^{68}Ga-PSMA-11 PET/MRI for detection of regional nodal and distant metastases in patients with intermediate and high-risk prostate cancer

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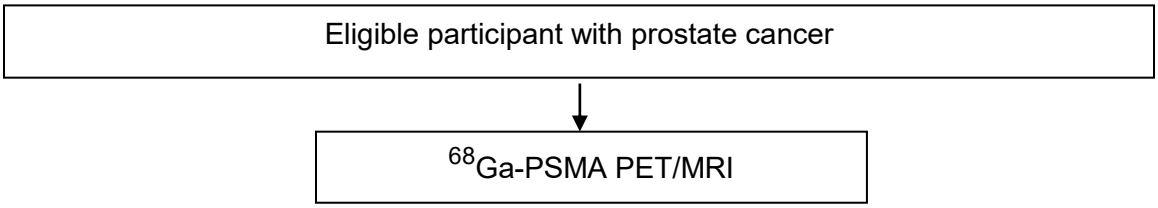
PROTOCOL SYNOPSIS

TITLE	^{68}Ga-PSMA-11 PET/MRI for detection of regional nodal and distant metastases in patients with intermediate and high-risk prostate cancer
STUDY PHASE	Phase 2-3
INDICATION	Prostate cancer
INVESTIGATIONAL PRODUCT	^{68}Ga-PSMA-11; also known as: • DFKZ-11 • HBED-CC PSMA • The “Heidelberg compound”
SAMPLE SIZE	200 participants
PRIMARY OBJECTIVE	To evaluate ^{68}Ga-PSMA-11 PET/MRI for detection of regional nodal and distant metastases in patients with intermediate and high-risk prostate cancer scheduled to undergo prostatectomy with lymph node dissection.
PRIMARY OBJECTIVE	Sensitivity, specificity, positive and negative predictive value of ^{68}Ga-PSMA-11 PET/MRI for the detection of regional nodal metastases compared to pathology at radical prostatectomy on a per patient basis using nodal regional correlation.
SECONDARY OBJECTIVES	Sensitivity, specificity, positive and negative predictive value of ^{68}Ga-PSMA-11 PET/MRI for the detection of extra-pelvic nodal metastases; visceral metastases; and osseous metastases compared to biopsy and imaging follow-up.
EXPLORATORY ENDPOINTS	• Sensitivity, specificity, negative and positive predictive value for detection of regional nodal metastases in comparison to cross sectional imaging performed contemporaneously with the PSMA-11 PET. • One-year PSA progression-free survival, comparing patients with and without pelvic nodal metastases. • Correlation between SUV_{max} from PSMA--11 PET and short axis diameter of nodal disease on cross-sectional imaging correlate to presence of true pathology. • Incidence of osseous and distant metastatic lesions.

SCHEMA



LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Ga-68; ^{68}Ga	Gallium-68
IRB	Institutional Review Board
IV	Intravenous
MRI	Magnetic resonance imaging
NPV	Negative predictive value
PPV	Positive predictive value
PET	Positron emission tomography
SUV	Standardized Uptake Value
PSMA	Prostate Specific Membrane Antigen

1. OBJECTIVE

Specific Aim

To evaluate ^{68}Ga-PSMA-11 PET/MRI for detection of regional nodal and distant metastases in patients with intermediate and high-risk prostate cancer scheduled to undergo prostatectomy with lymph node dissection.

2. BACKGROUND

2.1 Preliminary information

Data from the American Cancer Society suggests that for 2015 in the United States prostate cancer will continue to be the leading non-cutaneous cancer diagnosis in males with 220,800 estimated new cases, and has the second highest mortality (after lung) with 27,540 estimated deaths [1]. Initial screening and diagnosis relies on the digital rectal exam (DRE), prostate specific antigen (PSA), and transrectal ultrasound-guided core biopsies (1, 2). Subsequent treatment is multifaceted and may involve observation, surgery (prostatectomy), radiation therapy (external beam or brachytherapy), hormonal therapy, chemotherapy, or a combination of these (3-5).

The choice of treatment directly depends on the initial staging, as well as the patient's age, co-morbidities, and preferences. Prostate cancer staging is based on the tumor-node-metastases (TNM) classification. As outlined in the National Comprehensive Cancer Network guidelines, those patients requiring staging for additional therapy would need a bone scan and pelvic CT or MRI if the T-stage is greater than 2 or if the PSA or Gleason score is elevated (> 20 ng/mL and > 8, respectively). The CT or MRI is primarily used to identify locoregional lymph nodes (thereby altering the N-stage), while the bone scan is primarily used to identify osseous metastatic disease (thereby altering the M-stage). In particular, the prognostic importance of bone metastases in patients with prostate cancer has been established. Patients with an abnormal bone scan at the time of diagnosis have a mortality rate twice as high as patients with normal bone scans (6).

Currently, there is controversy regarding the most appropriate imaging modality for accurate evaluation of extent of disease. For instance, MRI can be an effective modality for evaluation of the musculoskeletal system, due to much better soft tissue contrast when compared to other imaging modalities. Additionally, the non-invasiveness, lack of ionizing radiation and multiplanar imaging capabilities are desirable features of MRI. Thus, MRI is commonly used to detect and evaluate bone and soft tissue tumors. Whole-body MR imaging for the evaluation of metastases compares well with the reference techniques of bone scintigraphy and CT. This imaging modality appears as a practical and acceptable alternative especially when extra-osseous metastases are also of concern (7). Modern MRI appears superior to skeletal scintigraphy with respect to sensitivity, specificity, as well as the extent of osseous metastasis and provides substantial, therapy-relevant additional information. Current efforts include the introduction of whole-body MRI for detection of skeletal metastases. However, whole-body MRI is a lengthy procedure which many patients cannot tolerate, and is also expensive.

Traditionally, however, ^{99m}Tc MDP bone scintigraphy is the method of choice for evaluation of osseous metastases, since it allows a whole body survey at a relatively reduced cost and because the sensitivity is based not only on the size of the tumor but the response of the

bone to the presence of metastasis. Skeletal scintigraphy is used for initial staging, monitoring the response to therapy and detection of areas at risk for pathological fracture. Although bone scintigraphy is sensitive for the detection of advanced skeletal metastases, early involvement may be missed in some cases in the absence of an osteoblastic response as this technique relies on the identification of this response rather than the detection of the tumor itself. Limitations imposed by the spatial resolution of planar scintigraphy and single photon emission computed tomography (SPECT) also affect the sensitivity of bone scintigraphy in detection of osseous metastases (8).

While bone scans have a proven role in certain cancers (including prostate and breast), within oncology more generally, it is the more recent advent of positron emission tomography (PET) that has sparked a renewed interest in molecular imaging because of the greater resolution/sensitivity of this modality and also because the radiotracer ^{18}F-FDG has proven to be very accurate for imaging a wide variety of malignancies (9,10). PET imaging technology advanced further after the introduction of the combined PET/CT scanner in 2001, which allowed merged visualization of functional and anatomical information. The role of ^{18}F-FDG PET/CT is proven in a variety of cancers, including lymphoma, colorectal carcinoma, lung cancer and melanoma, entities for which it has changed the practice of oncology. However, not all malignant lesions are identified reliably due to variable rates of glucose metabolism, contributing to the overall limitations of ^{18}F-FDG PET/CT.

Indeed, the initial reports and literature reviews suggested a limited role for ^{18}F-FDG PET/CT in the evaluation of prostate cancer (11). In particular, there is convincing evidence that for prostate cancer, ^{18}F-FDG PET is less sensitive than bone scintigraphy for the detection of skeletal metastases. But while ^{18}F-FDG PET is limited in the detection of osseous metastatic lesions, it may be useful in the detection of metastatic nodal and soft tissue disease (12). The morphology of the metastasis itself appears to be relevant for the ability of ^{18}F-FDG PET to detect disease. PET has been shown to be superior to scintigraphy in the detection of lytic metastases because it detects the presence of tumor directly by metabolic activity, rather than indirectly by showing tumor involvement due to increased bone mineral turnover. This has allowed the detection of metastatic foci earlier with ^{18}F-FDG PET than with bone scintigraphy (13, 14). This in part explains why the recently published results from the National Oncologic PET Registry (NOPR) suggest changes in management in one third of the patients with prostate cancer who were evaluated with ^{18}F-FDG PET/CT.

Another way to evaluate the skeleton using PET technology is with ^{18}F sodium fluoride (^{18}F-NaF). In fact, bone scintigraphy with ^{18}F was performed prior to introduction of ^{99m}Tc based agents, achieving excellent quality studies (15, 16). ^{18}F is an avid bone seeker, a property due to the fact that it is an analogue of the hydroxyl group found in the hydroxyapatite bone crystals. ^{18}F has the desirable characteristics of high and rapid bone uptake accompanied by very rapid blood clearance, which results in a high bone-to-background ratio in a short time. High-quality images of the skeleton can be obtained less than an hour after the intravenous administration of ^{18}F. ^{18}F is a positron emitter, allowing for PET imaging. Thus, imaging skeletal lesions with ^{18}F-PET/CT appears as a logical approach for acquisition of highly sensitive and specific images. The lack of

reimbursement and the high costs of ^{18}F currently prevent its clinical utilization, but ^{18}F-PET/CT was proved to be superior in bone lesion detection ^{99m}Tc MDP bone scan and SPECT in patients with prostate cancer.

However, at initial staging the issue is detection of pelvic and retroperitoneal small lymph node metastases that don't trigger size criteria on CT and MRI; bone metastases are a rare presentation.

Other tracers, such as ^{18}F- or ^{11}C-labeled choline and [^{11}C]-acetate, are used mainly for the diagnosis of recurrent (17-19) or metastatic (20) prostate cancer. Their feasibility in primary diagnosis is limited because of uptake in benign tissue such as benign prostatic hyperplasia or inflammatory lymph nodes (21, 22).

Although choline-based PET/CT is widely used outside the US for imaging prostate cancer, there have been numerous studies reporting a low sensitivity and specificity, especially at low prostate specific antigen (PSA) levels (23, 24). Consequently, improved imaging of prostate cancer is necessary. One novel promising method is PET imaging with ^{18}F-FACBC, a new synthetic amino acid. Recent evaluations by Nanni, *et al*. indicate that this tracer might be superior when compared to choline PET/CT (25). However, recent work indicates that ^{18}F-FACBC uptake in prostate cancer is similar to that in BPH nodules (26).

In addition, prostate-specific membrane antigen (PSMA) recently has received increased attention (27). This cell surface protein is significantly overexpressed in prostate cancer cells when compared to other PSMA-expressing tissues such as kidney, proximal small intestine or salivary glands (28). It therefore provides a promising target for prostate cancer-specific imaging (29). Recently methods have been developed to label PSMA ligands with ^{68}Ga enabling their use for PET imaging and therapy (30). Initial experience with PET/CT using Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga(HBED-CC)] (^{68}Ga-PSMA-11) as a ^{68}Ga-labelled PSMA ligand suggests that this novel tracer can detect prostate cancer relapses and metastases with high contrast by binding to the extracellular domain of PSMA, followed by internalization (31). Improved detection of occult metastatic disease will improve treatment efficacy by enabling better patient selection for treatment and prompting more extended pelvic node treatment with surgery or radiation for patients with evidence of nodal metastases outside the normal lymph node treatment area.

We conducted a pilot phase evaluation of ^{68}Ga-PSMA-11 under an RDRC-approved protocol at Stanford University. Ten men (age range: 67 to 83 year-old; mean ± SD: 73.1 ± 5.7) with biochemical recurrence of prostate cancer (PSA range: 2.6-36.4; mean ± SD: 12.4 ± 10.6) were enrolled. PET/CT images were acquired at 51 to 68 minutes (mean ± SD: 57.4 ± 6.3) after injection of 3.7 to 4.0 mCi (mean ± SD: 3.8 ± 0.1) of ^{68}Ga-PSMA. The uptake of ^{68}Ga-PSMA-11 was identified as described in previously published studies referenced above.

All participants had multiple standard of care imaging studies (CT, MRI, ^{18}F-FDG PET/CT, ^{18}F-NaF PET/CT, ^{99m}Tc MDP bone scan) prior to enrollment that were non-contributory, despite rising PSA values. The participants did not receive treatment in this interval as they were managed under a wait and watch strategy due to no identifiable disease. The interval

from biochemical recurrence to the ^{68}Ga-PSMA-11 PET/CT scan ranged 5 to 75 months (mean ± SD: 30.8 ± 20.4).

Biodistribution and localization of ^{68}Ga-PSMA-11

All participants tolerated the procedure without immediate or delayed (up to 7 days) complaints or complications. The areas with the highest ^{68}Ga-PSMA-11 accumulation are the lacrimal grand (mean SUV_{max}: 9.3 ± 3.3 [range: 4.6 to 14.9] and SUV_{mean}: 5.2 ± 2.3 [range: 2.5 to 8.8]), the parotid grand (mean SUV_{max}: 14.2 ± 2.6 [range: 9.9 to 19.1] and SUV_{mean}: 11.8 ± 2.6 [range: 7.2 to 16.1]), the submandibular grand (mean SUV_{max}: 16.8 ± 3.3 [range: 12.3 to 22.7] and SUV_{mean}: 13.5 ± 2.9 [range: 9.8 to 18.1]), small intestine (mean SUV_{max}: 14.6 ± 4.6 [range: 8.2 to 23.4] and SUV_{mean}: 11.0 ± 3.9 [range: 5.6 to 18.5]), kidney (mean SUV_{max}: 35.1 ± 9.9 [range: 14.4 to 46.2] and SUV_{mean}: 25.8 ± 7.5 [range: 12.0 to 36.0]) and bladder (mean SUV_{max}: 35.0 ± 24.7 [range: 9.6 to 78.5] and SUV_{mean}: 26.5 ± 17.4 [range: 7.8 to 67.9]), while moderate uptake was noted in the sublingual grand (mean SUV_{max}: 5.0 ± 2.4 [range: 1.9 to 10.6] and SUV_{mean}: 3.3 ± 1.6 [range: 1.5 to 7.1]), liver (mean SUV_{max}: 6.0 ± 1.3 [range: 4.1 to 9.0] and SUV_{mean}: 4.1 ± 0.8 [range: 3.2 to 5.7]) and spleen (mean SUV_{max}: 8.0 ± 3.3 [range: 2.6 to 12.3] and SUV_{mean}: 6.4 ± 2.7 [range: 2.0 to 10.5]). Other tissues analyzed had low ^{68}Ga-PSMA-11 uptake, with SUV_{mean} of less than 1.7. There were no differences between the ^{68}Ga-PSMA-11 biodistribution at 45 minutes post-injection among the 10 participants (Figure 2). The pattern of ^{68}Ga-PSMA-11 uptake is similar to previous reports.

^{68}Ga-PSMA-11 uptake outside the expected physiologic biodistribution

There were 45 areas of high ^{68}Ga-PSMA-11 uptake that corresponded on the CT images to bone marrow (*n* = 13), retroperitoneal lymph nodes (*n* = 12), mediastinal lymph nodes (*n* = 8), pelvic lymph nodes (*n* = 9), seminal vesicle (*n* = 2), subclavian lymph node (*n* = 1).

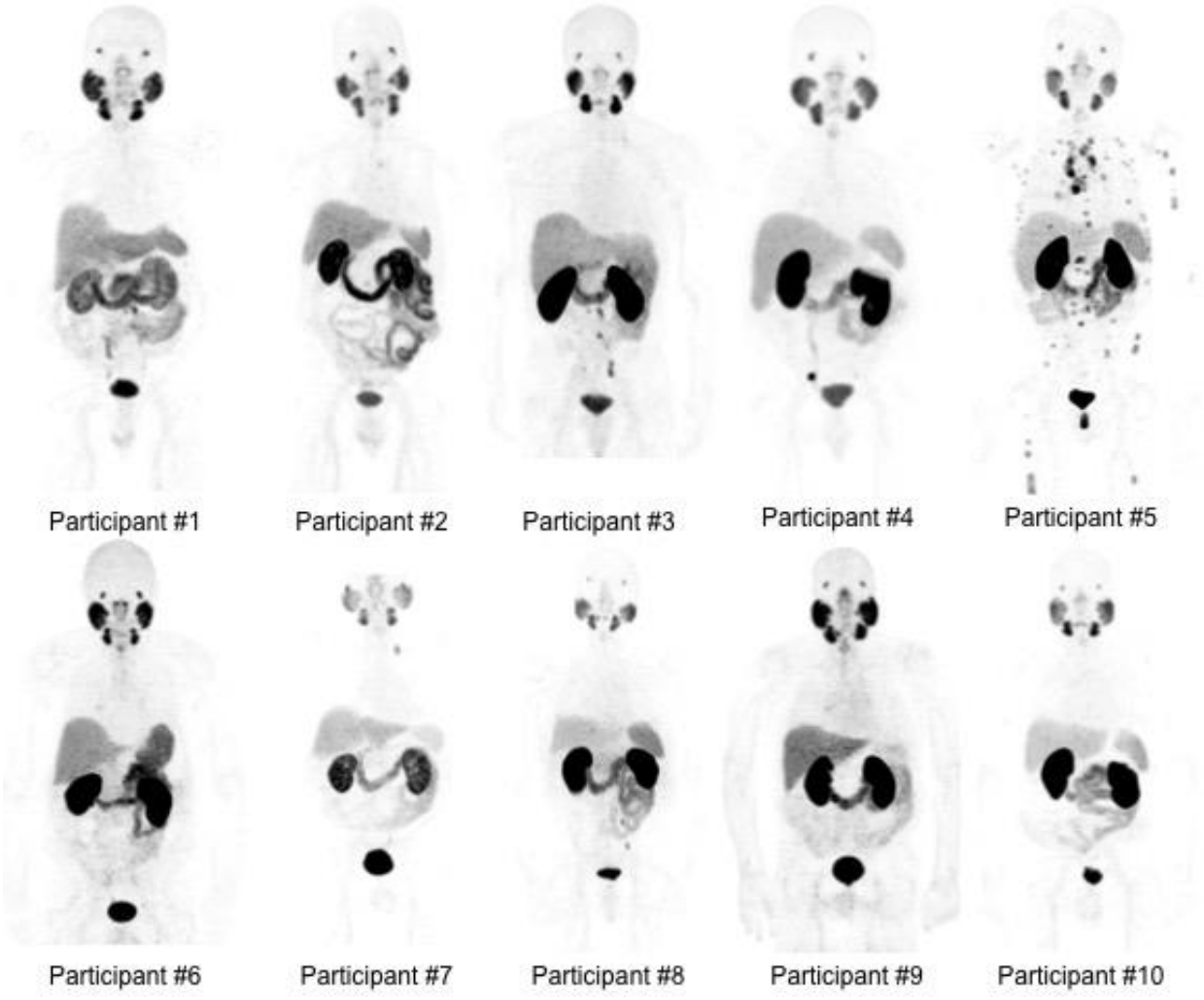


Figure 1: Maximum intensity projection (MIP) images from 10 participants in the pilot study of ^{68}Ga-PSMA-11 conducted at Stanford University.

2.2 Study Agent

We will use ^{68}Ga-PSMA-11 as the PET radiopharmaceutical. This agent has previously been identified as DFKZ-11; HBED-CC PSMA; or the "Heidelberg compound." This is not an FDA-approved product. This protocol is submitted to IND 128379.

2.3 Clinicaltrials.gov

Since ^{68}Ga-PSMA-11 is not an FDA-approved product, we will register the study on clinicaltrials.gov once all approvals will be in place.

2.4 Rationale

In this study, we propose to use a well-established PET isotope, Gallium-68 (^{68}Ga), bound to a PSMA ligand, (ie, ^{68}Ga-PSMA-11), which has high affinity for prostate specific membrane antigen. ^{68}Ga-PSMA-11 has been shown to be superior to other PET tracers used in prostate cancer such as ^{18}F-Fluoroethylcholine (FECH) and ^{18}F-Fluoromethylcholine (32, 33). Therefore, we propose the following aim:

To evaluate ^{68}Ga-PSMA-11 PET/MRI for detection of regional nodal and distant metastases in patients with intermediate and high-risk prostate cancer scheduled to undergo prostatectomy with lymph node dissection.

A prior first-in-human study investigated the biodistribution of ^{68}Ga-PSMA-11 and its ability to detect lesions. Thirty-seven men with prostate cancer underwent whole-body PET/CT after an intravenous injection of ^{68}Ga-PSMA-11 (median 121.0 MBq, range 52 to 212 MBq). Within healthy organs, kidneys and salivary glands demonstrated the highest radiotracer uptake. Lesions suspicious for PC presented with excellent contrast as early as 1 hour post-injection with high detection rates even at low PSA levels (31). In another study, a total of 78 lesions characteristic for prostate cancer were detected in 32 patients using ^{68}Ga-PSMA-11 PET/CT and 56 lesions were detected in 26 patients using choline PET/CT (33). The higher detection rate in ^{68}Ga-PSMA-11 PET/CT was statistically significant (P=0.04). All lesions detected by ^{18}F-fluoromethylcholine PET/CT were also seen by ^{68}Ga-PSMA-11 PET/CT. In conclusion, ^{68}Ga-PSMA-11 PET/CT can detect prostate cancer lesions with improved contrast when compared to ^{18}F-fluoromethylcholine PET/CT, especially at low PSA levels.

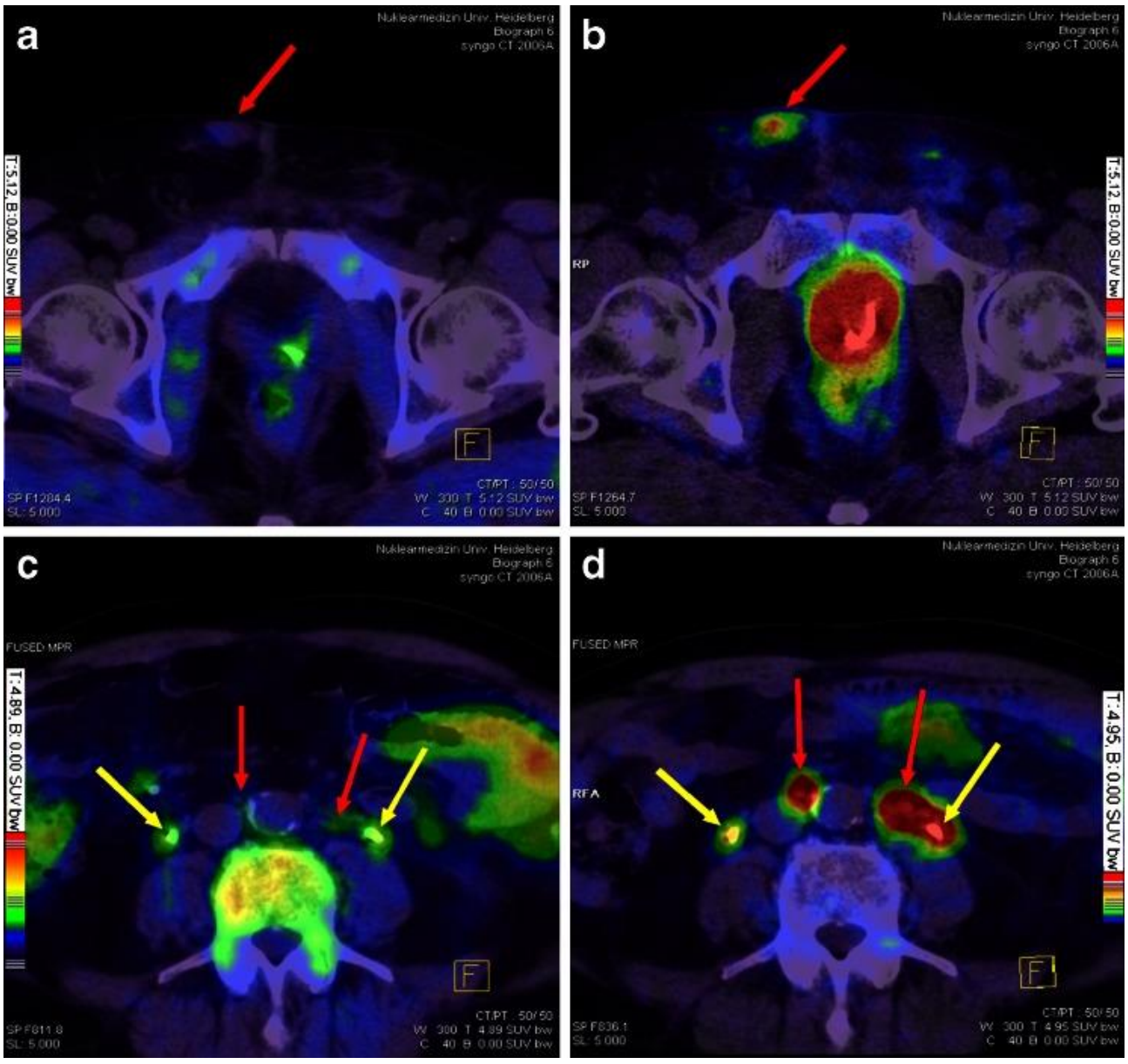


Figure 2: Red arrows point to a nodular pelvic wall metastasis (a, b, histologically-confirmed) and to small lymph nodes (c, d) which present with clearly pathological tracer uptake in ^{68}Ga-PSMA-11 PET/CT (b and d) only. Yellow arrows point to both catheterized ureters (c, d). Patient presented with a minimal PSA value (0.01 ng/mL) despite visible tumor lesions. The PSMA-11 ligand is therefore able to detect poorly differentiated PC. a + c Fusion of ^{18}F-fluoromethylcholine PET and CT; b + d fusion of ^{68}Ga-PSMA-11 PET and CT.

Our initial analysis of the first 33 participants enrolled in the study showed that prostate cancer was seen using ^{68}Ga-PSMA-11 PET in all patients, whereas multiparametric MR imaging depicted Prostate Imaging Reporting and Data System (PI-RADS) 4 or 5 lesions in 26 patients and PI-RADS 3 lesions in four patients. Focal uptake was seen in the pelvic lymph nodes in five patients. Pathologic examination confirmed prostate cancer in all patients, as well as nodal metastasis in three. All patients with normal pelvic nodes in PET/MR imaging had no metastases at pathologic examination (34).

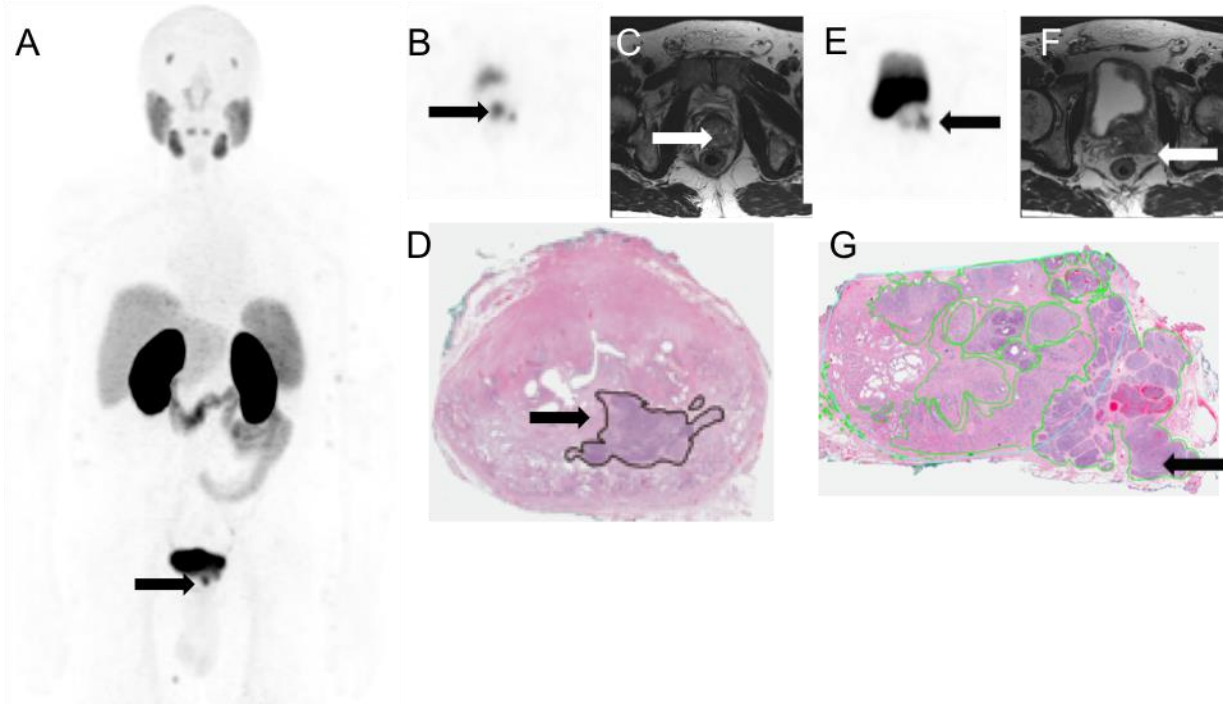


Figure 3: 74 year-old man (participant #4) with recently diagnosed intermediate risk, T1c, Gleason 4+4 prostate cancer presenting with PSA of 4.12 ng/mL. Maximum intensity projection (MIP) PET image (A), early transaxial PET (B) and delayed transaxial PET (C) showed focal uptake in histopathological proven prostate cancer (F). The milder focal uptake in the left lobe was likewise proven to be prostate cancer. Transaxial T2-weighted MRI (D) and DWI (B = 800) MRI (E) are also shown. Only the right -side tumor was mpMRI positive (PI-RADS 5).

2.5 Study Design

This is a phase 2-3 study with a total of 200 participants with newly-diagnosed intermediate or high-risk prostate cancer scheduled to undergo prostatectomy and lymph node dissection. Eligible participants will undergo baseline assessments at enrollment. Study participants will receive ^{68}Ga-PSMA-11 and undergo a PET/MRI. All patients will first be seen by a Stanford Cancer Institute physician (Drs Brooks, Gill, Skinner and Sonn) who will refer patients if appropriate on clinical grounds to Dr Iagaru or his colleagues for this study. The following steps will take place.

1. After signed the informed consent document, participants will be given a copy of the signed form.
2. Participant will be asked to drink 1 to 2 glasses of water before arrival at the clinic
3. Participants will be weighed and vital signs (heart rate and blood pressure) will be recorded
4. Study personnel (eg, technologist) will verify subject identify; radiopharmaceutical identity; dose; and administration route. Participant will be injected IV with 3 to 7 mCi of ^{68}Ga-PSMA-11
5. Participant will void immediately prior to the scan

6. Approximately 50 to 100 minutes after the radiopharmaceutical IV administration, data acquisition will begin in the pelvic region and move toward the head. First, localizer MRI scans will be performed to define the table positions. After correct positioning of the spatial acquisition windows is ensured, the combined PET/MRI acquisition will be initiated with 3 to 5 table positions at a 4-min acquisition time per table position.
7. Vital signs (heart rate and blood pressure) will be recorded again at the completion of the study.
8. Participants will be dismissed.
9. Participants will be contacted at 24 to 72 hours following the scan in order to capture potential late occurring Adverse Events.

The ^{68}Ga-PSMA-11 PET/MRI may be repeated at the completion of treatment to evaluate response to therapy, if requested by the treating physician.

Objectives of the Study

Primary

- Sensitivity, specificity, positive and negative predictive value of ^{68}Ga-PSMA-11 PET/MRI for the detection of regional nodal metastases compared to pathology at radical prostatectomy on a per patient basis using nodal regional correlation.

Secondary

- Sensitivity, specificity, positive and negative predictive value of ^{68}Ga-PSMA-11 PET/MRI for the detection of extra-pelvic nodal metastases, visceral metastases and osseous metastases compared to biopsy and imaging follow-up.

Exploratory

- Sensitivity, specificity, negative and positive predictive value for detection of regional nodal metastases in comparison to cross sectional imaging performed contemporaneously with the ^{68}Ga-PSMA-11 PET/MRI PET.
- One-year PSA progression free survival, comparing patients with and without pelvic nodal metastases.
- Correlation between SUV_{max} from ^{68}Ga-PSMA-11 PET/MRI and short axis diameter of nodal disease on cross sectional imaging correlate to presence of true pathology.
- Incidence of osseous and distant metastatic lesions.

Endpoints

Primary Endpoints

- PSMA-11 PET results for regional nodal disease.
- Nodal histology results from prostatectomy.

Secondary endpoints

- PSMA-11 PET results for extra-pelvic disease.

- Biopsy results and imaging follow-up results

Exploratory Endpoints

- Time to PSA progression
- SUV_{max} of lesions.
- Presence of osseous and distant metastasis.
- Safety: blood pressure, heart rate, self reported adverse events

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Inclusion Criteria

- ≥ 18 years-old
- Biopsy-proven prostate adenocarcinoma
- Planned prostatectomy with lymph node dissection
- Intermediate to high-risk disease (as determined by elevated PSA [PSA>10], T-stage [T2b or greater], Gleason score [Gleason score > 6] or other risk factors)
- Able to provide written consent.
- Karnofsky performance status of ≥ 50 (or ECOG/WHO equivalent)
- Diagnostic CT or MRI performed within 90 days of the research PET

3.2 Exclusion Criteria

- Patients not capable of getting PET study due to weight, claustrophobia, or inability to lay still for the duration of the exam
- Neoadjuvant chemotherapy or radiation therapy prior to prostatectomy, including focal ablation techniques (HiFu)
- Androgen deprivation therapy or other neoadjuvant treatments prior to PET imaging and surgery
- Metallic implants (contraindicated for MRI)

3.3 Informed Consent Process

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

3.4 Study Timeline

3.4.1 Primary Completion:

The study will reach primary completion 36 months from the time the study opens to accrual.

3.4.2. Study Completion:

The study will reach study completion 48 months from the time the study opens to accrual.

4. IMAGING AGENT INFORMATION

4.1 Study Agent

We will use ^{68}Ga-PSMA-11 as the PET radiopharmaceutical. This agent has previously been identified as DFKZ-11; HBED-CC PSMA; or the "Heidelberg compound."

The administered dosage of ^{68}Ga-PSMA-11 is 111 to 259 MBq (3 to 7 mCi) IV. We will use ^{68}Ga-PSMA-11 as the PET radiopharmaceutical. There are 2 publications on dosimetry for ^{68}Ga-PSMA-11 (PMID: 27260521; 28012435). The first lists 0.0236 mSv/MBq for the mean effective dose, while the other indicates 0.0258 mSv/MBq. We used the maximum potential administered activity of 7 mCi and the higher of the reported dosimetry values. Therefore, 259 MBq x 0.0258 mSv/MBq = 6.68 mSv.

To summarize the results of the published human studies, there were no observed adverse events to the radiopharmaceutical. The measured dosimetry showed that the critical organ with ^{68}Ga-PSMA-11 is the spleen, followed by the stomach wall; pancreas; and bladder wall. The effective dose of ^{68}Ga-PSMA-11 reported (0.0258 mSv/MBq) is similar to those of ^{68}Ga-DOTA-TOC (0.023 mSv/MBq), ^{68}Ga-DOTA-NOC (0.025 mSv/MBq), ^{68}Ga-DOTA-TATE (0.021 mSv/MBq) and ^{68}Ga-NOTA-RGD (0.022 mSv/MBq) (35-38).

4.2 Source of the Study Agent

Molecular Imaging Program at Stanford (MIPS)
Satellite Radiochemistry Facility
[redacted]
Stanford, CA 94305

4.3 Ordering

Ordered in Radiology Information System (RIS), address per above.

4.4 Agent Accountability

RIS is password protected and part of the electronic medical records.

5. IMAGING SPECIFICS

5.1 Modality or Modalities to be used

PET/MRI

5.2 Details of Imaging (ie, dynamic, static, number of scans, etc)

A localizer MRI scan will be performed at 45 minutes after injection of 3 to 7 mCi of ^{68}Ga-PSMA-11 to define the table positions. After correct positioning of the spatial acquisition windows is ensured, the combined PET/MRI acquisition will be initiated with 3 to 5 table positions at a 4-min acquisition time per table position. A volumetric T1 acquisition with fat-water separation and motion correction to enable free-breathing will be obtained at each table position and used for the generation of attenuation maps and for

anatomic allocation of the PET results. Simultaneously with the start of the T1 MRI sequence, the PET acquisition will start at the same table position, thus ensuring optimal temporal and regional correspondence between MRI and PET data. The PET acquisition time will be 4 min per table position, taking delayed acquisition times and radioactive decay into account. As the T1 will take less than 4 minutes, a rapid diffusion weighted MRI will also be performed. After completion of the PET acquisition, the table will be moved to the next table position and the procedure will be repeated. Upon completion of the PET acquisition for all stations, volumetric post-contrast T1- and T2-weighted MR images may be obtained at multiple stations as needed.

The PET emission scan is corrected using segmented attenuation data of the MRI scan. The PET images are reconstructed with a standard iterative algorithm. All images are reformatted into axial, coronal, and sagittal views and viewed with the software provided by the manufacturer (AW, GE Medical Systems).

5.3 Image interpretation

1. ^{68}Ga-PSMA-11 PET

PET images will initially be interpreted in random order at separate reading sessions by 3 board-certified nuclear medicine physicians. Cross-sectional MRI imaging from the PET will be available for anatomic correlate. Final reads for each patient will be interpreted as positive or negative for the presence of pelvic nodal disease, and positive or negative for the presence of osseous metastatic disease and soft tissue metastases outside of the pelvis.

Clinical Follow-up

a. Prostatectomy: patients without evidence of PSMA-11 PET positive nodal or metastatic disease noted on imaging will undergo radical prostatectomy. If a PSMA-11 PET positive regional pelvic node is noted, the urologist will be informed of the location of the suspicious node and the patient will undergo prostatectomy with nodal dissection.

    i. Patients with nodes seen on PSMA-11 PET without positive nodes on pathology, will be rescanned with CT or MRI to determine if the suspicious node was thought to be removed. A PSMA-11 PET may be repeated as well at the discretion of the treating physician.

b. If sites of PSMA-11 PET positive osseous or distant metastatic lesions are noted, the urologist will be informed, and further evaluation including further imaging (bone scan; NaF PET; CT; or MRI cross-section imaging) or targeted biopsy will be performed in order to restage the patient prior to the decision regarding whether or not a prostatectomy will be performed as per the responsible surgeon and standard of clinical care.

6. STUDY PROCEDURES

6.1 Criteria for Removal from Study

The Protocol Director may withdraw subjects from the study for one or more of the following reasons: failure to follow the instructions of the Protocol Director and/or study staff; determination that continuing the participation could be harmful to the subject; the study is cancelled or other administrative reasons.

6.2 Alternatives

The alternative is to not participate in the study.

7. STUDY CALENDAR

	Pre-Study	Scan Date	24 to 72 Hours Post-Study	12 Months
Informed consent	X			
Demographics	X			
Medical history	X			
^{68}Ga-PSMA-11		X		
Follow-up Call to Participant			X	
Data analysis				X

8. ADVERSE EVENTS AND REPORTING PROCEDURES

8.1 Potential Adverse Events

The administration of the radioactive substance will feel like a slight pinprick when given by IV injection. Patients who are claustrophobic may feel some anxiety while positioned in the scanner. Also, some patients find it uncomfortable to hold one position for more than a few minutes. The subjects will not feel anything related to the radioactivity of the substance in their body. Because the radioactivity is very short-lived, the radiation exposure is low. The substance amount is so small that it does not affect the normal processes of the body.

This research study involves exposure to radiation from one ^{68}Ga-PSMA-11 PET/MRI. The effective dose from one typical maximum of 259 MBq (range: 3 to 7 mCi) administration of ^{68}Ga-PSMA-11 is 6.68 mSv. There is no radiation exposure from MRI. Therefore, the effective dose from one ^{68}Ga-PSMA-11 PET/MRI is 6.68 mSv, approximately equal to 13% of the limit that radiation workers (eg, a hospital X-ray technician) are allowed to receive in one year.

8.2 Adverse Event Reporting

We do not anticipate hazardous situations for the subjects as a result of this protocol. However, standard of care procedures will be in place for verification of correct radiopharmaceutical dose and route of administration. The study Principal Investigator (PI) or his designee will report all serious adverse events (per 21CFR§312.32) to the Stanford CCTO Safety Coordinator within 10 working days of becoming aware of the event (5 days if the event is life-threatening or resulted in death) using the Adverse Events Communication Form. If the principal investigator determines the unanticipated adverse effect presents an unreasonable risk to subjects, the study will be terminated as soon as possible, but no later than 5 working days after the PI makes the determination and no later than 15 working days after first receiving notification of the effect.

9. REGULATORY CONSIDERATIONS

9.1 Institutional Review of Protocol

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

9.2 Data Management Plan

The CRFs will be stored in a locked office in the Nuclear Medicine clinic. Records will be kept using OnCore.

During the clinical investigation, the Protocol Director will evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome. Monitoring of the trial will occur every 8 weeks and a record of monitoring activities will be maintained by the study team.

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

10. Statistical Considerations and Evaluation of Results

10.1 Study Endpoints

Primary endpoints:

- PSMA-11 PET results for regional nodal disease.
- Nodal histology results from prostatectomy.

These will be expressed as range (mean $\pm$ SD) of number of lymph nodes identified by PET and by dissection during surgery plus histopathology.

10.2 Determination of Sample Size and Accrual Rate

10.2.1 Sample Size and Power Estimate

The estimated sample size will be 200 patients to adequately power the primary aim. The power analysis will be based on the comparison of sensitivity between conventional imaging and PSMA-11 PET. With a power of 80% and a significance level of 0.01, a sample size of 61 patients with nodal metastases is required. The following assumptions are made:

i. 30% of intermediate to high-risk patients have nodal metastases at prostatectomy.

ii. 25% of patients will not undergo the planned prostatectomy. Patients that do not undergo prostatectomy will not be included in the analysis population, and will not undergo central imaging review.

iii. Conventional imaging has a 45% detection sensitivity for nodal metastases on a per-patient basis (2).

iv. PSMA-11 PET has a 65% detection sensitivity for nodal metastases on a per-patient basis.

10.2.2 Accrual estimates

We anticipate enrolling 200 patients in total.

10.3 Analyses Plans

10.3.1 Analysis Population

All patients that undergo prostatectomy and have histology correlates will be included in the analysis for the primary endpoint.

10.3.2 Analysis of Primary Endpoint

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

PET images will be interpreted by 3 different readers in a random order at separate reading sessions. Cross-sectional imaging from the PET will be available for anatomic correlate. Final reads for each patient will be interpreted as positive or negative for the presence of pelvic nodal disease, and positive or negative for the presence of osseous metastatic disease and soft tissue metastases outside of the pelvis.

Visual interpretation of PET data:

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 1 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 adjacent background. 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.

b) Pathology analysis: Specimens from prostatectomy will be evaluated for the presence of nodal metastasis. This will be reported on a per-patient basis as positive or negative.

i) Nodes will be marked by location per site-specific protocol. For example if the urologist removed left and right nodal regions separately, then that patient will have two nodal regions (left/right). If a different surgeon removes nodes in six groups

(bilateral internal/external/obturator nodes), then that patient will have six nodal regions that will be analyzed.

ii) Although not routinely performed during standard practice, immunohistochemical staining for PSMA-11 of tumor specimens (primary and lymph node metastases) may be performed, but is not required for this study.

iii) The number of nodes counted on pathology will also be recorded.

c) Analysis plan for Primary Aim 1: For this study to reach success, 2 out of the 3 readers will have to demonstrate a detection sensitivity of 65% or greater for nodal metastases. Additionally, 2 out of the 3 readers will have to demonstrate a detection specificity of 90% or greater for regional nodal metastases based upon region as defined below on a per patient level. The sensitivity, specificity, positive and negative predictive value of PSMA-11 PET for the detection on a per patient basis will be determined using the below criteria:

i) True positive patient:

(1) PSMA-11 PET-positive for regional nodes; pathology at prostatectomy positive for regional nodes. Region will be defined by the granularity used by the urologist at time of prostatectomy. Sensitivity will be calculated at a patient level by region, meaning that one correct region would make a true positive on a patient level. Only one node needs to correspond between imaging and pathology for a patient to be considered a true positive.

(2) PSMA-11 PET-positive for regional nodes; pathology negative for regional nodes; imaging after prostatectomy demonstrates node was not removed at surgery; and follow-up biopsy or imaging demonstrates presence of nodal disease.

(a) Criteria for positive node on follow-up imaging: imaging within 3 to 12 months; the node decreases by more than 30% (for patients undergoing systemic treatment or focal therapy at this site); or increase by more than 20% in short axis diameter in the absence of treatment (with a minimum of 3 mm in change in size).

ii) True negative patient:

(1) PSMA-11 PET-negative for regional nodes; pathology at prostatectomy negative for regional nodes.

iii) False positive patient:

(1) PSMA-11 PET-positive for regional nodes; pathology at prostatectomy is negative; and imaging after prostatectomy demonstrates that node is no longer present.

(2) PSMA-11 PET positive for regional node, but pathology at prostatectomy is positive for node but in a different nodal region than that node seen on PSMA-11 PET.

iv) False negative patient:

(1) PSMA-11 PET negative for regional nodes, but pathology at prostatectomy is positive.

v) Non-evaluable:

(1) PSMA-11 PET positive for regional nodes; pathology negative for regional nodes; imaging after prostatectomy demonstrates node was not removed at surgery; and no definitive follow-up is available.

(2) Patients with extrapelvic nodal metastases will not be included in this analysis if patients do not undergo prostatectomy.

10.3.3 Analysis of Secondary Endpoints

We will report the sensitivity, specificity, positive and negative predictive value of PSMA-11 PET over all imaged regions as well as broken down by the following regions: extra-pelvic nodal metastases, visceral metastases and osseous metastases. Follow-up for extra-pelvic nodal metastases, visceral metastases and osseous metastases are defined as below:

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 to 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 (ie, 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 to 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 to 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 (ie, 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 to 12 months, sites of initial ^{68}Ga-PSMA-11 positive visceral 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 visceral 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) Histopathology correlation: for lesions that have biopsy correlation, we will use the following criteria to determine positive and negative lesions:

(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.

- 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.

- 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.

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

  - 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 ^{68}Ga-PSMA-11 PET-positive lesions will be further evaluated:

– If pathology demonstrates an alternative diagnoses that is known to be ^{68}Ga-PSMA-11-positive (eg, renal cell carcinoma (RCC) 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.

(c) 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.

10.3.4 Analysis of Exploratory Endpoints

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 paired McNemar's test will be used to compare the PPVs of ^{68}Ga-PSMA-11 PET imaging to the PPVs of conventional imaging.

Sensitivity, specificity, and NPVs on a per-patient basis of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy will be summarized in tabular format. Furthermore, the positive and negative likelihood ratios (LR+ and LR-) will be calculated and reported. 95 confidence intervals of sensitivity, specificity, and NPV will be calculated using the Wilson score method. The comparisons of sensitivity, specificity, and NPV on a per-patient basis of ^{68}Ga-PSMA-11 PET imaging will be compared to of sensitivity, specificity, and NPV on a per-patient basis of conventional imaging using a paired McNemar's test.

Detection rates on a per-patient basis of ^{68}Ga-PSMA-11 PET stratified by PSA value (0.2 to < 0.5; 0.5 to < 1.0; 1.0 to < 2.0; 2.0 to < 5.0; ≥ 5.0) will be summarized in tabular format and compared between PSA strata using chi-square analysis. The impact of ^{68}Ga-PSMA-11 PET on clinical management in BCR patients will be evaluated using descriptive statistics.

10.4 Accrual estimates

We expect the accrual of 40 patients each year for 5 years. There are approximately 120 radical prostatectomies performed on patients with newly diagnosed prostate cancer at Stanford each year. We plan to enroll 40 participants/year and this is achievable given our experience with other protocols and the support from the referring physicians, Drs Chung, Sonn, Brooks, and Gill.

Inclusion/Exclusion Criteria Checklist

Protocol Title:	^{68}Ga-PSMA-11 PET/MRI for detection of regional nodal and distant metastases in patients with intermediate and high-risk prostate cancer
Protocol Number:	**IRB-35931 / PROS0075**
Principal Investigator:	**Andrei Iagaru, MD**

Inclusion Criteria – Yes must be checked to be eligible (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation**
1. ≥ 18 years-old	☐	☐	☐
2. Biopsy-proven prostate adenocarcinoma	☐	☐	☐
3. Planned prostatectomy with lymph node dissection	☐	☐	☐
4. Intermediate to high-risk disease (as determined by elevated PSA [PSA>10], T-stage [T2b or greater], Gleason score [Gleason score > 6] or other risk factors)	☐	☐	☐
5. Able to provide written consent	☐	☐	☐
6. Karnofsky performance status of ≥ 50 (or ECOG/WHO equivalent)	☐	☐	☐
7. Diagnostic CT or MRI performed within 90 days of the research PET	☐	☐	☐

Exclusion Criteria –No must be checked to be eligible (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation**
1. Patients not capable of getting PET study due to weight, claustrophobia, or inability to lay still for the duration of the exam	☐	☐	☐
2. Neoadjuvant chemotherapy or radiation therapy prior to prostatectomy including focal ablation techniques (HiFu)	☐	☐	☐
3. Androgen deprivation therapy or other neoadjuvant treatments prior to PET imaging surgery	☐	☐	☐
4. Metallic implants (contraindicated for MRI)	☐	☐	☐

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

Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐**eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

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