Gallium-68 PSMA-11 PET in patients with biochemical recurrence

Study Drug: Gallium-68 PSMA-11

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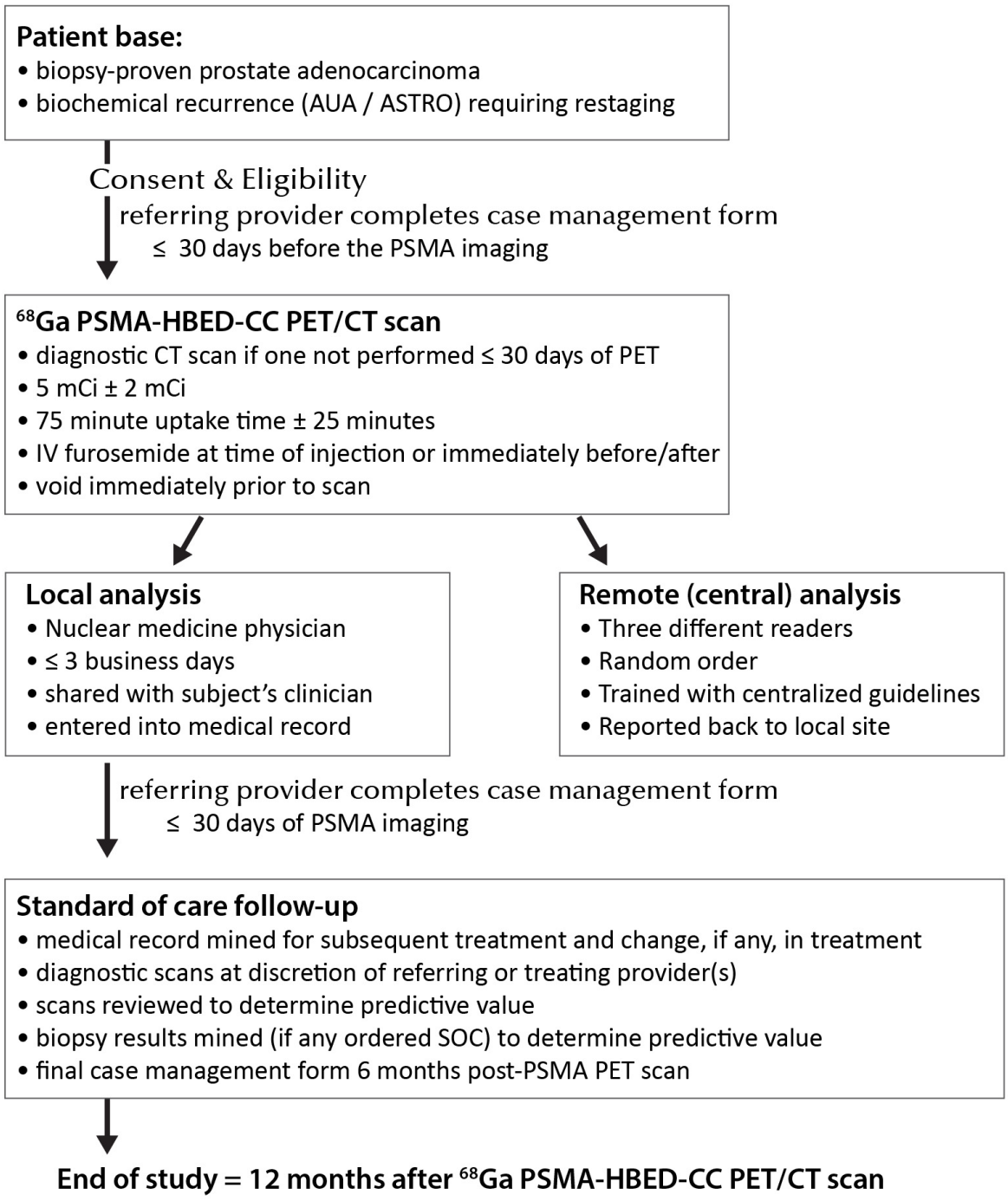
Note:

This study is a site-specific single center study; however together with other participating sites, the University of Michigan investigators will share obtained data regarding the performance of ^{68}Ga-PSMA-11 PET/CT in biochemical recurrence in order to allow for a future NDA filing for ^{68}Ga-PSMA-11 to the FDA. The study protocol has been designed in consultation with the FDA. The entire study process is organized by the Clinical Trials Network (CTN) of the Society of Nuclear Medicine. Specifically, data capture procedures and data management is organized by the CTN. The University of California at San Francisco (UCSF) site will host an electronic database for central anonymized data capture.

SCHEMA


Patient base:
• biopsy-proven prostate adenocarcinoma
• biochemical recurrence (AUA / ASTRO) requiring restaging
Consent & Eligibility
referring provider completes case management form
≤ 30 days before the PSMA imaging
68Ga PSMA-HBED-CC PET/CT scan
• diagnostic CT scan if one not performed ≤ 30 days of PET
• 5 mCi ± 2 mCi
• 75 minute uptake time ± 25 minutes
• IV furosemide at time of injection or immediately before/after
• void immediately prior to scan
Local analysis
• Nuclear medicine physician
• ≤ 3 business days
• shared with subject's clinician
• entered into medical record
Remote (central) analysis
• Three different readers
• Random order
• Trained with centralized guidelines
• Reported back to local site
referring provider completes case management form
≤ 30 days of PSMA imaging
Standard of care follow-up
• medical record mined for subsequent treatment and change, if any, in treatment
• diagnostic scans at discretion of referring or treating provider(s)
• scans reviewed to determine predictive value
• biopsy results mined (if any ordered SOC) to determine predictive value
• final case management form 6 months post-PSMA PET scan
End of study = 12 months after 68Ga PSMA-HBED-CC PET/CT scan

Abstract

Title	Gallium-68 PSMA-11 PET in patients with biochemical recurrence
Study population	Arm 1 (Prostate cancer patients): Rising PSA after definitive therapy with prostatectomy or radiation therapy (external beam or brachytherapy): Post radical prostatectomy (RP) – AUA recommendation PSA greater than 0.2 ng/mL measured more than 6 weeks after RP and, Confirmatory persistent PSA greater than 0.2 ng/mL Post-radiation therapy – ASTRO-Phoenix consensus definition Nadir + greater than or equal to 2 ng/mL rise in PSA Arm 2 (Physicians/practitioners): Ordering physicians/practitioners of study arm 1 patients will be surveyed whether ^{68}Ga PSMA-HBED-CC PET/CT has an impact on the clinical management of their respective patients.
Rationale for Study	^{68}Ga PSMA-HBED-CC (^{68}Ga-PSMA-11) has been shown to have a higher sensitivity for the detection of metastatic prostate cancer compared to choline based imaging.
Primary Objectives	Determine the positive predictive value (PPV) of ^{68}Ga PSMA-11 PET/CT for detecting prostate cancer on a per-patient basis, confirmed by histopathology
Secondary Objectives	Determine sensitivity and PPV on a per-patient and per-region-basis of ^{68}Ga-PSMA-11 PET/CT for detection of tumor location confirmed by conventional imaging, clinical follow-up, and histopathology/biopsy where available Determine detection rates on a per-subject basis of ^{68}Ga PSMA-HBED-CC PET/CT stratified by PSA value (0.2 - <0.5, 0.5 - <1.0, 1.0 - <2.0, 2.0 - < 5.0, 5.0 or greater) Determine the impact of ^{68}Ga PSMA-HBED-CC PET/CT on clinical management in patients who have prostate cancer with biochemical recurrence Continue to evaluate safety of ^{68}Ga PSMA-HBED-CC injection as categorized by CTCAE 4.0

Study Design	Single-center, open label phase 2.
Number of subjects	Study arm 1: The total number of patients at the University of Michigan is 750. The data will be shared with other sites within the CTN. The total population of patients will be 1,500 patients across all participating institutions. Study arm 2: the total number of physicians/practitioners ordering PET/CT scans will be small, but theoretically be as high as 750.
Duration of Therapy	The study will involve a single imaging study.
Duration of Safety Follow up	The patients will be followed-up by phone after PET/CT imaging.
Duration of study	The study will reach completion of recruitment 3 years from the time the study opens to accrual.
Study Drugs	Gallium-68 labeled PSMA-11 (PSMA-HBED-CC)
Safety Assessments	Patient vital signs will be taken immediately before and after the administration of the radiopharmaceutical. The patients will also be asked to report adverse events.

List of Abbreviations

^{68}Ga-PSMA	Glu-NH-CONH-Lys-(Ahx)-[68Ga(HBED-CC)], also called ^{68}Ga-PSMA-11
ADT	Androgen Deprivation Therapy
AE	Adverse Event
BCR	Biochemical Recurrence
CRF	Case Report Form
CT	Computed Tomography
CTN	Clinical Trials Network (of the Society of Nuclear Medicine)
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
F/u	Follow-up
IND	Investigational New Drug
IRB	Institutional Review Board
IV (or iv)	Intravenously
LN	Lymph node
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application
NRC	Nuclear Regulatory Commission
PET	Positron Emission Tomography
PI	Principal Investigator
PPV	Positive Predictive Value
PRC	Protocol Review Committee
PSA	Prostate-specific Antigen
PSMA	Prostate-specific Membrane Antigen
RDRC	Radioactive Drug Research Committee

List of Abbreviations

RECIST	Response Evaluation Criteria In Solid Tumors (Version 1.1)
SAE	Serious Adverse Event
SD	Standard Deviation
SHUR	Subcommittee on the Human Use of Radioisotopes
SUV	Standardized Uptake Value
UaP	Unanticipated Problem
WHO	World Health Organization
VOIs	Volumes of interest

Contents

1 Introduction

1.1 Overview

Imaging and staging of prostate cancer is critical for surgical and treatment planning. We aim to image patients with suspected metastatic prostate cancer using Gallium-68 labeled HBED-CC PSMA (more commonly called ^{68}Ga-PSMA-11) in order to demonstrate its utility. We plan to utilize this data to obtain further approvals of the ^{68}Ga-PSMA-11 compound, so that this agent will become available for clinical imaging in prostate cancer patients.

This compound has been shown to be superior to choline based PET agents for the staging of prostate cancer, both Carbon-11 and Fluorine-18 compounds. But this compound was not patented and therefore no company or private entity will make the investment required to bring HBED-CC PSMA to market. In the vacuum of availability, academic groups must take the lead in order to collect the necessary data for future FDA approval. This protocol was developed in

collaboration with the Clinical Trials Network of the Society of Nuclear Medicine and Molecular Imaging. The inclusion criteria and study endpoints have been aligned so that inter-institutional sharing of data can be performed in order to pool data for final NDA submission.

1.2 Background

Prostate cancer is the most commonly diagnosed cancer and second leading cause of cancer death in American men [1]. Biochemical recurrence (BCR) of prostate cancer is defined as a confirmed PSA value of ≥ 0.2 ng/dL if the patient has had a radical prostatectomy (RP) with or without postoperative radiation therapy (adjuvant or salvage). If the initial local therapy was definitive radiation therapy (RT), biochemical recurrence is defined as the nadir PSA value plus 2 ng/mL, since some benign PSA-producing tissue may remain. Patients with BCR after RP who have not received postoperative RT are frequently treated with salvage RT to the prostate bed, which can be curative for some. Patients with BCR after initial definitive RT may be salvaged with brachytherapy or in some cases with surgery. However, for patients with BCR and no further local therapy options, there is no consensus as to optimal management.

Typical management of BCR involves serial clinical and laboratory monitoring [2] with eventual initiation of androgen deprivation therapy (ADT) in many patients as the PSA rises. The risk of developing BCR is 15–20% at 5 and 25–30% at 10 years after initial therapy of prostate cancer [3,4]. The best threshold at which to initiate systemic androgen deprivation therapy (ADT) in patients with BCR remains controversial. In one retrospective cohort of over 5,000 patients treated with primary prostatectomy or radiotherapy, ADT was not associated with an all-cause mortality or prostate cancer-specific mortality benefit in the prostatectomy cohort. However, ADT did show improvement in all-cause and prostate-cancer specific mortality in patients with a PSA doubling time less than 9 months. This suggests that there is a potential role for aggressive, earlier intervention in the setting of BCR in select patients, and systemic therapy may also be necessary in these patients [5]. Recently, a randomized trial of early versus delayed use of ADT in men with BCR after local therapy showed a small improvement in survival with early ADT [6]. Nonetheless, the toxicity of ADT is not trivial, and the authors recommended a thorough discussion of the risks and benefits of early versus late ADT with each patient rather than blanket use of early ADT.

Current standard imaging of early recurrent prostate cancer is insufficient. Accurate detection of tumor locations is essential as the clinical management varies from active surveillance to targeted local to systemic therapy [7]. Per NCCN guidelines at the time of biochemical recurrence, imaging is performed to detect and characterize the disease to determine treatment or guide change in management. Imaging can evaluate anatomic or functional parameters and the following imaging is recommended as standard techniques at this time-point:

- Imaging is performed for the detection and characterization of disease to select treatment or guide change in management.
- Anatomic imaging techniques include plain film radiographs, ultrasound, CT, and MRI.
- Functional imaging techniques include radionuclide bone scan, PET, and advanced MRI techniques such as spectroscopy and diffusion-weighted imaging (DWI).

More specifically, Current U.S. guidelines recommend either a radionuclide bone scan, abdominopelvic CT, multi-parameter MRI or – where available - choline PET/CT for patients with rising PSA or clinical symptoms [7]. The probability of a positive bone scan is reported to be <5% with a serum PSA level of <7 ng/mL. A CT scan will only be positive in 11–14% of patients

with BCR [8]. Additionally, in a study with 132 patients, the mean PSA level of patients with a positive CT scan was 27.4 ng/ml [8].

Due to this limitation, of existing conventional imaging [9], numerous approaches to stage patients have been evaluated. Choline imaging has been frequently used, as prostate cancer exhibits increase choline uptake that has been associated with the presence of choline kinase [10]. Choline uptake is increased in comparison to FDG in both androgen dependent and independent prostate cancer patients [11]. Choline has also been shown to be sensitive for the detection of recurrent tumor in patients with PSA (prostate specific antigen) values of less than 1.0 ng/ml [12]. There are two forms of choline that are used in imaging prostate cancer, ^{11}C - and ^{18}F-choline. ^{11}C-choline has a short half-life of 20 minutes, which limits its detection for metastatic disease but results in improved local detection due to decreased urinary activity at the time of imaging. ^{18}F-choline has significant urinary excretion that limits evaluation of the prostate but, but has been shown to have better detection rates for distant metastatic disease [13]. ^{11}C-choline has limited sensitivity for osseous metastasis, possibly due to the decreased uptake time [14]. Additionally, the sensitivity of ^{11}C -choline is limited in patients with PSA values < 1.0 ng/ml [15-17]. Although choline PET may be limited in sensitivity, it clearly delineates more lesions than cross section imaging or bone scan in patients with known disease [18]. In 2012, the Mayo Clinic obtained NDA approval from the FDA for the use of ^{11}C-choline. MRI and choline PET/CT have been reported to have similar sensitivities in detecting bone metastasis [19]. However, the sensitivity for lymph node detection remains low. Choline PET/CT have shown variable results with the detection rates ranging between 11% and 75%, largely depending on serum PSA levels. For PSA levels <1.0 mg/ml, the detection rates range from 5% to 44%. The main limitation is the low sensitivity for micro-metastatic disease [20].

A different approach is to image the prostate specific membrane antigen (PSMA). PSMA is expressed on the majority of prostate cancer cells. The initial imaging approach to PSMA imaging was to target the intracellular domain of PSMA using Indium-111-capromab (Prostascint), a murine monoclonal antibody [21]. Although there was early promise for the detection of nodal metastasis [22], the agent was never able to adequately visualize osseous metastasis [23]. One main limitation to Indium-111-capromab is that it takes a prolonged time to localize to the target tissue, which likely relates to both the size of the monoclonal antibody and the fact that agent targets the intracellular domain of the PSMA protein. Additionally, Prostascint also recognizes an intracellular epitope so the antibody must cross the membrane to be effective. This likely only occurs in permeable dead or dying tumor cells.

Because of the limitations of Indium-111 capromab, there has been continued effort to develop agents that target the extracellular domain of the PSMA protein. ^{68}Ga-PSMA has become of particular interest in biochemical recurrent prostate cancer. Afshar-Oromieh et al. demonstrated that ^{68}Ga-PSMA-11 has a higher sensitivity for the detection of disease than 18F-choline in a head-to-head intra-patient comparison that included 37 patients [24]. Later the same group demonstrated a high sensitivity of ^{68}Ga-PSMA-11 in the detection of metastatic lesions at the time of recurrent prostate cancer [25]. Their results demonstrated a detection rate of 50% for patients with a PSA less than 1 ng/ml, and detection rate above 85% for patients with a PSA greater than 2 ng/ml. These detection rates are significantly higher than that reported by groups using choline [12]. Newer extensive retrospective data of more than 1600 patients further support these earlier data suggesting that ^{68}Ga-PSMA is an excellent radiotracer for biochemically recurrent prostate cancer with particular benefits over choline PET/CT at very low PSA levels (< 0.5 ng/mL) [26-29]. ^{68}Ga-PSMA has also been shown in head-to-head comparisons to outperform conventional imaging for detection of nodal metastatic disease by a large margin [30].

Factors influencing the probability for a positive ^{68}Ga-PSMA PET/CT study have been evaluated in larger retrospective patient populations [31]. These factors including the absolute level of PSA

at the time of scanning, PSA doubling time, PSA velocity, initial Gleason score, ongoing androgen deprivation therapy, patient age and amount of injected tracer activity in cohorts of 319, 248 and 1007 patients with BCR [25,27,29]. All studies suggested that the absolute PSA level and androgen deprivation therapy were associated with a positive ^{68}Ga-PSMA scan, while the PSA doubling time and Gleason score at initial presentation were not a significant predictors of scan positivity.

Improvements in the detection of recurrent prostate cancer have profound effects on patient management [28]. In a recently published Australian multi-center trial including 323 patients with biochemical evidence of recurrent disease and equivocal conventional imaging, ^{68}Ga-PSMA PET/CT changed the management of prostate cancer in 62% of cases. In this study, a substantial impact was documented with a significant reduction in the number of men in whom the site of disease recurrence was unknown and significant increases in the detection of presumed oligometastatic and polymetastatic disease. Compared to standard of care diagnostics (including imaging), additional sites of disease were detection in 32% as local recurrence, 43% as nodal disease and 20% as metastatic (mostly to bone) [32]. ^{68}Ga-PSMA has a significantly higher sensitivity and specificity than 99mTc-bone scanning in 126 patients with prostate cancer, of whom 75 were found to present with osseous metastatic disease [33].

Overtreatment and undertreatment of BCR occurs [34]. Due to the lack of accurate imaging, salvage RT of prostate bed without identification of the disease location is commonly performed. The lack of targeted focal treatment of metastatic disease may limit the success of such treatment. Also, ^{68}Ga-PSMA identifies a high detection rate of prostate cancer recurrence outside of the prostatic fossa [35]. This clearly indicates the need for prospective trials to evaluate the changes in RT volumes or disease management and their outcomes.

Earlier detection of macroscopic metastatic disease in castration sensitive prostate cancer by novel highly sensitive molecular imaging techniques could lead to detection of prostate cancer metastases at lower tumor burdens presenting as oligometastatic prostate cancer rather than as diffusely metastatic prostate cancer. While the definition of oligometastatic disease varies, the addition of locoregional ablative therapies directed at sites of macroscopic disease to conventional systemic therapy has shown promise with respect to delaying progression of disease in other cancer types. A recent randomized trial in oligometastatic non-small cell lung cancer demonstrated that the addition of locoregional therapy to systemic therapy improved progression-free survival [36]. More importantly, the addition of locoregional therapy doubled the time to the appearance of disease at new sites, indicating that the overall natural history of the disease was altered.

In prostate cancer, multiple studies suggest a benefit from locoregional therapy in oligometastatic disease. Given that maximally effective use of locoregional therapy requires accurate knowledge of disease extent, further investigation of the clinical impact of highly sensitive molecular imaging is critical. Incorporation of additional focal or targeted therapeutic modalities could be valuable in this patient population, but is currently limited by the low sensitivity of standard imaging modalities. The STOMP trial is an ongoing randomized phase study utilizing metastases-directed therapy with either surgery or sterotactic body radiotherapy, with less than or equal to 3 metastases defining oligometastatic disease diagnosed on choline PET/CT [37]. The ORIOLE trial is also an ongoing randomized phase II study assessing the efficacy of stereotactic ablative radiotherapy in patients who have failed primary treatment and have developed oligometastatic disease with three or fewer bone metastases [38].

Based on the available data, it is evident that the full extent of metastatic disease patients with biochemically recurrent prostate cancer is frequently underestimated on conventional imaging when compared to advanced molecular imaging techniques. Importantly, the utility of ^{68}Ga-PSMA PET/CT to identify such metastatic lesions earlier prior their appearance on standard imaging has not yet been evaluated in the randomized setting.

In HUM00106254, a small pilot trial, we are currently evaluating ^{68}Ga-PSMA for the detection of primary prostate cancer and BCR. Examples of the potential of this excellent radiotracer for the identification of significant primary disease (Figure 1), and low-volume metastatic disease are given in figures 2-3.

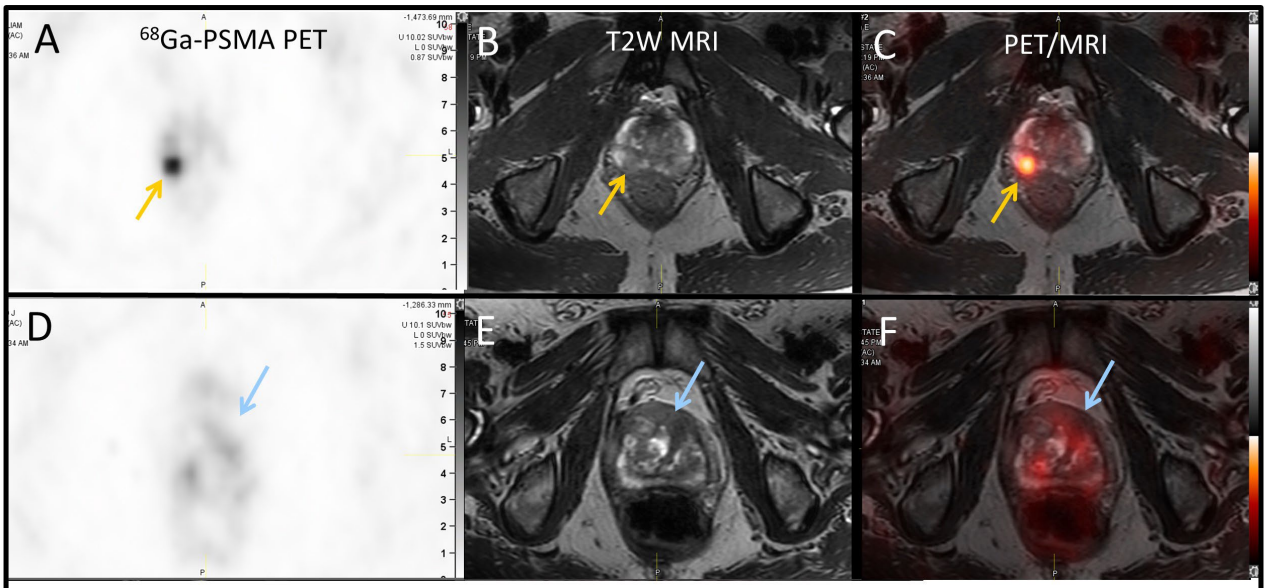


Figure 1: Co-registered axial ^{68}Ga-PSMA PET (A,D; SUV range 0 – 10 for both scans), T2W MRI (B,E) and PET/MRI (C,F) of two subjects for which a mpMRI resulted in a PI-RADS 5 lesion. Upper panel (A-C), case 1: Gleason 4+3 cancer at the right apex (orange arrows), identified at targeted biopsy with intense focal ^{68}Ga-PSMA uptake (SUV median 7.0). Lower panel (D-F), case 2: targeted biopsy resulted in active and chronic granulomatous inflammation (blue arrows) without elevated ^{68}Ga-PSMA uptake (SUV median 1.4).

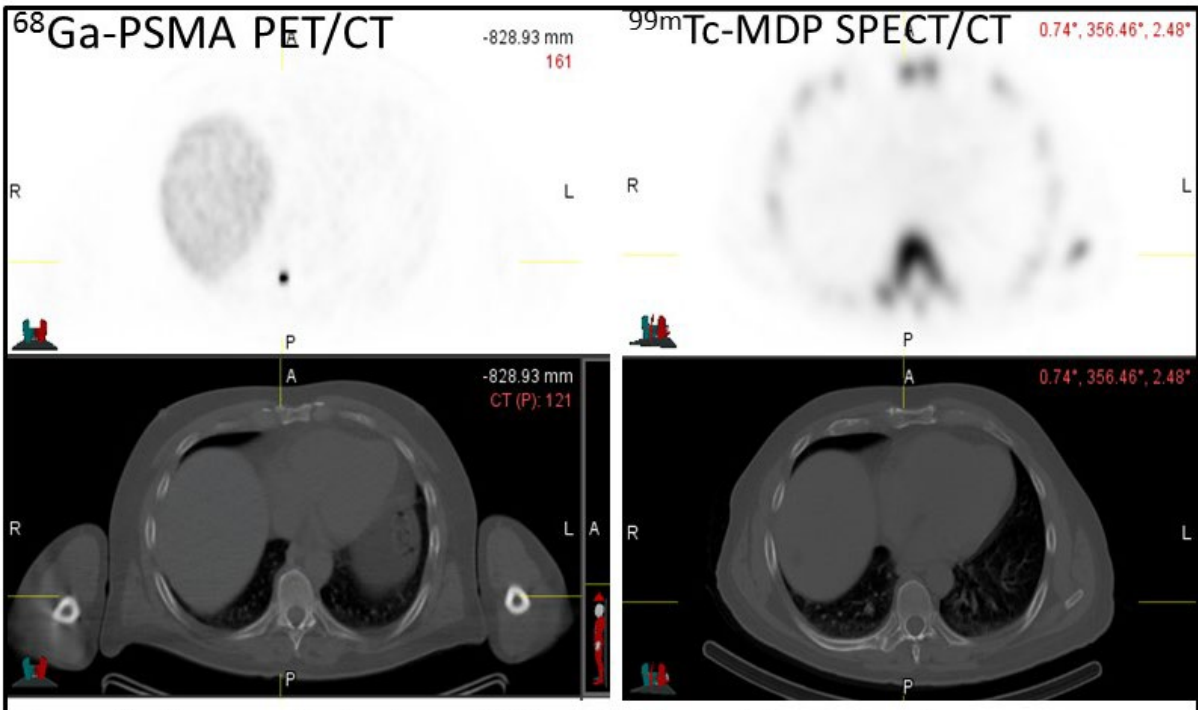


Figure 2: Bone metastasis on 68Ga-PSMA, undetected on bone scan.

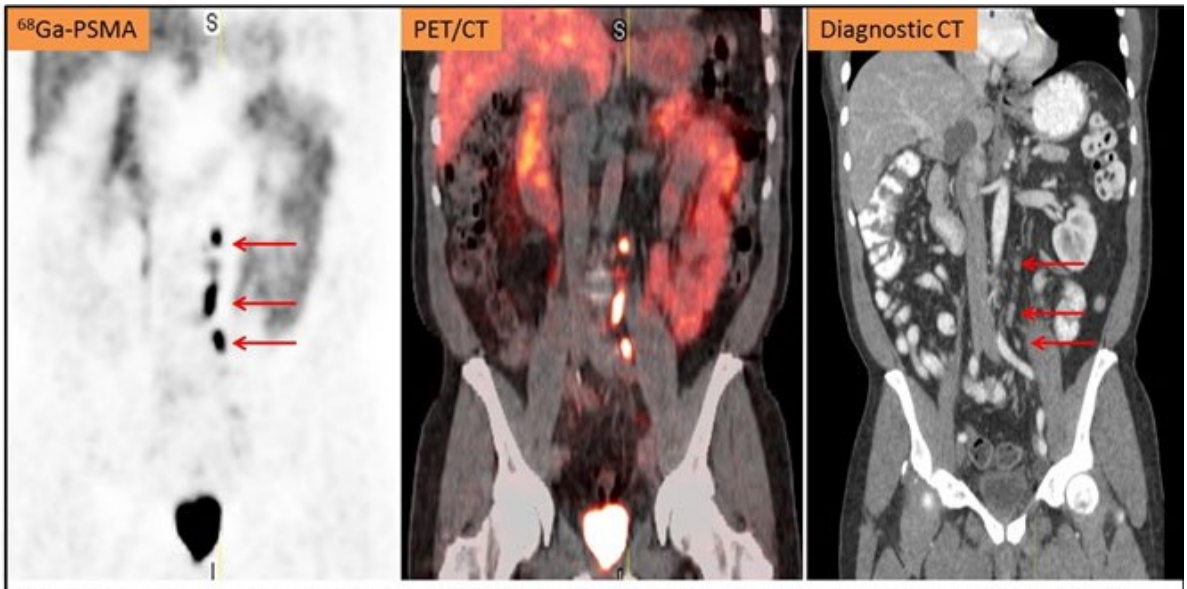


Figure 3: S/p prostatectomy (Gleason 4+4) and gradual PSA increase over 3 years to 11.2 ng/mL. Bone scan and diagnostic CT negative. 68Ga-PSMA shows positive retroperitoneal lymph nodes. Biopsy resulted positive for metastatic disease.

Because of the improved resolution and image quality with PET, ability to quantitate uptake, increased sensitivity compared to choline PET/CT, we intend to evaluate the utility of ^{68}Ga-

PSMA-11 in patient with BCR. We expect that the data from this study will support an NDA application to the FDA, which may ultimately lead to FDA approval for the United States.

1.3 Patient Population

Arm 1 (Prostate cancer patients)

Patients with biochemical recurrence after prostatectomy or radiation therapy:

- Post radical prostatectomy (RP) – AUA recommendation *
  - PSA greater than 0.2 ng/mL measured more than 6 weeks after RP and,
  - Confirmatory persistent PSA greater than 0.2 ng/mL.
- Post-radiation therapy –ASTRO-Phoenix consensus definition **
  - Nadir + greater than or equal to 2 ng/mL rise in PSA.

  * Biochemical recurrence will be defined using the AUA and ASTRO-Phoenix definitions. Specifically, post radical prostatectomy (RP) – AUA recommendation[39] is PSA greater than 0.2 ng/mL measured 6–13 weeks after RP and confirmatory persistent PSA greater than 0.2 ng/mL.

  ** Post-radiation therapy – ASTRO-Phoenix consensus definition[40] nadir + greater than or equal to 2 ng/mL rise in PSA.

Arm 2 (Physicians/practitioners)

Physicians/practitioners of study arm 1 patients will be surveyed to assess whether ^{68}Ga PSMA-HBED-CC PET/CT has an impact on the clinical management of their respective patients.

2 Objectives of the Study

2.1 Primary

- Determine the positive predictive value (PPV) of ^{68}Ga PSMA-11 PET/CT for detecting prostate cancer on a per-patient basis, confirmed by histopathology.

2.2 Secondary

- Determine sensitivity and PPV on a per-patient and per-region-basis of ^{68}Ga-PSMA-11 PET/CT for detection of tumor location confirmed by conventional imaging, clinical follow-up, and histopathology/biopsy where available.
- Determine detection rates on a per-subject basis of ^{68}Ga PSMA-11 PET/CT stratified by PSA value (0.2 - <0.5, 0.5 - <1.0, 1.0 - <2.0, 2.0 - < 5.0, 5.0 or greater).
- Determine the impact of ^{68}Ga PSMA-11 PET/CT on clinical management in patients who have prostate cancer with biochemical recurrence.

- Continue to evaluate safety of ^{68}Ga-PSMA-11.

2.3 Endpoints

2.3.1 Primary Endpoints

- Per patient ^{68}Ga-PSMA-11 positivity.
- Histological correlation with ^{68}Ga-PSMA-11 lesion results.

2.3.2 Secondary Endpoints

- Per patient and per region detection sensitivity and PPV using a combined histology and conventional imaging correlate. *
- Change in management: survey based results. *
- Safety: blood pressure, heart rate, self-reported adverse events. *

Note: * secondary endpoints are assessed at central data analysis in the entire patient population (n=1500) across participating institutions (see section 8.3.3)

Table 1

Region	Description
1	Prostate Bed
2	Pelvis outside of prostate bed including lymph nodes
3	Extrapelvic soft tissue, lymph nodes and organ metastases (non-bone)
4	Bone metastases

3 Study Design

3.1 Characteristics

This is a prospective, phase 2, open-label study in patients with prostate cancer performed at the University of Michigan. Eligible participants will undergo baseline assessments at enrollment. Study participants will receive a one-time administration of Gallium-68 PSMA-11 and undergo a PET/CT imaging study.

3.1 Number of Subjects

It is anticipated that in study arm 1 up to 750 patients will be enrolled at the University of Michigan in this study. Total population of patients will be 1,500 patients across participating institutions.

The total number of physicians/practitioners (study arm 2) will be small, but theoretically be as high as 750.

3.2 Eligibility Criteria

Patients must have baseline evaluations performed prior to the administration of the radiopharmaceutical and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.2.1 Inclusion Criteria

1. Histopathological proven prostate adenocarcinoma.
2. Rising PSA after definitive therapy with prostatectomy or radiation therapy (external beam or brachytherapy).
    a. Post radical prostatectomy (RP) – AUA recommendation
        i. PSA greater than 0.2 ng/mL measured more than 6 weeks after RP and,
        ii. Confirmatory persistent PSA greater than 0.2 ng/mL
    b. Post-radiation therapy –ASTRO-Phoenix consensus definition
        i. Nadir + greater than or equal to 2 ng/mL rise in PSA
3. Karnofsky performance status of ≥ 50 (or ECOG/WHO equivalent).
4. Age ≥ 18.
5. Ability to understand a written informed consent document, and the willingness to sign it.

3.2.2 Exclusion Criteria

1. Current investigational therapy for prostate cancer.
2. Unable to lie flat, still or tolerate a PET scan.
3. Prior history of any other malignancy within the last 2 years, other than skin basal cell or cutaneous superficial squamous cell carcinoma that has not metastasized and superficial bladder cancer.
4. Prisoner.

3.3 Duration of Follow Up

3.3.1 Active Safety Follow-up

Patients will be followed for acute adverse events for one day (allowed range 1 to 3 calendar days) after the administration of the radiopharmaceutical.

3.3.2 Long-term Follow-up

After the active safety follow-up period, the subject will return to standard follow-up with their physician. Subject's outcome will be followed through passive chart review. Contact with subject and/or subject's treating physicians may occur to better define treatment outcomes.

3.4 Study Timeline

3.4.1 Primary Completion

The study is expected to reach completion of active recruitment 36 months from the time the study opens to accrual.

3.4.2 Study Completion

The study is expected to reach its final completion 48 months from the time the study opens to accrual.

4 Study Drugs

4.1 Description, Supply and Storage of Investigational Drugs

4.1.1 Investigational Drug #1

Gallium-68 labeled PSMA-11 (or PSMA-HBED-CC) is a radiopharmaceutical that will be produced under cGMP at the Cyclotron Radiochemistry of the University of Michigan as described in IND #133858. Inventory recordkeeping requirements, disposition, handling, etc. of the radioactive product is regulated by the NRC. The local regulatory body is the SHUR committee as part of the IRB process.

4.1.2 Furosemide (optional)

Description of furosemide (Trade name: Lasix) Source: Sanofi-Aventis.

A dose of 20 mg of furosemide (Lasix) may be injected i.v. together with, shortly before or after administration of the radiotracer ^{68}Ga-PSMA in order to minimize PET scatter artifacts from excreted radiotracer accumulation in the kidney and urinary bladder. Patients with known adverse effects to furosemide may participate in the study but will not receive Furosemide IV. Potential adverse effects of furosemide include urticaria, rash, and anaphylaxis (rare).

5 Treatment Plan

5.1 Dosage and Administration

The imaging agent (^{68}Ga-PSMA-11) will be administered. It will be administered a single time intravenously prior to the PET imaging. The one-time nominal injected dose will be 3 to 7 mCi of ^{68}Ga-PSMA-11.

5.1.1 Other Modality(ies) or Procedures

5.1.1.1 Change in Management Surveys

Referring clinicians will be required to fill out a pre-imaging survey prior to imaging. Additionally, within 30 days of the completion of imaging, the referring physician will be requested to fill out a post-imaging physician survey, and finally six months (allowed range 3 – 12 months) after imaging, a third physician survey will be filled out.

5.1.1.2 PET Imaging

a) ^{68}Ga-PSMA-11 PET preparation and injection:

The injected dose will be 111-259 MBq (3-7 mCi) of ^{68}Ga-PSMA-11 PET. PET imaging will begin 50-100 minutes after injection (target 75 minutes). Scan time per bed position will be determined based on expected count statistics related to the administered dose.

b) Patient preparation: no fasting is required. Participants will be asked to void prior to radiotracer injection.

c) Furosemide administration: A single dose of 20 mg of furosemide (Lasix) may be administered i.v. together with, shortly before or after administration of the radiotracer in order to minimize PET scatter artifacts from excreted radiotracer accumulation in the kidney and urinary bladder. Furosemide should not be administered in subjects with medical contraindications to furosemide administration including allergies and adverse reactions including sulfa allergies.

d) PET protocol: Scan coverage will extend from mid-thigh to the base of the skull, starting from the mid-thighs to prevent urinary bladder radiotracer accumulation at the start of PET imaging. Additional body parts may be included as deemed necessary based on clinical information, including information from prior diagnostic scans. Scan time per bed position will be determined based on expected count statistics, which is determined mainly by the administered dose. Scan time will therefore be between 15 and 40 minutes.

e) Patient monitoring: Vital signs will be assessed immediately before and after injection of ^{68}Ga-PSMA-11 (HR and supine BP). Patients will be monitored for adverse events during injection and for two hours after radiotracer administration. Additionally, patient's vitals (HR and supine BP) will be checked at the completion of the imaging study prior to leaving the imaging center.

f) Results dissemination. Scan results will be shared with the subject's clinician and will be reported and stored in the electronic medical record.

5.2 Monitoring and Toxicity Management

Each patient receiving ^{68}Ga-PSMA-11 will be evaluable for safety. The safety parameters include physical findings and spontaneous reports of adverse events reported to the investigator by patients.

5.3 Follow-up Standard of Care Imaging

All subjects should be followed as per standard of care consistent with the institution/physician. Reports and copies of any conventional imaging obtained during the 12-month window following the ^{68}Ga-PSMA-11 scan will be obtained. Clinical notes will also be reviewed to identify metastatic lesions. Interpretation of follow-up imaging is performed by local institution following standard procedures. Preferable comparison imaging would be the same imaging device as the initial re-staging work-up as per RECIST guidelines. ^{68}Ga-PSMA-11 positive findings will be validated as true positive or false positive as outlined in greater detail below.

5.3.1.1 PSMA-positive Lymph Nodes

^{68}Ga-PSMA-11 positive nodes will be assessed for change in size using standard of care follow-up imaging.

5.3.1.2 PSMA-positive Osseous or Metastatic Lesions

^{68}Ga-PSMA-11 positive osseous or distant metastatic lesions will be followed by other imaging (bone scan, 18F-NaF PET, CT or MRI) at the treating physician's discretion and local standard of care.

5.3.1.3 Biopsy

Biopsies are performed to determine presence of absence of prostate cancer at the discretion of treating physicians according to standard of care.

5.4 General Concomitant Medication and Supportive Care Guidelines

In general, subjects may receive full concomitant and supportive care throughout this trial.

6 Study Procedures and Observations

See also appendix 2 and 3.

6.1 Schedule of Procedures and Observations

Screening assessments must be performed within 30 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the electronic medical record. The original will be kept on file with the study records.

6.1.1.1 Screening Assessments

The Screening procedures and assessments must be completed within 30 days of the day 1 Visit.

- Laboratory values: all patients should have a recent PSA (within 30 days prior to study enrollment) consistent with BCR
- Pathology: all patients must have histopathology/biopsy of the prostate with a documented Gleason score
- Performance status: all patients must have their Karnofsky performance status (or ECOG/WHO equivalent) evaluated (Appendix 1).

6.1.2 Treatment Period

6.1.2.1 Study Procedures, Imaging Day 1

- Vital signs
- Evaluation of adverse events

6.1.3 Post-treatment Safety Follow Up

Patients will be followed for acute adverse events for one day (allowed range 1 to 3 calendar days) after the administration of the radiopharmaceutical.

- Evaluation of adverse events

6.2 Prohibited Medications

There are no prohibited medications.

7 Reporting and Documentation of Results

7.1 Evaluation of Efficacy (or Activity)

7.1.1.1 Definitions

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of ^{68}Ga-PSMA-11 administration.

7.2 Evaluation of Safety

Analyses will be performed for all patients receiving ^{68}Ga-PSMA-11. The study will use the CTCAE v4.0 for reporting of adverse events.

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.3.2 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.3.2.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

7.3.2.3 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.3.2.4 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.4 Recording of an Adverse Event

All grade 3 and above adverse events will be recorded using the NCI CTCAE v4.0. The Investigator will assign attribution of the possible association of the event with use of the investigational drug.

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

7.5 Data and Safety Monitoring

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected cases in which the injection of the investigational radiotracer was stopped (for instance partial or complete paravenous injection), a repeat injection of the subject with the investigational radiotracer may be conducted if considered both safe and ethical by the Investigator.

This trial will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan. The study team will meet every 3 months or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness. At these regular meetings, the protocol specific Data and Safety Monitoring Report form will be completed and signed by the Principal Investigator or by one of the designated co-investigators.

Data and Safety Monitoring Reports will be submitted to the University of Michigan Rogel Cancer Center Data and Safety Monitoring Committee every 3 months for independent review.

7.6 Expedited Reporting

Reporting to the Institutional Review Board

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the University of Michigan IRB within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Expedited Reporting to the Food and Drug Administration

As the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in 7.3.2.1)
- Unexpected (as defined in 7.3.2.2)
- Serious (as defined in 7.3.2.3)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

8 Statistical Considerations and Evaluation of Results

8.1 Study Endpoints

- Per patient ^{68}Ga-PSMA-11 positivity.
- Histological correlation with ^{68}Ga-PSMA-11 lesion results.

8.1.1 Randomization

There will be no randomization performed. There will be no blinding performed.

8.2 Determination of Sample Size and Accrual Rate

8.2.1 Sample Size and Power Estimate

The primary endpoint is to evaluate the positive predictive value (PPV) (true positives / (true positives + false positives)) of ^{68}Ga-PSMA-11 PET for presence or absence of prostate cancer

confirmed by histopathology on a per-patient basis. It is anticipated that – on a per-patient basis - the PPV of conventional imaging ranges between 30-50%. An overall PPV for ^{68}Ga-PSMA-11 PET of at most 50% will be considered as unacceptably low. Hence, the null hypothesis that the PPV is at most 50% will be tested against the alternative hypothesis that the PPV is greater than 50%.

Given recently published data from ^{68}Ga-PSMA-11 indicating a substantially higher PPV than previously assumed [41], we now hypothesize that ^{68}Ga-PSMA-11 PET imaging will substantially increase the PPV to at least 75% in our patient population.

We previously expected that approximately 25% of the accrued patients will undergo a biopsy and 95% of the biopsied patients will have positive ^{68}Ga-PSMA-11 PET scan at the biopsied site (about 5% of patients may receive a biopsy of a ^{68}Ga-PSMA-11 negative site, which was however identified on conventional imaging). However, we were able to obtain biopsies from ^{68}Ga-PSMA-11 positive lesions in only 13 of 316 evaluable subjects, and no biopsies of ^{68}Ga-PSMA-11 negative lesions identified by conventional imaging were obtained.

When 750 (instead of 375) patients are accrued at the University of Michigan, we now expect that about 24 patients who are to receive a biopsy will receive the biopsy of a ^{68}Ga-PSMA-11 positive lesion. Then, the attainable power is estimated at 80% for detecting an increase in the PPV from 50% to 75% at the one-sided 0.05 significance level.

Within the first secondary objective, the region-specific PPV will be determined (confirmed by conventional imaging, clinical follow-up, and/or histopathology/biopsy where available). Based on the results of previous studies, the following distribution of biopsied disease across the four regions are anticipated [1,2]:

a) Prostate bed: 30%
b) Pelvis: 15%
c) Extrapelvic soft tissue: 20%
d) Bone metastases: 35%

In summary, a sample size of 750 UM patients would be sufficient to achieve adequate power for detecting an increase in the per-patient PPV from 50% to 75% for the primary objective. Regarding the first secondary objective (region-specific PPV), the per-region tests would have adequate power in the 1,500 pooled sample from all participating sites.

8.3 Analyses Plans

8.3.1 Analysis Population

Patients with histopathology correlates will be analyzed for the primary aim. All remaining patients will be analyzed for the secondary endpoints.

8.3.2 Scan Interpretations

^{68}Ga-PSMA-11 PET/CT images will initially be interpreted by a board certified nuclear medicine physician or a board-certified radiologist experienced in reading PET/CT at the time of the imaging study at the institution that the study is being performed. These interpretations will be made available to the treating physician and will become part of the patient's electronic record. These interpretations will however not be used for final evaluation.

8.3.3 Central Data Analysis

Anonymized coded patient information (case report forms) will be captured in a central REDCap database hosted at the University of California at San Francisco (UCSF).

Anonymized and de-identified imaging data will be uploaded to a central website hosted at the Clinical Trials Network (CTN). PET data will be interpreted by three different readers in a random order at separate reading sessions. Cross sectional imaging (CT) obtained with the ^{68}Ga PSMA-11 PET will be available as anatomic correlate.

Central Read Interpretation: Final reads by the central read physicians for each subject will be interpreted as positive or negative for the presence of disease in the regions defined in section 8.2.1 (see table).

Reader Positivity and Negativity Definition: Regions of suspected disease will be graded on a two-point scale by each reader (0=Negative or 1=Positive). A region will be judged as positive if at least one lesion in this region is visually positive. Criteria for visual interpretation is described in section 8.3.3.

Reader Training: ^{68}Ga PSMA-11 PET/CT reading training set and guides will be provided and completion of this training will be required for all central review readers.

Case report forms will be provided to the FDA for review, when requested.

8.3.4 Analysis of Primary Endpoints

Primary endpoint: PPV on a per-patient basis of ^{68}Ga-PSMA-11 PET for detection of prostate cancer confirmed by histopathology will be calculated and reported along with the corresponding two-sided 95% confidence intervals. The confidence intervals will be constructed using the Wilson score method.

a) Imaging interpretation ^{68}Ga-PSMA-11 PET:

   PET images will initially be interpreted by a board certified nuclear medicine physician or a board certified radiologist experienced in reading PET at the time of the imaging study at the University of Michigan. These interpretations will not be used for final evaluation. Upon request, anonymized ^{68}Ga-PSMA PET/CT imaging data are sent to the FDA for further review.

   Visual interpretation:

   Regions of suspected disease will be graded on a two-point scale by each reader (0=Negative or 1= Positive). A region will be judged as positive if at least one lesion in this region is visually positive.

   i) Lymph nodes will be considered positive if the ^{68}Ga-PSMA-11 uptake is focal and greater than blood pool (adjacent or mediastinal blood pool). Pelvic lymph nodes will be subclassified according to their localization as follows: R/L obturator, R/L external iliac, R/L internal iliac and other (total of 7 subgroups).

   ii) Visceral lesions will be considered positive if the ^{68}Ga-PSMA-11 uptake is focal and greater than physiologic background activity of the involvement organ or anatomic site.

iii) Bone lesions will be considered positive if the ^{68}Ga-PSMA-11 uptake is focal and greater than physiologic bone marrow.

iv) Prostate bed and prostate lesions will be considered positive if the ^{68}Ga-PSMA-11 uptake is focal and greater than physiologic background activity of the involvement organ or anatomic site.

b) Follow-up Imaging:

All patients are expected to be followed up as part of clinical care within 3-12 months with conventional imaging (dedicated CT, MRI and/or bone scan). Interpretation of follow-up imaging will be performed by local read. The follow-up conventional imaging should be the same modality/modalities as the initial staging work-up to allow reproducible and accurate comparisons.

^{68}Ga-PSMA-11 PET positive findings will be validated as true or false positive as outlined in more detail below. False negative ^{68}Ga-PSMA-11 PET findings may be determined based on biopsies obtained from lesion identified on conventional imaging that are negative on ^{68}Ga-PSMA-11.

Rationale for applied response criteria:

RECIST 1.1 defines a size decrease of at least 30% as response (either partial or complete), while an increase of at least 20% is considered progressive disease [42,43]. The decline of serum PSA of 50% or more is a commonly used criterion for treatment response following systemic treatment of metastatic prostate cancer [44-46].

Following the ^{68}Ga-PSMA-11 PET/CT scan, focal therapies of metastatic lesions may be performed without systemic treatment. Therefore, anatomic size variations can be suitable endpoints in absence of histological verification. In patients with solitary lesions, PSA reductions following focal treatment may indicate a true positive scan finding even in absence of significant size changes.

^{68}Ga-PSMA-11 PET validation based on follow-up imaging:

i) Lymph nodes will be assessed by change in size. ^{68}Ga-PSMA-11 positive lymph nodes will be considered:

(1) True positive:

- If on follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI decrease by more than 30% (for patients undergoing systemic treatment of focal therapy at this site) or increase by more than 20% in short axis diameter (with a minimum of 3 mm in change in size).

- If patients with solitary lymph node regions show a decrease of PSA by greater than 50% after targeted treatment (i.e. external beam radiation) and the lymph nodes do not change in size (less than 30% decrease or less than 20% increase in short axis diameter).

(2) False positive:

- If on follow-up imaging within 3-12 months, sites of initial ^{68}Ga-PSMA-11 positive lymph node lesions seen on CT or MRI decrease by more than 30% *without* systemic therapy or focal therapy at this site.

- If ^{68}Ga-PSMA-11 positive lymph node lesions do not meet the criteria for above false positive or true positive findings.

ii) Visceral lesions (non-lymph node soft tissue or organ) will be assessed by change in size. ^{68}Ga-PSMA-11 positive visceral lesions will be considered:

(1) True positive:

- If on follow-up imaging within 3-12 months, visceral lesions seen on CT or MRI decrease by 30% (for patients undergoing systemic treatment of focal therapy at this site) or increase by 20% in largest diameter.

- If patients with solitary visceral metastasis show a decrease of PSA by greater than 50% after targeted treatment (i.e. external beam radiation) and lesions do not change in size (less than 30% decrease or 20% increase in largest diameter).

(2) False positive:

- If on follow-up imaging within 3-12 months, sites of initial ^{68}Ga-PSMA-11 positive lymph node lesions seen on CT or MRI decrease by more than 30% *without* systemic therapy or focal therapy at this site.

- If ^{68}Ga-PSMA-11 positive lymph node lesions do not meet the criteria for above false positive or true positive findings.

iii) ^{68}Ga-PSMA-11 positive bone lesions will be considered:

(1) True positive:

- If there was a corresponding positive sclerotic lesion on the CT portion of the ^{68}Ga-PSMA-11 PET.

- If there is focal uptake seen on the baseline bone scan performed within one month of ^{68}Ga-PSMA-11 PET.

- If there is a lesion noted on the initial MRI performed within one month of ^{68}Ga-PSMA-11 PET.

- If within 12 months follow-up CT demonstrates development of sclerosis.

- If within 12 months follow-up MRI demonstrates a new bone lesion.

- If within 12 months follow-up bone scan demonstrates new focal uptake.

(2) False positive:

- If ^{68}Ga-PSMA-11 positive bone lesions do not meet the criteria for true positive findings.

iv) ^{68}Ga-PSMA-11 positive prostate bed and prostate lesions will be considered:

(1) True positive:

- If on follow-up imaging within 12 months, lesions seen on CT or MRI decrease by 30% (for patients undergoing systemic treatment of focal therapy at this site) or increase by 20% in largest diameter.

- If patients with prostate bed lesions show a decrease of PSA by greater than 50% after targeted treatment (i.e. external beam radiation) and lesions do not change in size (less than 30% decrease or 20% increase in largest diameter).

(2) False positive:

- If on follow-up imaging within 3-12 months, sites of initial ^{68}Ga-PSMA-11 positive lymph node lesions seen on CT or MRI decrease by more than 30% *without* systemic therapy or focal therapy at this site.

- If ^{68}Ga-PSMA-11 positive lymph node lesions do not meet the criteria for above false positive or true positive findings.

c) Histopathology/Biopsy:

i) Localization of lesions for histopathology/biopsy will be a classified according to the regions in table 1.

ii) ^{68}Ga-PSMA-11 positive findings are aimed to be confirmed by histopathology/biopsy if clinically feasible.

iii) Histopathological procedures and biopsies will be performed as clinically indicated and as per institutional protocol.

(1) Positive HP/Biopsy: Confirmed sites of metastatic or tumor involvement by histopathology/biopsy will be discussed with the responsible physician/surgeon.

(2) Negative Biopsy: Patients with suspected tumor recurrence on ^{68}Ga-PSMA-11 PET with negative histopathology/biopsy will be handled as outlined below:

(a) Lymph nodes:

- For patients undergoing nodal dissection: Patients will be rescanned with dedicated CT or MRI to determine if the suspicious ^{68}Ga-PSMA-11 positive node was removed.

1. If ^{68}Ga-PSMA-11 positive lymph node is still present, a repeat biopsy can be pursued if clinically feasible and applicable, or follow-up using imaging as described above will be performed.

2. If the corresponding node was removed, then this will be considered a False Positive.

- For patients undergoing needle biopsy: Images of the procedure will be reviewed to determine if the correct node was biopsied.

1. If the correct node was biopsied, then a negative biopsy will be considered a False Positive.

2. If the incorrect node was biopsied, then follow-up imaging as described above will be performed.

(b) Bone lesions: Given the high rate of false negative biopsies for osseous metastases in patients with prostate cancer, patients with negative bone biopsies of PSMA PET positive lesions will be further evaluated:

- If pathology demonstrates an alternative diagnosis that is known to be PSMA positive (eg Renal Cell Carcinoma metastases, Paget's disease), then this will be considered a False Positive.
- If pathology is indeterminate, then follow-up imaging as described above will be performed to determine if the lesion is a True Positive or False Positive.
- Additionally, a repeat ^{68}Ga-PSMA-11 can also be obtained, as allowable, in addition to repeat conventional imaging (CT and/or MRI) in cases of negative biopsy to determine if the biopsy was true negative or false negative.

(3) Although not routinely performed during standard practice, immunohistochemical staining for PSMA of tumor specimens (primary and lymph node metastases) may be performed, although not required.

8.3.5 Central Analysis of Secondary Endpoints

1. PPVs on a per-patient and per-region-basis of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy and conventional imaging follow-up will be calculated and reported along with the corresponding two-sided 95% confidence intervals. The confidence intervals will be constructed using the Wilson score method.

2. Sensitivity on a per-patient and per-region basis of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy will be summarized in tabular format. Ninety-five percent confidence intervals of sensitivity and PPV will be calculated using the Wilson score method.

3. Detection rates on a per-patient basis of ^{68}Ga-PSMA-11 PET stratified by PSA value (0.2 - <0.5, 0.5 - <1.0, 1.0 - <2.0, 2.0 - <5.0, 5.0) will be summarized in tabular format and compared between PSA strata using chi-square analysis.

4. The impact of ^{68}Ga-PSMA-11 PET on clinical management in BCR patients will be evaluated using surveys of the treating physician or practitioner before, at 1 (2-30 days) and 6 (range 3 - 12) months after the ^{68}Ga-PSMA-11 PET scan (see data collection sheet, section 44 eResearch). The results will be analyzed and provided in coded form for central analysis.

5. Safety will be reported descriptively as rates of patient reported adverse events.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the University of Michigan Institutional Review Board (IRB) including the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the approved informed consent form 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 research file and a copy may be stored in the electronic medical record.

9.4 Changes in the Protocol

Once the protocol has been approved by the University of Michigan IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be submitted by the Investigator and approved by PRC and IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, the study will be halted and the IRB will be informed within five (5) working days.

10 Protection of Human Subjects

10.1 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the informed consent document. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

Appendices

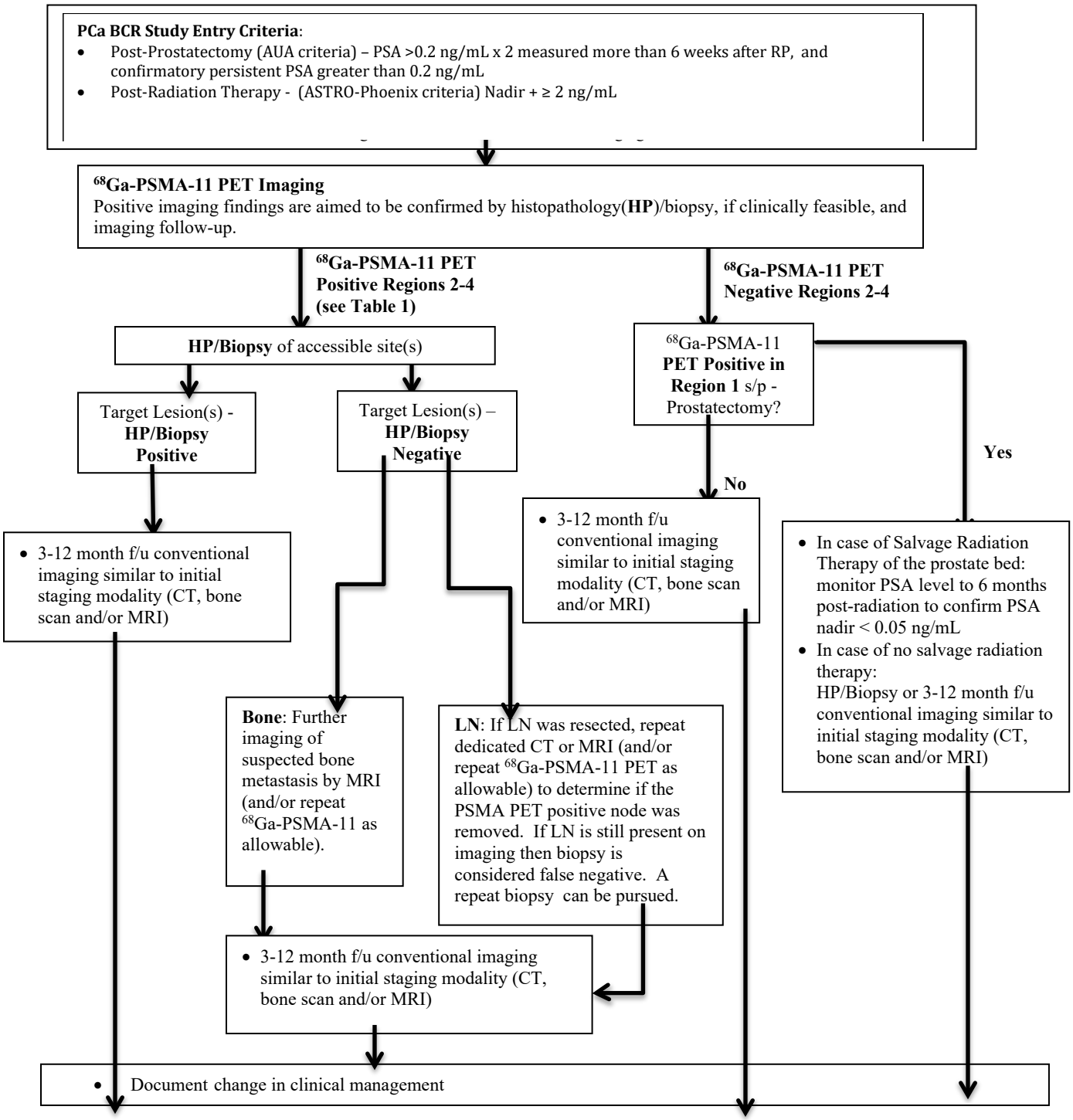
Appendix 1 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed <=50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed >=50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2 Schedule of Study Procedures and Assessments

Schedule of Study Procedures and Assessments				
Period/ Procedure	**Screening**	**Imaging day 1**	**One day post imaging**	**Follow-up surveys**
Study Day/Visit Day	-30 to 1	1	2 (allowed range day 2-4)	
Informed consent	X			
Laboratory values, history from medical record	X			
Pre-survey	X			
Performance status	X			
Blood Pressure, HR	X	X		
Imaging Procedure				
^{68}Ga-PSMA-11		X		
PET/CT or PET/MRI		X		
Furosemide 20 mg IV		X		
Follow-up				
Adverse event reporting			X	
1. Post-survey (within 2-30 days of PET)				X
2. Post-survey (within 3-12 months of PET)				X

Appendix 3 (Flow chart)



References

1. Edwards BK, Noone AM, Mariotto AB, et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer* 2014; **120**(9): 1290-314.
2. van den Bergh RC, van Casteren NJ, van den Broeck T, et al. Role of Hormonal Treatment in Prostate Cancer Patients with Nonmetastatic Disease Recurrence After Local Curative Treatment: A Systematic Review. *Eur Urol* 2016; **69**(5): 802-20.
3. Amling CL, Blute ML, Bergstralh EJ, Seay TM, Slezak J, Zincke H. Long-term hazard of progression after radical prostatectomy for clinically localized prostate cancer: continued risk of biochemical failure after 5 years. *J Urol* 2000; **164**(1): 101-5.
4. Beresford MJ, Gillatt D, Benson RJ, Ajithkumar T. A Systematic Review of the Role of Imaging before Salvage Radiotherapy for Post-prostatectomy Biochemical Recurrence. *Clin Oncol-Uk* 2010; **22**(1): 46-55.
5. Fu AZ, Tsai HT, Haque R, et al. Mortality and Androgen Deprivation Therapy as Salvage Treatment for Biochemical Recurrence after Primary Therapy for Clinically Localized Prostate Cancer. *J Urol* 2016.
6. Duchesne GM, Woo HH, Bassett JK, et al. Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. *Lancet Oncol* 2016; **17**(6): 727-37.
7. Bratan F, Niaf E, Melodelima C, et al. Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study. *Eur Radiol* 2013; **23**(7): 2019-29.
8. Luboldt W, Kufer R, Blumstein N, et al. Prostate carcinoma: diffusion-weighted imaging as potential alternative to conventional MR and 11C-choline PET/CT for detection of bone metastases. *Radiology* 2008; **249**(3): 1017-25.
9. Oyen RH, Van Poppel HP, Ameye FE, Van de Voorde WA, Baert AL, Baert LV. Lymph node staging of localized prostatic carcinoma with CT and CT-guided fine-needle aspiration biopsy: prospective study of 285 patients. *Radiology* 1994; **190**(2): 315-22.
10. Contractor K, Challapalli A, Barwick T, et al. Use of [11C]choline PET-CT as a noninvasive method for detecting pelvic lymph node status from prostate cancer and relationship with choline kinase expression. *Clin Cancer Res* 2011; **17**(24): 7673-83.
11. Price DT, Coleman RE, Liao RP, Robertson CN, Polascik TJ, DeGrado TR. Comparison of [18 F]fluorocholine and [18 F]fluorodeoxyglucose for positron emission tomography of androgen dependent and androgen independent prostate cancer. *The Journal of Urology* 2002; **168**(1): 273-80.
12. Castellucci P, Ceci F, Graziani T, et al. Early biochemical relapse after radical prostatectomy: which prostate cancer patients may benefit from a restaging 11C-Choline PET/CT scan before salvage radiation therapy? *J Nucl Med* 2014; **55**(9): 1424-9.
13. Brogsitter C, Zophel K, Kotzerke J. F-Choline, C-choline and C-acetate PET/CT: comparative analysis for imaging prostate cancer patients. *European Journal of Nuclear Medicine and Molecular Imaging* 2013.
14. Picchio M, Spinapolice EG, Fallanca F, et al. [11C]Choline PET/CT detection of bone metastases in patients with PSA progression after primary treatment for prostate cancer: comparison with bone scintigraphy. *Eur J Nucl Med Mol Imaging* 2012; **39**(1): 13-26.
15. Souvatzoglou M, Krause BJ, Purschel A, et al. Influence of (11)C-choline PET/CT on the treatment planning for salvage radiation therapy in patients with biochemical recurrence of prostate cancer. *Radiother Oncol* 2011; **99**(2): 193-200.

16. Castellucci P, Fuccio C, Rubello D, et al. Is there a role for (11)C-choline PET/CT in the early detection of metastatic disease in surgically treated prostate cancer patients with a mild PSA increase <1.5 ng/ml? *European Journal of Nuclear Medicine and Molecular Imaging* 2011; **38**(1): 55-63.
17. Giovacchini G, Picchio M, Scattoni V, et al. PSA doubling time for prediction of [(11)C]choline PET/CT findings in prostate cancer patients with biochemical failure after radical prostatectomy. *Eur J Nucl Med Mol Imaging* 2010; **37**(6): 1106-16.
18. Fuccio C, Castellucci P, Schiavina R, et al. Role of 11C-choline PET/CT in the restaging of prostate cancer patients showing a single lesion on bone scintigraphy. *Ann Nucl Med* 2010; **24**(6): 485-92.
19. Budiharto T, Joniau S, Lerut E, et al. Prospective evaluation of 11C-choline positron emission tomography/computed tomography and diffusion-weighted magnetic resonance imaging for the nodal staging of prostate cancer with a high risk of lymph node metastases. *Eur Urol* 2011; **60**(1): 125-30.
20. Barrio M, Fendler WP, Czernin J, Herrmann K. Prostate specific membrane antigen (PSMA) ligands for diagnosis and therapy of prostate cancer. *Expert Review of Molecular Diagnostics* 2016; **16**(11): 1177-88.
21. Seltzer MA, Barbaric Z, Belldegrun A, et al. Comparison of helical computerized tomography, positron emission tomography and monoclonal antibody scans for evaluation of lymph node metastases in patients with prostate specific antigen relapse after treatment for localized prostate cancer. *J Urol* 1999; **162**(4): 1322-8.
22. Manyak MJ, Hinkle GH, Olsen JO, et al. Immunoscintigraphy with indium-111-capromab pendetide: evaluation before definitive therapy in patients with prostate cancer. *Urology* 1999; **54**(6): 1058-63.
23. Raj GV, Partin AW, Polascik TJ. Clinical utility of indium 111-capromab pendetide immunoscintigraphy in the detection of early, recurrent prostate carcinoma after radical prostatectomy. *Cancer* 2002; **94**(4): 987-96.
24. Afshar-Oromieh A, Zechmann CM, Malcher A, et al. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. *European Journal of Nuclear Medicine and Molecular Imaging* 2014; **41**(1): 11-20.
25. Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* 2015; **42**(2): 197-209.
26. Eiber M, Weirich G, Holzapfel K, et al. Simultaneous Ga-PSMA HBED-CC PET/MRI Improves the Localization of Primary Prostate Cancer. *Eur Urol* 2016; **70**: 829-36.
27. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid 68Ga-PSMA-ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med* 2015; **56**(5): 668-74.
28. Maurer T, Eiber M, Schwaiger M, Gschwend JE. Current use of PSMA-PET in prostate cancer management. *Nat Rev Urol* 2016.
29. Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al. Diagnostic performance of 68Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. *Eur J Nucl Med Mol Imaging* 2017.
30. Maurer T, Gschwend JE, Rauscher I, et al. Diagnostic Efficacy of (68)Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients with Intermediate to High Risk Prostate Cancer. *J Urol* 2016; **195**(5): 1436-43.
31. Perera M, Papa N, Christidis D, et al. Sensitivity, Specificity, and Predictors of Positive 68Ga–Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer: A Systematic Review and Meta-analysis. *European Urology* 2016; **70**(6): 926-37.

32. Roach PJ, Francis R, Emmett L, et al. The impact of 68Ga-PSMA PET/CT on management intent in prostate cancer: results of an Australian prospective multicenter study. *J Nucl Med* 2017.
33. Pyka T, Okamoto S, Dahlbender M, et al. Comparison of bone scintigraphy and 68Ga-PSMA PET for skeletal staging in prostate cancer. *European Journal of Nuclear Medicine and Molecular Imaging* 2016; **43**(12): 2114-21.
34. Silberstein JL, Pal SK, Lewis B, Sartor O. Current clinical challenges in prostate cancer. *Transl Androl Urol* 2013; **2**(3): 122-36.
35. van Leeuwen PJ, Stricker P, Hruby G, et al. (68) Ga-PSMA has a high detection rate of prostate cancer recurrence outside the prostatic fossa in patients being considered for salvage radiation treatment. *BJU Int* 2016; **117**(5): 732-9.
36. Gomez DR, Blumenschein GR, Jr., Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* 2016; **17**(12): 1672-82.
37. Decaestecker K, De Meerleer G, Ameye F, et al. Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP): study protocol for a randomized phase II trial. *BMC Cancer* 2014; **14**: 671.
38. Radwan N, Phillips R, Ross A, et al. A phase II randomized trial of Observation versus stereotactic ablative RadiatIon for OLigometastatic prostate CancEr (ORIOLE). *BMC Cancer* 2017; **17**(1): 453.
39. Cookson MS, Aus G, Burnett AL, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. *J Urol* 2007; **177**(2): 540-5.
40. Roach M, 3rd, Hanks G, Thames H, Jr., et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *International journal of radiation oncology, biology, physics* 2006; **65**(4): 965-74.
41. Fendler WP, Calais J, Eiber M, et al. Assessment of 68Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial. *JAMA Oncol* 2019.
42. Aras M, Erdil TY, Dane F, et al. Comparison of WHO, RECIST 1.1, EORTC, and PERCIST criteria in the evaluation of treatment response in malignant solid tumors. *Nucl Med Commun* 2016; **37**(1): 9-15.
43. Costelloe CM, Chuang HH, Madewell JE, Ueno NT. Cancer Response Criteria and Bone Metastases: RECIST 1.1, MDA and PERCIST. *J Cancer* 2010; **1**: 80-92.
44. Ryan CJ, Peng W, Kheoh T, et al. Androgen dynamics and serum PSA in patients treated with abiraterone acetate. *Prostate Cancer Prostatic Dis* 2014; **17**(2): 192-8.
45. Tanaka N, Nishimura K, Okajima E, et al. The efficacy and safety of docetaxel-based chemotherapy combined with dexamethasone 1 mg daily oral administration: JMTO Pca 10-01 phase II trial. *Jpn J Clin Oncol* 2017; **47**(3): 247-51.
46. Song G, Lee C, You D, et al. Prostate-specific antigen response rate of sequential chemotherapy in castration-resistant prostate cancer: the results of real life practice. *Prostate Int* 2013; **1**(3): 125-32.