MELVIN AND BREN SIMON CANCER CENTER
INDIANA UNIVERSITY

# The Role of $^{68}$Ga-PSMA-11 PET in Surgery Guidance in Prostate Cancer: A prospective Pilot trial

## INDIANA UNIVERSITY PROTOCOL

**IUSCCC-0760, IRB#11330**

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**IND#:** 141706

**Date of Protocol:** March 29, 2022

## INVESTIGATOR'S AGREEMENT

By signing below, I confirm that I have read this protocol and agree:

- To assume responsibility for the proper conduct of this study at this site
- To conduct the study according to the procedures described in this protocol and any future amendments
- Not to implement any deviation from, or changes to, the protocol without written approval from the Institutional Review Board (IRB), except where necessary to eliminate immediate hazard to the subject(s)
- That I am aware of all updates and will comply with all applicable regulations and guidelines

| Principal investigator's signature | Date |
|---|---|

Clinton D. Bahler, MD, MS

Principal investigator's name (print)

Assistant Professor of Urology,
Indiana University School of Medicine

Principal investigator's title (print)

# PROTOCOL SYNOPSIS

| | | |
|---|---|---|
| **Study Design:** | Prospective, pilot phase 2 clinical trial, single arm (non-randomized) | |
| **Test Factor/Exposure:** | PSMA PET-CT: $^{68}$Ga-PSMA-11 PET-CT with Siemens Biograph Vision scanner or similar PET-CT to guide surgical planning. This will be compared to the standard of care MRI. | |
| **Duration of Treatment:** | Patients will undergo injection of $^{68}$Ga-PSMA-11 PET-CT prior to definitive surgery. Quality-of-life will be tracked through 12-months follow-up. | |
| **Enrollment:** | n=55 | |
| **Primary Objective and Endpoint:** | **Objective**:<br>Obtain PSMA-PET imaging preoperatively and calculate performance for predicting extra-prostatic extension based on whole-mount pathology (gold standard). | **Endpoint**:<br>Sensitivity and Specificity for detecting extra-prostatic extension of cancer at the nerve bundles |
| **Secondary Objectives and endpoints** | **Objectives**:<br>1) Quantify the frequency of proper treatment changes directed by PSMA-PET, focusing on appropriate preservation of surrounding structures important for genito-urinary function including: 1) Bladder neck, 2) Nerve bundles, 3) Urethral Sphincter (Figure 4). | **Endpoints**:<br>1) Rate of treatment changes and rate of treatment changes that were appropriate based on pathology. |
| **Exploratory** | 2) Directly compare PSMA-PET performance for predicting extra-prostatic extension to standard-of-care assessments. | 2) Sensitivity/ Specificity/ PPV/ NPV for PSMA-PET vs. MRI vs. ultrasound-based nomogram. |

| | | |
|---|---|---|
| | 3) Assess quality of life changes from preoperative baseline.<br>4) To assess whether kinetic modeling tools are useful for improving detection of the location and extent of tumor in $^{68}$Ga-PSMA-11 PET/CT images (going beyond the standard PET map of regional radiotracer concentrations, additionally examining differences in regional pharmacokinetics to possibly further differentiate benign and neoplastic tissue). | 3) Quality-of-life: IIEF-15 (Erectile function score), EPIC-26 (Pad use), SF-36 (overall mental and physical health domains).<br>4) Qualitative and quantitative changes in PET image appearance after voxel-by-voxel application of kinetic modeling tools to define regional pharmacokinetics (compared to standard PET reconstructions showing simply the integrated concentration of regional radioactivity over the imaging period). |
| **Inclusion Criteria:** | **1.** Men diagnosed with clinically significant prostate cancer who are scheduled or scheduling for prostatectomy<br>**2.** Prostate pathology results consistent with:<br>a. Gleason 3+4 ≥1 core with pattern 4 ≥20% or<br>b. ≥3 cores of Gleason 3+4 or<br>c. NCCN unfavorable intermediate risk or<br>d. NCCN high-risk or<br>e. NCCN very-high risk<br>**3.** Scheduled for standard of care MRI or has recently completed standard of care MRI (within 6 months). Willing and able to lie still for approximately 50 minutes in an enclosed space for the PET/CT and MRI | |
| **Exclusion Criteria:** | **1.** Participation in another investigational trial involving research exposure to ionizing radiation concurrently or within 30 days.<br>**2.** Does not meet safety criteria for MRI scan (e.g. metal implant that could affect prostate imaging).<br>**3.** Significant acute or chronic medical, neurologic, or illness in the subject that, in the judgment of the Principal Investigator, could compromise subject safety, limit the ability to complete the study, and/or compromise the objectives of the study. | |

| | |
|---|---|
| **Number of Sites:** | Indiana University Simon Cancer Center, IU Health University Hospital, IU Health North, IU Health North medical office building, IU Health Schwarz Cancer Center, IU Health Methodist Hospital, IU Health Neuroscience Center/Goodman Hall |

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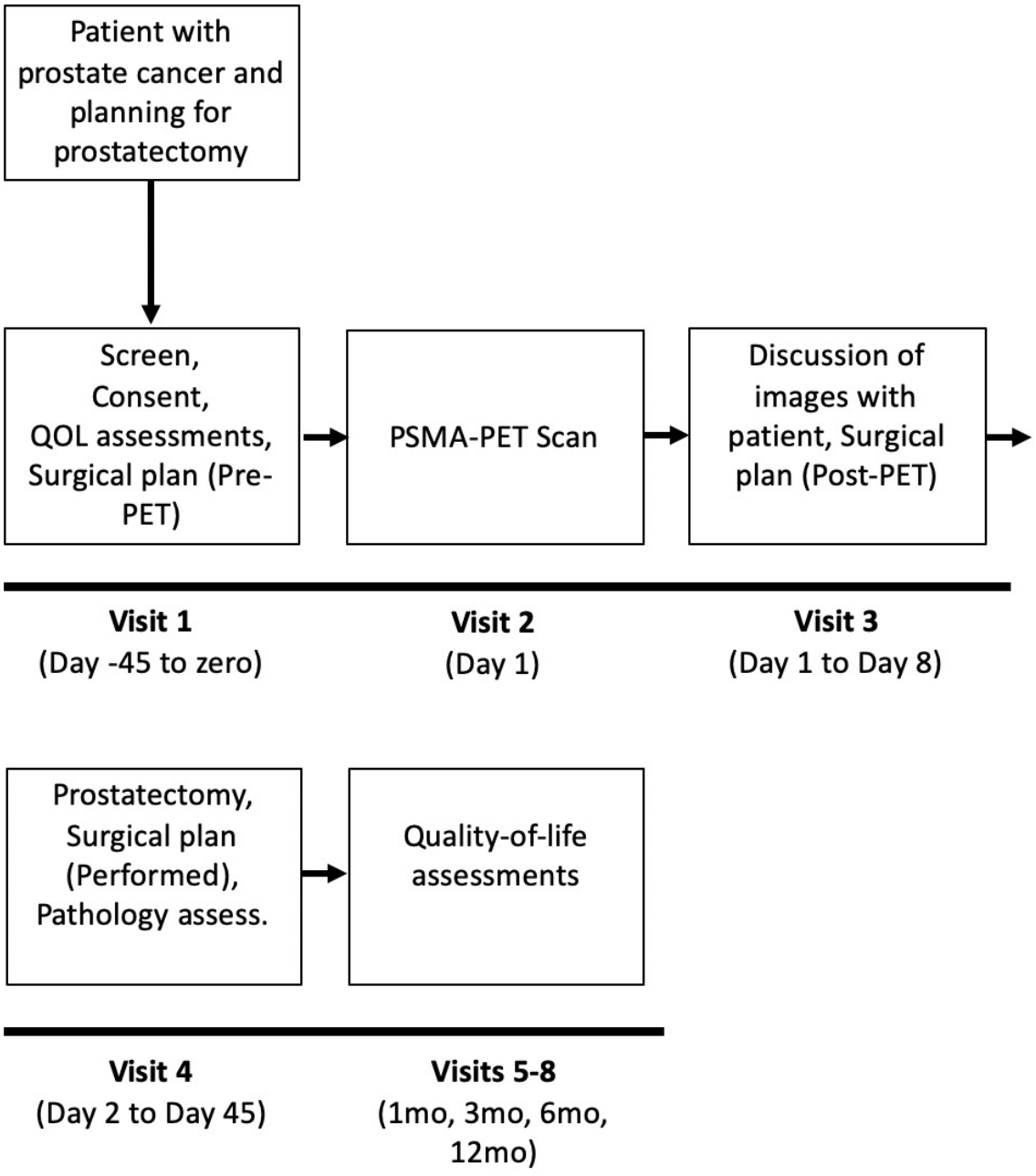
## 2 SCHEMA


Patient with prostate cancer and planning for prostatectomy
Screen, Consent, QOL assessments, Surgical plan (Pre-PET)
PSMA-PET Scan
Discussion of images with patient, Surgical plan (Post-PET)
Visit 1 (Day -45 to zero)
Visit 2 (Day 1)
Visit 3 (Day 1 to Day 8)
Prostatectomy, Surgical plan (Performed), Pathology assess.
Quality-of-life assessments
Visit 4 (Day 2 to Day 45)
Visits 5-8 (1mo, 3mo, 6mo, 12mo)

# 3 BACKGROUND

## 3.1 Background & Preliminary Work

Metastatic prostate cancer rates have dropped significantly over the past 30-years, due to early aggressive prostatectomy and radiation therapy. However, hundreds of thousands of survivors have significant treatment-related side-effects, including urinary incontinence and erectile dysfunction. Treatment related side-effects result from collateral damage to structures alongside the prostate, such as nerves (erections) and sphincter muscle (incontinence). Injury or wide resection of sphincter and nerves is frequently intentional, or planned, to ensure all cancer is removed; yet, in hindsight it often appears this wide resection was not required. That is, a high percentage of the time the cancer is not extending outside the prostate as suspected or feared from biopsy and imaging-based staging. Prostate cancer is unique — most cases of extra-prostatic extension (extension into muscle and nerves) is not visible either on standard preoperative imaging, or to the operating surgeon during resection. Extra-prostatic extension is instead discovered on pathologic analysis *after* the patient has left the operating room. Prostate cancer has other unique features that make operative planning difficult: *(1)* it is multi-focal in up to 80% of subjects (Fig. 1); *(2)* it often presents with mixed grade lesions (Fig. 1); and *(3)* conventional imaging modalities (ultrasound, MRI) can miss significant cancers entirely.

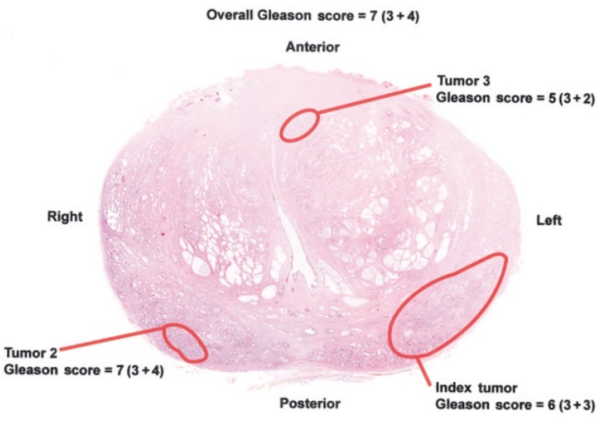



**Figure 1**. Whole-mount pathology slide

Hundreds of thousands of men could have peace of mind and improved outcomes, if new imaging could accurately detect extra-prostatic extension of prostate cancer to better guide treatment. Recent studies on treatment-related regret in prostate cancer show key drivers of regret are: nerve related injury (erectile dysfunction), loss of masculinity, and positive surgical margins (van Stan, et al. 2020, Baunake, et al. 2020). Cellularly targeted molecular imaging (PSMA-PET) appears to have the needed ability to detect aggressive prostate cancer, but requires further testing to validate its usefulness in surgical guidance.

## INNOVATION

We currently use multiparametric 3-T MRI (mpMRI), in addition to ultrasound biopsies, to guide surgical therapy, but significant uncertainty remains due to limited sensitivity. Incorporating MRI-guidance does increase the detection of clinically significant prostate cancer compared to systematic biopsy alone (Hu, et al. 2014, Pokorny, et al. 2017, Wysock, et al. 2014). However, recent studies mapping MRI lesions to final whole-mount pathology show significant limitations remain with this imaging approach. For example, a recent study showed only 80% of index (largest) tumors were seen by MRI, and even fewer secondary lesions (Le, et al. 2014). Another recent study showed MRI missed a clinically significant lesion in 26% of patients using whole-mount analysis (Borofsky, et al. 2017). Fittingly, Borofsky titled their paper, *"What are we missing? False negative cancers at Multiparametric MR imaging of the prostate."* MRI interpretation has also been shown to vary substantially between radiologists, which persisted after correcting for radiologist practice volume (Sonn, et al. 2017, Sonn, et al. 2020).

We have performed thousands of prostatectomies at Indiana University and note that many patients have *"prostate confined"* cancer that could have been cured with nerve sparing treatment. The converse is also concerningly true: many patients have positive surgical margins where nerve sparing surgery was performed at sites of extra-prostate extension leaving cancer behind. We were early investigators of PSMA-PET imaging, and since 2017 have been observing whether PSMA-PET could aid in surgical resection. **Using a molecular targeted agent such as $^{68}$Ga-PSMA-11 to guide resection represents a significant innovation in surgical planning, appearing to offer better individualization of the treatment plan with reduced surgical margins*, when appropriate,* and consequently improving quality of life.**

### Preliminary Studies

PSMA PET imaging in primary prostate cancer has been reported primarily out of Germany and Australia with few prospective studies in the United States. Few studies utilize the labor-intensive whole-mount pathology as the "gold standard" for rigorous disease characterization, and few studies have comprehensively looked specifically at extra-prostatic extension and surgical resection guidance. Furthermore, the published studies have focused on a small percentage of aggressive prostate cancer (high-risk disease) rather than the majority of pre-metastatic cancers (intermediate risk disease). For example, the only study reported out of the United States was a retrospective

review of 32 higher risk aggressive cancers (≥4+3) removed by prostatectomy, which found PSMA PET-MRI to be superior to mpMRI (Sensitivity 74% vs 50%, p<0.001, Hicks, et al. 2018). A retrospective trial out of Australia compared $^{68}$Ga-PSMA-11 PET-CT and mpMRI using a per lesion approach (Berger, et al. 2018). They found index lesion localization was better for PSMA-PET than MRI (100% vs 94%). Secondary lesion sensitivity was much higher for PSMA-PET than for MRI (94% vs 52%). *We need larger prospective studies focused on improved surgical guidance in the patient population posing the greatest challenge in urologic decision-making, patients with intermediate risk disease.*

### *Preliminary Studies/Data*

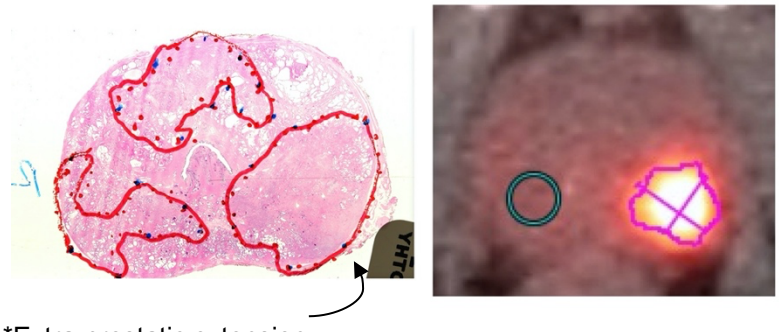
*$^{68}$Ga-PSMA-11 PET for Early Metastatic Disease.* The project investigators have significant experience in PET imaging with $^{68}$Ga-PSMA-11. Our initial human experience with $^{68}$Ga-PSMA-11 PET was for dosimetry assessment, studying ten prostate cancer patients with biochemical recurrence who had been previously clinically imaged with $^{11}$C-acetate under an Expanded Access IND (Green, *et al.* 2017). The expected utility of $^{68}$Ga-PSMA-11 PET was apparent even in that limited series, with $^{68}$Ga detecting sites of metastasis not seen in $^{11}$C-acetate imaging. We have subsequently dropped $^{11}$C-acetate imaging in prostate cancer patients with biochemical recurrence in favor of $^{68}$Ga-PSMA-11 PET, and have performed clinical imaging on over 400 patients under Expanded Access IND 131,806.

*$^{68}$Ga-PSMA-11 PET for Diagnosis and Surgical Planning.* We recently published an observational trial evaluating $^{68}$Ga-PSMA-11 PET-CT or PET-MRI preoperatively in 15 patients with biopsy-proven *high or intermediate-risk* prostate cancer (Bahler, et al. 2019). The PSMA-PET exam was obtained prior to scheduled surgical resection for correlation of imaging findings with whole-mount pathology. All staging $^{68}$Ga-PSMA-11 PET/CT scans (15/15) showed suspicious prostate lesions (index lesion) with median (IQR) SUV of 10.0 (6-13); benign prostate had a median (IQR) $SUV_{max}$ of 2.2 (2-3). Good registration was seen between PSMA-PET and whole mount imaging for lethal cancer. For secondary lesions, 8/11 (82%) were detected with $^{68}$Ga-PSMA-11 PET; the three missed lesions were of ≤10% Pattern 4 (>90% pattern 3). Our study was published with the following Editorial Comment: *"This study is…one of the few that has done so for intermediate risk disease and it delineates the accuracy of PSMA imaging to differentiate histological grade groups 1- 3**. Prospective well-designed trials validating PSMA imaging in these low prevalence populations are critical and a logical next step based on these study results**" (Emmett and Hofman, 2020).*


**Figure 2.** A lesion at the base of the prostate is seen (30% pattern 4) with $^{68}$Ga-PSMA-11 PET-CT scanner.

*$^{68}$Ga-PSMA-11 PET for predicting extra-prostatic extension.* Currently, we have 33 prostatectomy cases (each case has right and left nerve bundle) available with preoperative PSMA-PET imaging. Extra-prostatic extension was noted in 26/66 (39%) nerve bundles, and this was predicted in 24/26 (92%) of the cases on PSMA-PET. The PSMA-PET would have changed the treatment plan in 18/33 (55%) of cases, including choosing to spare 12 nerve bundles, while also avoiding nerve sparing in 4 cases of extra-prostatic extension. See **Appendix A** for example PSMA-PET surgeon's report to guide resection.

**Figure 3.** A lesion is noted along the left posterior near the nerve bundle but not the right. Final pathology was consistent with the PSMA-PET showing extra-prostatic extension only on the left. This patient safely had right-sided nerve-sparing without positive margin due to the PET.



Prostatectomy carries significant risk for post-treatment urinary and erectile dysfunction. PSMA-PET imaging offers the potential of both cancer control and excellent quality of life for patients whose disease is localized to the prostate. There is an immediate clinical need for validation of advanced imaging (PSMA-PET) in the context of enabling more precise surgical guidance.

## 3.2 Rationale

Our long-term goal is to improve cancer outcomes and quality of life for prostate cancer patients by bringing novel imaging agents and systems to the diagnosis and treatment of prostate cancer. Prostatectomy carries significant risk for post-treatment urinary and erectile dysfunction. PSMA-PET imaging offers the potential of both cancer control and excellent quality of life for patients whose disease is localized to the prostate (see figure below). There is an immediate clinical need for validation of advanced imaging (PSMA-PET) in the context of enabling more precise surgical guidance.

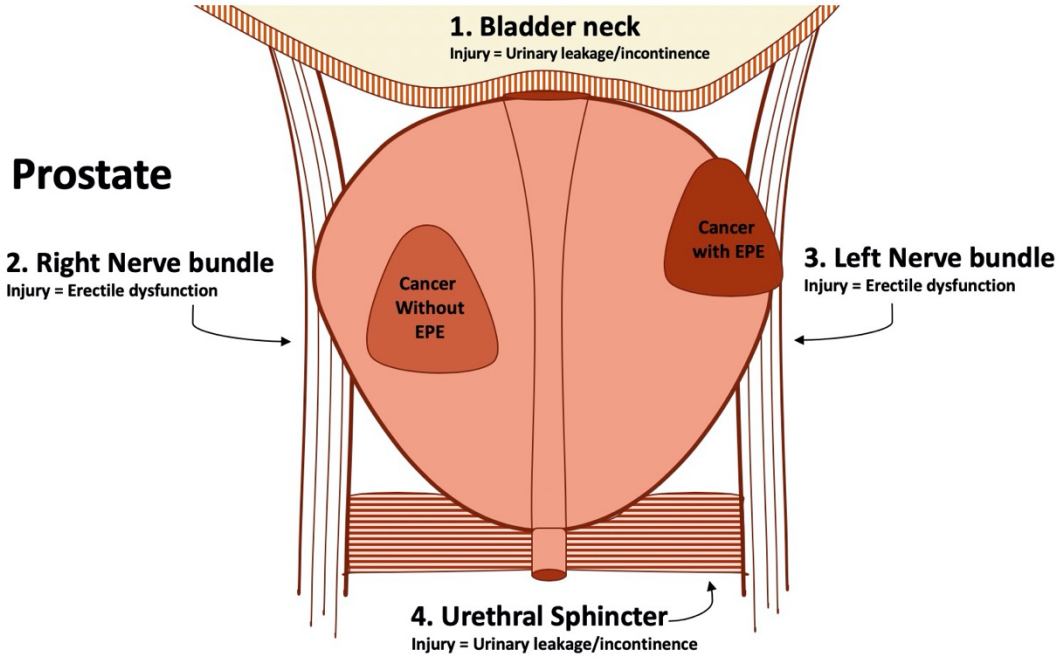



Figure 4. The prostate is located near several anatomic structures important for genito-urinary function. Advanced imaging is important to avoid unnecessary treatment of surrounding structures, while ensuring all malignant lesions are treated. We aim to improve quality of life by appropriately avoiding injury to structures 1-4 shown at left. EPE = extra-prostatic extension.

# 4 STUDY OBJECTIVES

## 4.1 Primary

1) Evaluate PSMA-PET imaging preoperatively and calculate performance for predicting extra-prostatic extension based on the whole-mount pathology gold standard.

## 4.2 Secondary

1) Quantify the frequency of proper treatment changes directed by PSMA-PET

2) Compare PSMA-PET performance for predicting extra-prostatic extension to standard-of-care assessments.

**Exploratory Endpoints:**

3) Assess quality of life changes from preoperative baseline:

IEF-15 (Erectile function score),

EPIC-26 (Pad use),

SF-36 (Overall mental and physical health domains)

4) To assess whether kinetic modeling tools are useful for improving detection of the location and extent of tumor in $^{68}$Ga-PSMA-11 PET/CT images. (Going beyond the standard PET map of regional radiotracer concentrations, to additionally examine differences in regional pharmacokinetics in order to possibly better differentiate benign and neoplastic tissue.)

# 5 CRITERIA FOR EVALUATION

## 5.1 Primary

1) Sensitivity and Specificity of PSMA-PET imaging for detecting extra-prostatic extension of cancer at the nerve bundles

## 5.2 Secondary

1) Rate of treatment changes and rate of treatment changes that were appropriate based on pathology.

**Exploratory Endpoints**

2) Sensitivity/ Specificity/ PPV/ NPV for PSMA-PET vs. MRI vs. ultrasound-based nomogram.

3) IIEF-15 (Erectile function score), EPIC-26 (Pad use), SF-36 (overall mental and physical health domains).

4) Qualitative and quantitative evaluation of changes in PET image appearance after voxel-by-voxel application of kinetic modeling tools to define regional pharmacokinetics (compared to standard PET reconstructions showing simply the integrated concentration of regional radioactivity over the imaging period).

# 6 ELIGIBILITY CRITERIA

## 6.1 Inclusion Criteria

To be considered eligible to participate in this study, a patient must meet all the inclusion criteria listed below:

1. Men diagnosed with clinically significant prostate cancer and are scheduling prostatectomy.
2. Prostate pathology results consistent with:
    a. Gleason 3+4 ≥1 core with pattern 4 ≥20% or
    b. ≥ 3 cores of Gleason 3+4 or
    c. NCCN unfavorable intermediate risk or
    d. NCCN high-risk or
    e. NCCN very-high risk
3. Scheduled for standard of care MRI or has recently completed standard of care MRI (within 6 months). Willing and able to lie still for approximately 50 minutes in an enclosed space for the MRI.

## 6.2 Exclusion Criteria

1. Participation in another investigational trial involving research exposure to ionizing radiation concurrently or within 30 days.
2. Does not meet safety criteria for MRI scan (e.g. metal implant that is not allowed, since this is required for comparison).
3. Significant acute or chronic medical, neurologic, or illness in the subject that, in the judgment of the Principal Investigator, could compromise subject safety, limit the ability to complete the study, and/or compromise the objectives of the study.

# 7 PATIENT REGISTRATION

Patient enrollment will take place over 12 months at a single institution – Indiana University Simon Cancer Center (IUSCC) encompassing Indiana University Hospital (IUH), IU Health North, IU Health North medical office building, IU Health Methodist Hospital and IU Health Neuroscience Center/Goodman Hall, and IU Health Schwarz Cancer Center. Potential patients will be identified in the Urology clinic, or by physician referrals, mostly likely but not exclusively during pre-operative consultations for surgical removal of prostate cancer. All study procedures will take place at IUSCC/IUH/IU-Health Methodist Hospital, with the research imaging performed at the IU Health Goodman Hall outpatient facility or R2 research facility within the Indiana University Department of Radiology and Imagining Sciences. All patients will be registered with the Indiana University (IU) Department of Urology. Regulatory files will be maintained by the Department of Urology. Applicable regulatory documents must be completed and on file prior to registration of any patients. Patients who appear to be eligible for this trial will undergo the Informed Consent Process and be screened for eligibility utilizing the Eligibility Criteria. Individual patient registration will be done in the REDCap database. The original signed Institutional Review Board (IRB) approved Informed Consent Document and completed eligibility checklist will be stored in the following location: Indiana University Department of Urology, 535 N. Barnhill Dr., Ste 150, Indianapolis, IN, 46202.

# 8 STUDY PROCEDURES

## 8.1 Summary

This patient population will have clinically significant prostate cancer and either already be scheduled for, or in the process of scheduling a prostatectomy. Patients will either have recently had (within 6-months) a standard of care prostate MRI as part of routine care for their prostate cancer. Following the informed consent process, patients who enroll in the study will receive a $^{68}$Ga-PSMA-11 PET-CT. The sensitivity and specificity for lesion characterization will be evaluated, along with the ability of the tracer to inform the treatment planning. After patients undergo surgical removal of the prostate it will have a slice-by-slice whole mount analysis to assess the sensitivity and specificity the PSMA PET.

## 8.2 Study Calendar

| | Screening/ Baseline (-90 days) | Imaging (Day 1) | Surgery (Day 2-45) | 1[6] month F/U | 3[6] Month F/U | 6[6] month F/U | 1[6] year F/U |
|---|---|---|---|---|---|---|---|
| **REQUIRED ASSESSMENTS** | | | | | | | |
| Informed Consent | X | | | | | | |
| Inclusion/Exclusion | X | | | | | | |
| Medical History[1] | X | | | | | | |
| Quality of life Assessments[2] | X | | | X | X | X | X |
| Surgeon plan (pre-PET) | X | | | | | | |
| PSMA dose and PET scan | | X | | | | | |
| SOC MRI[3] | | X | | | | | |
| Surgeon plan (post-PET)[4] | | X | | | | | |
| SOC prostatectomy | | | X | | | | |
| Surgery plan (performed) | | | X | | | | |
| Pathologic assessment of whole mount[5] | | | X | | | | |

Footnotes:

1. Medical history may be obtained via medical records, as necessary.
2. Quality of Life Assessments include the following:
    a. IIEF-15 Score (Erectile function)
    b. EPIC-26 Questionnaire (Urinary function)
    c. SF-36 Quality-of-life assessment
3. If the patient does not already have a recent SOC MRI (within 6 months), it will need to be completed as per SOC prior to the PSMA-PET scan.
4. This should be completed within 9 days of the scan.
5. The pathologic whole mount assessments may be batch completed per pathology discretion
6. 1-month follow-up is 4-6weeks. 3-month follow-up is +/-1-month, 6-month and 12-month follow-up are +/-2-months

## 8.3 Assessments by Visit

### 8.3.1 Baseline/Screening (within 3 months of scan):

- Informed consent: investigators or their designees will discuss with subjects the nature of the study, its requirements, risks, and restrictions to obtain informed consent for participation in the study. Subjects should have sufficient time to review the study information and consent form and to ask any questions necessary to make an informed decision regarding their participation in the study. Written informed consent is to be obtained before any other study-specific procedure.

- Eligibility criteria: make sure patient meets study eligibility criteria.

- Medical history: includes past medical history, past surgical history, allergies, any ongoing medical conditions, and including medications noted in patients record at time of screening. This can be collected from medical records.

- Quality of Life Assessments (see study calendar):

### 8.3.2 Imaging

- Eligibility criteria: ensure subject continues to meet study eligibility (if longer than 60 days since screening)
- Medical history: capture additional medical history since screening (if longer than 60 days since screening)
- Concomitant medications: record medications taken since screening through day of surgery (if longer than 60 days since screening)

- $^{68}$Ga-PSMA-11 PET-CT:

    - Patient receives a ~3-5 mCi dose of $^{68}$Ga-PSMA-11. (A physician-sponsored IND has been successfully obtained)

    - Patient will undergo research Vision PET-CT at Goodman Hall which is anticipated to last approximately 60 minutes (or similar scanner). Per our institutional standard of care, patients will receive intravenous iodinated contrast with the PET-CT unless medically contraindicated.

Imaging Protocol for $^{68}$Ga-PSMA-11 PET Data Acquisition

| **Time (minutes)** | **Activity** |
|---|---|
| - 60 | Patient arrives, and completes consent forms, while radiopharmaceutical synthesis and quality control procedures are completed. |
| -5-0 | Dual Energy CT for Attenuation Correction |
| 0 | Start PET/CT acquisition and administer $^{68}$Ga-PSMA-11, 3-5 mCi (inside the camera). |
| 0-60 | Flow motion list-mode acquisition of PET data, allowing reconstruction of static images of radiopharmaceutical distribution over various time windows, as well as tracer kinetic modeling to determine whether and how regional pharmacokinetics are affected by the underlying regional (patho)physiology. |
| 60-65 | Contrast-CT to assist in prostate segmentation from the PET acquisition for fusion to both the mpMRI and the lesion mapping from whole-mount pathology. (Contrast CT will be omitted, if contrast agent is contraindicated based on standard clinical criteria for contrast administration.) |
| 65 | Patient can leave camera and depart. |

- Reconstruction of static images showing the distribution of radioactivity in the pelvis in various time windows (e.g., 3-7 minutes; 10-15 minutes; 20-30 minutes; 40-55 minutes) to examine definition of the location and extent of prostate cancer.

- Input function formation for multi-parametric PET analysis: The input function will be generated by placing a 3D volume-of-interest in left atrium / left ventricle blood pool of the heart. The input function frame sequence will consist of 12x5s followed by 9x10s frames during the peak and a 150 s frame at 7.5 minutes, a 300 s frames at 15, 30, and 55 minutes.

  Alternatively, we will also assess characterization of the input function will be generated by placing a 3D volume of interest over the abdominal aorta (possibly including the bifurcation) to capture the needed measures of blood pool radioactivity.

- The PET read will be done by a board-certified nuclear medicine specialist (e.g. Mark Tann, MD or similar) and the MRI read will be done by a board certified MR radiologist (e.g. Jordan Swensson, MD or similar). Suspicious lesions will be marked in a blinded fashion.

- AE assessment: AEs will be assessed at the time of $^{68}$Ga-PSMA-11 administration any event **not expected** is collected including but not limited to: rash and shortness of breath.

- Safety monitoring following radiopharmaceutical administration will consist of visual and verbal monitoring of the patent after injection, and during and at the conclusion of the PET/CT procedure, with any apparent patient abnormalities, reactions or reported effects noted in the study records.

- The nuclear medicine technologists administering the radiopharmaceutical are responsible for immediately reporting any adverse or unexpected events to the principal investigator or clinical designee, who will report the occurrence of any adverse events to the IRB.

- As in most clinical nuclear medicine procedures, these radiopharmaceuticals are administered at a sub-pharmacologic doses. Adverse events are exceedingly unlikely, as $^{68}$Ga-HBED-CC has been clinically employed, extensively and without reported incident, in clinical patient diagnostic imaging studies in prostate cancer patients in Germany and other European countries, as well as in over 400 patients locally.

- If there is a discrepancy between the PSMA and conventional MRI scan, the investigators will discuss the treatment plan with the patient at the investigator's discretion. This will be completed through a pre-surgery clinic or virtual visit within 9days of the PET/CT scan.

### 8.3.3 Surgery and Pathology

- The standard of care surgical procedure is performed as indicated by the cancer.
- Pathologic assessment: whole mount sections of prostate tissue and routine sections of lymph nodes if applicable will be fixed and analyzed by licensed pathologist per routine care. This typically happens within 2 weeks of prostatectomy.
- Additional study-related pathologic assessment: intraprostatic lesion-based assessment will be done to document the % Gleason pattern 3, 4, and 5 within each lesion. The Extra-prostatic extension and positive margins will be documented. This may be "batched" at the discretion of the pathology department.
- How the knowledge of the PSMA-PET informs treatment will be tracked. Examples of informing the decision include the number and location of $^{68}$Ga-PSMA-PET detected: additional intraprostatic cancer lesions diagnosed, extra-prostatic extension, seminal vesicle invasion, and lymph node invasion.

# 9 STUDY WITHDRAWAL/DISCONTINUATION

Subjects must be discontinued from the study for the following reasons:

- Withdrawal of consent
- Investigator deems withdrawal necessary at any time if it is determined that it is not in the subjects best interest to continue, or if the subject is found to be noncompliant with study procedures.

If subject discontinues after administration of study drug, he or she will be encouraged to continue on study for safety procedures per protocol. Reason(s) for discontinuing must be clearly documented in the appropriate source documents.

# 10 STATISTICAL CONSIDERATIONS

## 10.1 Study Design

A prospective, single arm, pilot study for evaluating the performance of PSMA-PET

## 10.2 Study Population

The enrolled population comprises all patients who meet the eligibility criteria and are registered onto the study.

## 10.3 Sample Size

The sample size justification of the pilot study is based on the primary objective of estimating the sensitivity and specificity for PSMA-PET for detecting extra-prostatic extension of cancer at the nerve bundles. The sensitivity and specificity will be calculated using both the left and right nerve bundles, based on the gold standard of whole-mount pathology. A sample size of 50 patients would therefore generate 100 data points. Assuming about 20% of the 100 left and right nerve bundles are not evaluable. Then we could have at least 80 data points.

Based on the preliminary data, the prevalence of extra-prostatic extension is about 35%. The sensitivity of PSMA-PET is anticipated to be 90%. A sample size of 80 would provide a two-sided 95% sensitivity confidence interval with a width of at most 0.23. The specificity of PSMA-PET is anticipated to be 76%. A sample size of 80 would provide a two-sided 95% specificity confidence interval with a width of at most 0.25. All calculations will be based on the simple asymptotic method with continuity correction.

## 10.4 Participant Characteristics

Demographic characteristics will be summarized using descriptive statistics.

## 10.5 Analysis of Primary Objective

The sensitivity and specificity will be summarized along with 95% CI using the simple asymptotic method with continuity correction. PPV and NPV will also be summarized along with 95% CI using the simple asymptotic method with continuity correction.

## 10.6 Analysis of Secondary Objectives

The frequency of proper treatment changes directed by PSMA-PET compared to MRI will be summarized along 95% CI for all evaluable subjects, and separated for 3 areas important for genito-urinary function including: 1) Bladder neck, 2) Nerve bundles, 3) Urethral Sphincter (Figure 4). We will use the McNemar test to compare the sensitivity and specificity values between PET and MRI although data from this pilot study is considered hypothesis generating only due to the small sample size.

The quality of life data including IIEF-15 (Erectile function score), EPIC-26 (Pad use), SF-36 (overall mental and physical health domains) are longitudinal data, which will be analyzed separately. The analysis will start with the graphical representation of the data, where

mean and the standard of mean at each time point will be plotted and linked over time. An exploratory statistical modelling approach will be conducted to analyze the change over time. In particular, a mixed effects model will be used to analyze the data.

The parametric kinetic modeling data will be assessed for goodness-of-fit of the measured regional tissue time-activity curves to the applied kinetic model. Additionally, the images derived by voxel-wise kinetic modeling will be visually compared to standard reconstructions of the integrated regional concentration of radioactivity, assessing apparent lesion size, lesion position, and lesion/background contrast.

# 11 DATA FORMS AND SUBMISSION SCHEDULE

This study will utilize the secure, web-based, Research Electronic Data Capture (REDCap) system for data input. REDCap was developed by Vanderbilt University and is provided by Indiana University through their community license. REDCap is managed by the Indiana University Department of Biostatistics and secured by University Information Technology Services Advanced IT Core. Access to the password protected database will be limited to the investigators of this study, and any data that is distributed will be either de-identified or authorized by written permission from the subject.

All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines.

# 12 DATA AND SAFETY MONITORING PLAN

This study will be conducted in accordance with the IU Simon Cancer Center Institutional DSMP for High Risk Trials.

Investigators will conduct continuous review of data and subject safety. Weekly review meetings for high risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). Weekly meeting summaries should include review of data and subject safety by including for each dose level: the number of subjects, significant toxicities as described in the protocol, dose adjustments and responses observed. Study teams should maintain meeting minutes and attendance for submission to the DSMC upon request.

**Data and Safety Monitoring Committee**

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will

review this study semi-annually to review overall trial progress, toxicity, compliance, data integrity, and accrual per the Institutional DSMP.

Furthermore, the DSMC conducts an administrative review of serious adverse events (SAEs), deviations, reportable events, and any other outstanding business. Major issues may require further DSMC review or action.

For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the principal investigator will notify the DSMC Chair immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the subject warrant early closure of the study, the DSMC Chair and Compliance Officer must be notified within 1 business day via email, and the IRB must be notified within 5 business days. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

## 12.1 IND Annual Reports

For trials with an IND held locally by the IU principal investigator or university, the IND Annual Report will be prepared and submitted to the Compliance Team. This report will be reviewed by the DSMC at the time of FDA submission.

## 12.2 Study Auditing and Monitoring

All trials conducted at the IUSCC are subject to auditing/monitoring. Reports will be forwarded to the DSMC for review.

## 12.3 Data Management/OnCore Reporting Requirements

The DSMC reviews data and study progress directly from Oncore; therefore, timely data entry and status updates are vital. Study data must be entered within Oncore promptly, no later than one week from study visit occurrence. Subject status in Oncore will be

updated in real time, as this may affect overall trial enrollment status. Global SAEs and deviations will be reviewed on a monthly basis by the DSMC Chair directly from Oncore.

## 12.4 OnCore Safety Reporting

In addition to protocol- and regulatory-required safety reporting, all serious adverse events (SAEs) will be captured in the Oncore system within 1 business day of notification. Initial SAE reporting will include as much detail as available, with follow-up to provide complete information.

Attributions will be assessed to study drugs, procedures, study disease, and other alternate etiology.

## 12.5 Study Accrual Oversight

Accrual data will be entered into the IU Simon Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year while the PPC coordinator reviews accrual quarterly.

## 12.6 Protocol Deviation Reporting

Protocol deviations will be entered into OnCore within 5 days of discovery and reviewed by the DSMC Chair on a monthly basis. Findings will be reported to the full DSMC at the time of study review. For serious or repetitive protocol deviations, additional action may be required by the DSMC.

# 13 ADVERSE EVENTS

## 13.1 Definitions of Adverse Events

### 13.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. Adverse events will be graded according to the NCI Common Toxicity Criteria, Version 4.0 (Appendix A).

### 13.1.2 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death or ANY death occurring within 28 days of last dose of study drug (even if it is not felt to be drug related)
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Hospitalizations that are not considered SAEs are:

  - Hospitalization planned prior to first administration of study drug
  - Hospitalization for elective treatment of a pre-existing condition unrelated to the study medication

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

### 13.1.3 Unexpected Adverse Event

An adverse event not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's brochure or package insert.

### 13.1.4 Determining Attribution to the Investigational Agent(s)

**Attribution:** An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily *"caused by a therapeutic intervention"*. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

| Relationship | Attribution | Description |
|---|---|---|

| | | |
|---|---|---|
| Unrelated to investigational agent/intervention | Unrelated | The AE is clearly **NO**T related |
| | Unlikely | The AE is **doubtfully related** |
| Related to investigational agent/intervention | Possible | The AE **may be related** |
| | Probable | The AE **is likely related** |
| | Definite | The AE **is clearly related** |

## 13.2 Adverse Event Reporting Requirements:

Adverse events will be recorded for the study drug administration) regardless of whether or not the event(s) are considered related to trial medications. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

### 13.2.1 Reporting to the IRB:

Unanticipated problems involving risks to subjects or others will be reported **promptly** to the IRB if they:

- unexpected;
- related or possibly related to participation in the research; and
- suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the serious adverse event does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the IU IRB. However, it should be reported at the time of continuing review.

**Prompt** reporting of unanticipated problems to the IRB is defined as within 5 days from becoming aware of the event.

### 13.2.2 Reporting to the IUSCC Data Safety Monitoring Committee:

Regardless of study sponsorship, the study team must enter all initial and follow-up SAE, expedited, and noncompliance reports into OnCore® for review by the DSMC chair and/or coordinator. Expedited reports may include IRB Prompt Report Forms, AdEERS reports, MedWatch, and additional SAE forms as required by the sponsor. When follow-up information is received, a follow-up report should also be created in OnCore®. This DSMC reporting requirement is in addition to any other regulatory bodies to be notified (i.e. IRB, FDA, pharmaceutical company, etc.). The DSMC chair and/or coordinator will review all SAE, expedited, and noncompliance reports monthly.

# 14 PATIENT CONSENT AND PEER JUDGEMENT

The protocol and informed consent form for this study must be approved in writing by the appropriate IRB prior to any patient being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator and are subject to inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

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# 16 APPENDICES

## 16.1 Appendix A

## NCI Common Toxicity Criteria (Version 4.0)

Due to the size of the latest version of the Common Toxicity Criteria, copies of this appendix are not included with this protocol document.

An electronic copy is available on the CTEP web site,
http://ctep.cancer.gov/reporting/ctc.html