Y; Bostwick,DG; and Humphrey,PA. Is there a better way to biopsy the prostate? Prospects for a novel transrectal systematic biopsy approach. *Urology*. 70:22-26. 2007.

Bao,P; Warmath,J; Galloway,R, Jr.; and Herline,A. Ultrasound-to-computer-tomography registration for image-guided laparoscopic liver surgery. *Surg.Endosc.* 19:424-429. 2005.

Barratt,DC; Chan,CS; Edwards,PJ; Penney,GP; Slomczykowski,M; Carter,TJ; and Hawkes,DJ. Instantiation and registration of statistical shape models of the femur and pelvis using 3D ultrasound imaging. *Med.Image Anal.* 12:358-374. 2008.

Barratt,DC; Penney,GP; Chan,CS; Slomczykowski,M; Carter,TJ; Edwards,PJ; and Hawkes,DJ. Self-calibrating 3D-ultrasound-based bone registration for minimally invasive orthopedic surgery. *IEEE Trans.Med.Imaging*. 25:312-323. 2006.

Bax,J; Cool,D; Gardi,L; Knight,K; Smith,D; Montreuil,J; Sherebrin,S; Romagnoli,C; and Fenster,A. Mechanically assisted 3D ultrasound guided prostate biopsy system. *Med.Phys.* 35:5397-5410. 2008.

Beck,M. The man, the gland, the deilemmas. *The Wall Street Journal*. http://online.wsj.com/article/SB123845699393571631.html: 2009.

Betrouni,N; Dewalle,AS; Puech,P; Vermandel,M; and Rousseau,J. 3D delineation of prostate, rectum and bladder on MR images. *Comput.Med.Imaging Graph.* 32:622-630. 2008.

Betrouni,N; Vermandel,M; Pasquier,D; Maouche,S; and Rousseau,J. Segmentation of abdominal ultrasound images of the prostate using a priori information and an adapted noise filter. *Comput.Med.Imaging Graph.* 29:43-51. 2005.

Bharatha,A; Hirose,M; Hata,N; Warfield,SK; Ferrant,M; Zou,KH; Suarez-Santana,E; Ruiz-Alzola,J; D'Amico,A; Cormack,RA; Kikinis,R; Jolesz,FA; and Tempany,CM. Evaluation of three-dimensional finite element-based deformable registration of pre- and intraoperative prostate imaging. *Med.Phys.* 28:2551-2560. 2001.

Blackall,JM; Penney,GP; King,AP; and Hawkes,DJ. Alignment of sparse freehand 3-D ultrasound with preoperative images of the liver using models of respiratory motion and deformation. *IEEE Trans.Med.Imaging*. 24:1405-1416. 2005.

Brendel,B; Winter,S; Rick,A; Stockheim,M; and Ermert,H. Registration of 3D CT and ultrasound datasets of the spine using bone structures. *Comput.Aided Surg.* 7:146-155. 2002.

Carlani,M; Mancino,S; Bonanno,E; Finazzi,AE; and Simonetti,G. Combined morphological, [1H]-MR spectroscopic and contrast-enhanced imaging of human prostate cancer with a 3-Tesla scanner: preliminary experience. *Radiol.Med.* 113:670-688. 2008.

Chen,TK; Abolmaesumi,P; Pichora,DR; and Ellis,RE. A system for ultrasound-guided computer-assisted orthopaedic surgery. *Comput.Aided Surg.* 10:281-292. 2005.

Cheng,LL; Burns,MA; Taylor,JL; He,W; Halpern,EF; McDougal,WS; and Wu,CL. Metabolic characterization of human prostate cancer with tissue magnetic resonance spectroscopy. *Cancer Res.* 65:3030-3034. 2005.

Chiu,B; Freeman,GH; Salama,MM; and Fenster,A. Prostate segmentation algorithm using dyadic wavelet transform and discrete dynamic contour. *Phys.Med.Biol.* 49:4943-4960. 2004.

Cleary,K; Melzer,A; Watson,V; Kronreif,G; and Stoianovici,D. Interventional robotic systems: applications and technology state-of-the-art. *Minim.Invasive.Ther.Allied Technol.* 15:101-113. 2006.

Coakley,FV; Teh,HS; Qayyum,A; Swanson,MG; Lu,Y; Roach,M, III; Pickett,B; Shinohara,K; Vigneron,DB; and Kurhanewicz,J. Endorectal MR imaging and MR spectroscopic imaging for locally recurrent prostate cancer after external beam radiation therapy: preliminary experience. *Radiology*. 233:441-448. 2004.

Cool,D; Sherebrin,S; Izawa,J; Chin,J; and Fenster,A. Design and evaluation of a 3D transrectal ultrasound prostate biopsy system. *Med.Phys.* 35:4695-4707. 2008.

Cosio,FA. Automatic initialization of an active shape model of the prostate. *Med.Image Anal.* 12:469-483. 2008.

Crocetti,L; Lencioni,R; Debeni,S; See,TC; Pina,CD; and Bartolozzi,C. Targeting liver lesions for radiofrequency ablation: an experimental feasibility study using a CT-US fusion imaging system. *Invest Radiol.* 43:33-39. 2008.

DeGrado,TR; Coleman,RE; Wang,S; Baldwin,SW; Orr,MD; Robertson,CN; Polascik,TJ; and Price,DT. Synthesis and evaluation of 18F-labeled choline as an oncologic tracer for positron emission tomography: initial findings in prostate cancer. *Cancer Res.* 61:110-117. 2001.

Ding,M; Chiu,B; Gyacskov,I; Yuan,X; Drangova,M; Downey,DB; and Fenster,A. Fast prostate segmentation in 3D TRUS images based on continuity constraint using an autoregressive model. *Med.Phys.* 34:4109-4125. 2007.

DOD. Prostate Cancer Research Program 2003 Annual Report - New Detection Method for Prostate Cancer. Department of Defense Congressionally Directed Medical Research Programs . IV-13-IV13. 2003.

DOD. Department of Defense Congressionally Directed Medical Research Programs - New imaging method provides a 'before and after' snapshot of the prostate. http://cdmrp.army.mil/highlights/2006.htm#2. 2006a.

DOD. Department of Defense Congressionally Directed Medical Research Programs 2006 Annual Report . New imaging method provides a 'before and after' snapshot of the prostate. III-18-III-18. 2006b.

Epstein,JI; Sanderson,H; Carter,HB; and Scharfstein,DO. Utility of saturation biopsy to predict insignificant cancer at radical prostatectomy. *Urology*. 66:356-360. 2005.

Estepar,RS; Stylopoulos,N; Ellis,R; Samset,E; Westin,CF; Thompson,C; and Vosburgh,K. Towards scarless surgery: an endoscopic ultrasound navigation system for transgastric access procedures. *Comput.Aided Surg.* 12:311-324. 2007.

Fahmy,TS; Mlcochova,H; Wazni,OM; Patel,D; Cihak,R; Kanj,M; Beheiry,S; Burkhardt,JD; Dresing,T; Hao,S; Tchou,P; Kautzner,J; Schweikert,RA; Arruda,M; Saliba,W; and Natale,A. Intracardiac echo-guided image integration: optimizing strategies for registration. *J.Cardiovasc.Electrophysiol.* 18:276-282. 2007.

Fei,B; Duerk,JL; Boll,DT; Lewin,JS; and Wilson,DL. Slice-to-volume registration and its potential application to interventional MRI-guided radio-frequency thermal ablation of prostate cancer. *IEEE Trans.Med.Imaging*. 22:515-525. 2003a.

Fei,B; Duerk,JL; Sodee,DB; and Wilson,DL. Semiautomatic nonrigid registration for the prostate and pelvic MR volumes. *Acad.Radiol.* 12:815-824. 2005.

Fei,B; Kemper,C; and Wilson,DL. A comparative study of warping and rigid body registration for the prostate and pelvic MR volumes. *Comput.Med.Imaging Graph.* 27:267-281. 2003b.

Fei,B; Lee,ZH; Boll,DT; Duerk,JL; Sodee,DB; Lewin,JS; and Wilson,DL. Registration and fusion of SPECT, high-resolution MRI, and interventional MRI for thermal ablation of prostate cancer. *Ieee Transactions on Nuclear Science*. 51:177-183. 2004.

Fei,B; Ng,WS; Chauhan,S; and Kwoh,CK. The safety issues of medical robotics. *Reliability Engineering & System Safety*. 73:183-192. 2001.

Fei,B; Wang,H; Muzic,RF, Jr.; Flask,C; Wilson,DL; Duerk,JL; Feyes,DK; and Oleinick,NL. Deformable and rigid registration of MRI and microPET images for photodynamic therapy of cancer in mice. *Med Phys.* 33:753-760. 2006.

Fei,B; Wheaton,A; Lee,Z; Duerk,JL; and Wilson,DL. Automatic MR volume registration and its evaluation for the pelvis and prostate. *Phys.Med.Biol.* 47:823-838. 2002.

Fenster,A and Downey,DB. Three-dimensional ultrasound imaging and its use in quantifying organ and pathology volumes. *Anal.Bioanal.Chem.* 377:982-989. 2003.

Foroughi,P; Song,D; Chintalapani,G; Taylor,RH; and Fichtinger,G. Localization of pelvic anatomical coordinate system using US/atlas registration for total hip replacement. *Med.Image Comput.Comput.Assist.Interv.* 11:871-879. 2008.

Foskey,M; Davis,B; Goyal,L; Chang,S; Chaney,E; Strehl,N; Tomei,S; Rosenman,J; and Joshi,S. Large deformation three-dimensional image registration in image-guided radiation therapy. *Phys.Med.Biol.* 50:5869-5892. 2005.

Freedman,D; Radke,RJ; Zhang,T; Jeong,Y; Lovelock,DM; and Chen,GT. Model-based segmentation of medical imagery by matching distributions. *IEEE Trans.Med.Imaging*. 24:281-292. 2005.

Galloway,RL. The process and development of image-guided procedures. *Annu.Rev.Biomed.Eng*. 3:83-108. 2001.

Ghanei,A and Soltanian-Zadeh,H. A discrete curvature-based deformable surface model with application to segmentation of volumetric images. *IEEE Trans.Inf.Technol.Biomed.* 6:285-295. 2002.

Gray,H. Anatomy, Descriptive and Surgical. New York: Bramercy Books.1010-1010. 1997.

Han,Q; Merck,D; Levy,J; Villarruel,C; Damon,JN; Chaney,EL; and Pizer,SM. Geometrically proper models in statistical training. *Inf.Process Med.Imaging*. 20:751-762. 2007.

Hara,T; Kosaka,N; and Kishi,H. PET imaging of prostate cancer using carbon-11-choline. *J.Nucl.Med.* 39:990-995. 1998.

Hasumi,M; Suzuki,K; Oya,N; Ito,K; Kurokawa,K; Fukabori,Y; and Yamanaka,H. MR spectroscopy as a reliable diagnostic tool for localization of prostate cancer. *Anticancer Res.* 22:1205-1208. 2002.

Hedlund,P; Larsson,B; Alm,P; and Andersson,KE. Nitric oxide synthase-containing nerves and ganglia in the dog prostate: a comparison with other transmitters. *Histochem.J.* 28:635-642. 1996.

Herline,AJ; Herring,JL; Stefansic,JD; Chapman,WC; Galloway,RL, Jr.; and Dawant,BM. Surface registration for use in interactive, image-guided liver surgery. *Comput.Aided Surg.* 5:11-17. 2000.

Hricak,H. MR imaging and MR spectroscopic imaging in the pre-treatment evaluation of prostate cancer. *Br.J.Radiol.* 78 Spec No 2:S103-S111. 2005.

Hu,N; Downey,DB; Fenster,A; and Ladak,HM. Prostate boundary segmentation from 3D ultrasound images. *Med.Phys.* 30:1648-1659. 2003.

Huang,X; Moore,J; Guiraudon,G; Jones,DL; Bainbridge,D; Ren,J; and Peters,TM. Dynamic 2D ultrasound and 3D CT image registration of the beating heart. *IEEE Trans.Med.Imaging*. 28:1179-1189. 2009a.

Huang,X; Ren,J; Guiraudon,G; Boughner,D; and Peters,TM. Rapid dynamic image registration of the beating heart for diagnosis and surgical navigation. *IEEE Trans.Med.Imaging*. 28:1802-1814. 2009b.

Hummel,J; Figl,M; Bax,M; Bergmann,H; and Birkfellner,W. 2D/3D registration of endoscopic ultrasound to CT volume data. *Phys.Med.Biol.* 53:4303-4316. 2008.

Iczkowski,KA; Bassler,TJ; Schwob,VS; Bassler,IC; Kunnel,BS; Orozco,RE; and Bostwick,DG. Diagnosis of "suspicious for malignancy" in prostate biopsies: predictive value for cancer. *Urology*. 51:749-757. 1998.

Jemal,A; Center,MM; Ward,E; and Thun,MJ. Cancer occurrence. *Methods Mol.Biol.* 471:3-29. 2009.

Jolesz,FA. Future perspectives for intraoperative MRI. *Neurosurg.Clin.N.Am.* 16:201-213. 2005.

Kaspersen,JH; Sjolie,E; Wesche,J; Asland,J; Lundbom,J; Odegard,A; Lindseth,F; and Nagelhus Hernes,TA. Three-dimensional ultrasound-based navigation combined with preoperative CT during abdominal interventions: a feasibility study. *Cardiovasc.Intervent.Radiol.* 26:347-356. 2003.

Kranzfelder,M; Dobritz,M; Wilhelm,D; Doundoulakis,E; Schneider,A; and Feussner,H. CT-navigated real-time ultrasonography: evaluation of registration accuracy for clinical application. *Biomed.Tech.(Berl)*. 53:279-284. 2008.

Kurhanewicz,J; Swanson,MG; Nelson,SJ; and Vigneron,DB. Combined magnetic resonance imaging and spectroscopic imaging approach to molecular imaging of prostate cancer. *J.Magn Reson.Imaging*. 16:451-463. 2002.

Ladak,HM; Mao,F; Wang,Y; Downey,DB; Steinman,DA; and Fenster,A. Prostate boundary segmentation from 2D ultrasound images. *Med.Phys.* 27:1777-1788. 2000.

Lange,T; Eulenstein,S; Hunerbein,M; and Schlag,PM. Vessel-based non-rigid registration of MR/CT and 3D ultrasound for navigation in liver surgery. *Comput.Aided Surg.* 8:228-240. 2003.

Li,K and Fei,B. A New 3D Model-Based Minimal Path Segmentation Method for Kidney MR Images. Proceedings of the 2nd Int'l Conference of IEEE on Bioinformatics and Biomedical Engineering. 2342-2344. 2008.

Lian,J; Xing,L; Hunjan,S; Dumoulin,C; Levin,J; Lo,A; Watkins,R; Rohling,K; Giaquinto,R; Kim,D; Spielman,D; and Daniel,B. Mapping of the prostate in endorectal coil-based MRI/MRSI and CT: a deformable registration and validation study. *Med.Phys.* 31:3087-3094. 2004.

Long,JA; Daanen,V; Moreau-Gaudry,A; Troccaz,J; Rambeaud,JJ; and Descotes,JL. Prostate biopsies guided by three-dimensional real-time (4-D) transrectal ultrasonography on a phantom: comparative study versus two-dimensional transrectal ultrasound-guided biopsies. *Eur.Urol.* 52:1097-1104. 2007.

Lunn,KE; Paulsen,KD; Roberts,DW; Kennedy,FE; Hartov,A; and West,JD. Displacement estimation with co-registered ultrasound for image guided neurosurgery: a quantitative in vivo porcine study. *IEEE Trans.Med.Imaging*. 22:1358-1368. 2003.

Manenti,G; Squillaci,E; Carlani,M; Mancino,S; Di Roma,M; and Simonetti,G. Magnetic resonance imaging of the prostate with spectroscopic imaging using a surface coil. Initial clinical experience. *Radiol.Med.(Torino)*. 111:22-32. 2006.

Markert,M; Weber,S; and Lueth,TC. Manual registration of ultrasound with CT/planning data for hepatic surgery. *Stud.Health Technol.Inform.* 125:319-321. 2007.

Marks,LS. UC Denver and UCLA First to Receive Revolutionary Prostate Biopsy Systems. http://www.eigen.com/about/events.cfm?EventID=7DC995B3-FFE3-371E-E3831F85A19D7526&category=4. 2010.

Mizowaki,T; Cohen,GN; Fung,AY; and Zaider,M. Towards integrating functional imaging in the treatment of prostate cancer with radiation: the registration of the MR spectroscopy imaging to ultrasound/CT images and its implementation in treatment planning. *Int.J.Radiat.Oncol.Biol.Phys.* 54:1558-1564. 2002.

Moghari,MH and Abolmaesumi,P. A novel incremental technique for ultrasound to CT bone surface registration using Unscented Kalman Filtering. *Med.Image Comput.Comput.Assist.Interv.* 8:197-204. 2005.

Moghari,MH and Abolmaesumi,P. Point-based rigid-body registration using an unscented Kalman filter. *IEEE Trans.Med.Imaging*. 26:1708-1728. 2007.

Molloy,JA and Oldham,SA. Benchmarking a novel ultrasound-CT fusion system for respiratory motion management in radiotherapy: assessment of spatio-temporal characteristics and comparison to 4DCT. *Med.Phys.* 35:291-300. 2008.

Morr,J; DiPetrillo,T; Tsai,JS; Engler,M; and Wazer,DE. Implementation and utility of a daily ultrasound-based localization system with intensity-modulated radiotherapy for prostate cancer. *Int.J.Radiat.Oncol.Biol.Phys.* 53:1124-1129. 2002.

Mueller-Lisse,UG and Scherr,MK. Proton MR spectroscopy of the prostate. *Eur.J.Radiol.* 63:351-360. 2007.

Murtha,PE; Watterson,N; Nikou,C; and Jaramaz,B. Accuracy of ultrasound to MR registration of the knee. *Int.J.Med.Robot.* 4:51-57. 2008.

Nanayakkara,ND; Samarabandu,J; and Fenster,A. Prostate segmentation by feature enhancement using domain knowledge and adaptive region based operations. *Phys.Med.Biol.* 51:1831-1848. 2006.

Ng,A; Beiki-Ardakan,A; Tong,S; Moseley,D; Siewerdsen,J; Jaffray,D; and Yeung,IW. A dual modality phantom for cone beam CT and ultrasound image fusion in prostate implant. *Med.Phys.* 35:2062-2071. 2008.

Nowatschin,S; Markert,M; Weber,S; and Lueth,TC. A system for analyzing intraoperative B-Mode ultrasound scans of the liver. *Conf.Proc.IEEE Eng Med.Biol.Soc.* 2007:1346-1349. 2007.

Nunez,R; Macapinlac,HA; Yeung,HW; Akhurst,T; Cai,S; Osman,I; Gonen,M; Riedel,E; Scher,HI; and Larson,SM. Combined 18F-FDG and 11C-methionine PET scans in patients with newly progressive metastatic prostate cancer. *J.Nucl.Med.* 43:46-55. 2002.

Oka,S; Hattori,R; Kurosaki,F; Toyama,M; Williams,LA; Yu,W; Votaw,JR; Yoshida,Y; Goodman,MM; and Ito,O. A preliminary study of anti-1-amino-3-18F-fluorocyclobutyl-1-carboxylic acid for the detection of prostate cancer. *J.Nucl.Med.* 48:46-55. 2007.

Oyama,N; Miller,TR; Dehdashti,F; Siegel,BA; Fischer,KC; Michalski,JM; Kibel,AS; Andriole,GL; Picus,J; and Welch,MJ. 11C-acetate PET imaging of prostate cancer: detection of recurrent disease at PSA relapse. *J.Nucl.Med.* 44:549-555. 2003.

Park,H; Piert,MR; Khan,A; Shah,R; Hussain,H; Siddiqui,J; Chenevert,TL; and Meyer,CR. Registration methodology for histological sections and in vivo imaging of human prostate. *Acad.Radiol.* 15:1027-1039. 2008.

Penney,GP; Barratt,DC; Chan,CS; Slomczykowski,M; Carter,TJ; Edwards,PJ; and Hawkes,DJ. Cadaver validation of intensity-based ultrasound to CT registration. *Med.Image Comput.Comput.Assist.Interv.* 8:1000-1007. 2005.

Penney,GP; Barratt,DC; Chan,CS; Slomczykowski,M; Carter,TJ; Edwards,PJ; and Hawkes,DJ. Cadaver validation of intensity-based ultrasound to CT registration. *Med.Image Anal.* 10:385-395. 2006.

Qin,B; Gu,Z; Sun,X; and Lv,Y. Registration of images with outliers using joint saliency map. *IEEE Signal Processing Letters*. 17:91-94. 2010.

Rueckert,D; Sonoda,LI; Hayes,C; Hill,DL; Leach,MO; and Hawkes,DJ. Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Trans Med Imaging*. 18:712-721. 1999.

Schilling,D; Schlemmer,HP; Wagner,PH; Bottcher,P; Merseburger,AS; Aschoff,P; Bares,R; Pfannenberg,C; Ganswindt,U; Corvin,S; and Stenzl,A. Histological verification of 11C-choline-positron emission/computed tomography-positive lymph nodes in patients with biochemical failure after treatment for localized prostate cancer. *BJU.Int.* 102:446-451. 2008.

Schoder,H; Herrmann,K; Gonen,M; Hricak,H; Eberhard,S; Scardino,P; Scher,HI; and Larson,SM. 2-[18F]fluoro-2-deoxyglucose positron emission tomography for the detection of disease in patients with prostate-specific antigen relapse after radical prostatectomy. *Clin.Cancer Res.* 11:4761-4769. 2005.

Schuster,DM; Votaw,JR; Nieh,PT; Yu,W; Nye,JA; Master,V; Bowman,FD; Issa,MM; and Goodman,MM. Initial experience with the radiotracer anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid with PET/CT in prostate carcinoma. *J.Nucl.Med.* 48:56-63. 2007.

Shen,D; Zhan,Y; and Davatzikos,C. Segmentation of prostate boundaries from ultrasound images using statistical shape model. *IEEE Trans.Med.Imaging*. 22:539-551. 2003.

Shen,F; Shinohara,K; Kumar,D; Khemka,A; Simoneau,AR; Werahera,PN; Li,L; Guo,Y; Narayanan,R; Wei,L; Barqawi,A; Crawford,ED; Davatzikos,C; and Suri,JS. Three-dimensional sonography with needle tracking: role in diagnosis and treatment of prostate cancer. *J.Ultrasound Med.* 27:895-905. 2008.

Steggerda,M; Schneider,C; van Herk,M; Zijp,L; Moonen,L; and van der,PH. The applicability of simultaneous TRUS-CT imaging for the evaluation of prostate seed implants. *Med.Phys.* 32:2262-2270. 2005.

Stough,JV; Broadhurst,RE; Pizer,SM; and Chaney,EL. Regional appearance in deformable model segmentation. *Inf.Process Med.Imaging*. 20:532-543. 2007.

Swindle,P; McCredie,S; Russell,P; Himmelreich,U; Khadra,M; Lean,C; and Mountford,C. Pathologic characterization of human prostate tissue with proton MR spectroscopy. *Radiology*. 228:144-151. 2003.

Tsai,A; Wells,W; Tempany,C; Grimson,E; and Willsky,A. Mutual information in coupled multi-shape model for medical image segmentation. *Med.Image Anal.* 8:429-445. 2004.

Tyryshkin,K; Mousavi,P; Pichora,DR; and Abolmaesumi,P. Identification of anatomical landmarks for registration of CT and ultrasound images in computer-assisted shoulder arthroscopy. *Conf.Proc.IEEE Eng Med.Biol.Soc.* 1:416-419. 2006.

Verhey,JF; Wisser,J; Warfield,SK; Rexilius,J; and Kikinis,R. Non-rigid registration of a 3D ultrasound and a MR image data set of the female pelvic floor using a biomechanical model. *Biomed.Eng Online.* 4:19- 2005.

Viswanath,S; Bloch,BN; Genega,E; Rofsky,N; Lenkinski,R; Chappelow,J; Toth,R; and Madabhushi,A. A comprehensive segmentation, registration, and cancer detection scheme on 3 Tesla in vivo prostate DCE-MRI. *Med.Image Comput.Comput.Assist.Interv.* 11:662-669. 2008.

Wang,H and Fei,B. A Robust B-Splines-Based Point Match Method for Non-Rigid Surface Registration. *The 2rd International Conference on Bioinformatics and Biomedical Engineering*. 2353-2356. 2008.

Wang,Y; Cardinal,HN; Downey,DB; and Fenster,A. Semiautomatic three-dimensional segmentation of the prostate using two-dimensional ultrasound images. *Med.Phys.* 30:887-897. 2003.

Warmath,JR; Bao,P; Clements,LW; Herline,AJ; and Galloway,RL. Development of a three-dimensional freehand endorectal ultrasound system for use in rectal cancer imaging. *Med.Phys.* 32:1757-1766. 2005.

Wein,W; Brunke,S; Khamene,A; Callstrom,MR; and Navab,N. Automatic CT-ultrasound registration for diagnostic imaging and image-guided intervention. *Med.Image Anal.* 12:577-585. 2008.

Wein,W; Roper,B; and Navab,N. Automatic registration and fusion of ultrasound with CT for radiotherapy. *Med.Image Comput.Comput.Assist.Interv.* 8:303-311. 2005.

Wein,W; Roper,B; and Navab,N. Integrating diagnostic B-mode ultrasonography into CT-based radiation treatment planning. *IEEE Trans.Med.Imaging*. 26:866-879. 2007.

Winter,S; Brendel,B; Rick,A; Stockheim,M; Schmieder,K; and Ermert,H. Registration of bone surfaces, extracted from CT-datasets, with 3D ultrasound. *Biomed.Tech.(Berl)*. 47 Suppl 1 Pt 1:57-60. 2002.

Xiong,L; Viswanathan,A; Stewart,AJ; Haker,S; Tempany,CM; Chin,LM; and Cormack,RA. Deformable structure registration of bladder through surface mapping. *Med.Phys.* 33:1848-1856. 2006.

Yu,Y; Molloy,JA; and Acton,ST. Segmentation of the prostate from suprapubic ultrasound images. *Med.Phys.* 31:3474-3484. 2004.

Zhan,Y and Shen,D. Deformable segmentation of 3-D ultrasound prostate images using statistical texture matching method. *Medical Imaging, IEEE Transactions on*. 25:256-272. 2006.

Zhang,Y; Sankar,R; and Qian,W. Boundary delineation in transrectal ultrasound image for prostate cancer. *Comput.Biol.Med.* 37:1591-1599. 2007.