^{68}Ga-PSMA-11 PET/CT for detection of recurrent prostate cancer after initial therapy in patients with elevated PSA

Principal Investigator / Protocol Director
Andrei Iagaru, MD
300 Pasteur Drive, Room H-2230
Stanford, CA 94305
Phone: xxx-xxx-xxxx
Fax: xxx-xxx-xxxx
Email: aiagaru@stanford.edu

Co-investigators	
Steven Hancock, MD 875 Blake Wilbur Dr; Stanford, CA 94305 Phone: [redacted] Email: shancock@stanford.edu	Guido Davidzon, MD 300 Pasteur Dr, Stanford, CA 94305 Phone [redacted] Email: gdavidzon@stanford.edu
Sandy Srinivas, MD 875 Blake Wilbur Dr; Stanford, CA 94305 Phone: : [redacted] Email: sandysri@stanford.edu	Carina Mari Aparici, MD 300 Pasteur Dr, Stanford, CA 94305 Phone: [redacted] Email: drmari@stanford.edu
Biostatistician Jarrett Rosenberg, PhD 1201 Welch Road, Stanford, CA 94305 Phone: [redacted] Email: Jarrett.rosenberg@stanford.edu	**Study Coordinator** Jordan Cisneros or designate Phone: [redacted] Email: jdcis@stanford.edu

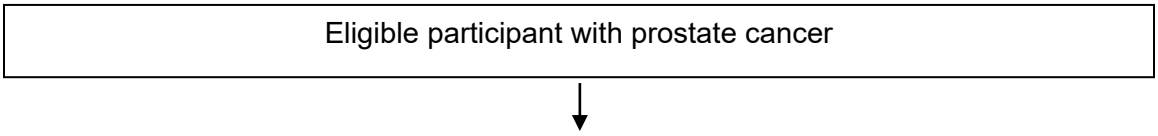
Protocol IRB-35932 // PROS0076 // **NCT02673151**
Protocol Amendment 3 // 12 July 2018

TABLE OF CONTENTS

PROTOCOL SYNOPSIS

TITLE	^{68}Ga-PSMA-11 PET/CT for detection of recurrent prostate cancer after initial therapy in patients with elevated PSA
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”
PRIMARY OBJECTIVE	To evaluate ^{68}Ga-PSMA-11 PET/CT for detection of recurrent prostate cancer after initial therapy in patients with elevated PSA
SAMPLE SIZE	200 participants
GOALS	Prospective single-center, single-arm study. HYPOTHESES 1. At least 30% of these patients will have one or more lesions detected on ^{68}Ga-PSMA-11 PET/CT. 2. ^{68}Ga-PSMA-11 PET/CT will have sensitivity and specificity of at least 70% in this context. STATISTICAL TEST We will calculate point estimates and 95% confidence intervals for: 1. Percentage of patients who had true lesions. 2. Sensitivity and specificity of ^{68}Ga-PSMA-11 PET/CT. STATISTICAL POWER AND SAMPLE SIZE We expect to recruit 200 patients over the course of this trial. The number of lesions cannot be predicted at this time, however, if our expectation of a 30% discovery rate is correct, the resulting confidence interval would be roughly +/- 7 percentage points, and confidence intervals for specificity/sensitivity would be roughly +/- 10 percentage points.

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/CT for detection of recurrent prostate cancer after initial therapy in patients with elevated SA.

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). Subsequent treatment is multifaceted and may involve observation, surgery (prostatectomy), radiation therapy (external beam or brachytherapy), hormonal therapy, chemotherapy, or a combination of these (2-4).

Up to 40% of the patients with prostate cancer develop biochemical recurrence within 10 years after initial treatment (5). Usually an increase of the PSA-level precedes a clinically detectable recurrence by months to years (6). However, it cannot differentiate between local, regional or systemic disease with the necessary precision that is essential for further disease management (7).

Morphological imaging methods exhibit considerable limitations: sensitivity ranges between 25% and 54% for the detection of local recurrence by transrectal ultrasound (TRUS) or contrast-enhanced CT and is moderately improved by using functional MRI techniques (7-9). The sensitivity for detection of lymph node metastases of CT or MRI is reported to be 30-80% (10). Ultra-small particles of iron oxides (USPIOs) proved to be very effective, but are yet to be approved by regulatory authorities (11). Bone metastases presenting as osteoblastic lesions can be effectively detected by bone scintigraphy, PET, CT and MRI (12, 13).

Various targets have been addressed by molecular imaging to improve the detection of recurrent prostate cancer. PET tracers such as ^{18}F- or ^{11}C-labeled choline and ^{11}C-acetate have been investigated for the diagnosis of recurrent (14-16) prostate cancer. Their feasibility in primary diagnosis is limited because of uptake in benign tissue such as benign prostatic hyperplasia or inflammatory lymph nodes (9, 17). In addition, fluorinated versions are not available in the United States, while ^{11}C-labeled tracers cannot be widely used due to the requirement for an on-site cyclotron due to the short half-life. ^{18}F-FACBC, a new synthetic amino acid, might be superior when compared to ^{11}C-choline PET/CT (18).

However, recent work indicates that ^{18}F-FACBC uptake in prostate cancer is similar to that in BPH nodules (19). Prostate-specific membrane antigen (PSMA) continues to elicit high interest. 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. It therefore provides a promising target for prostate cancer-specific imaging. Recently methods have been developed to label PSMA ligands with ^{68}Ga and ^{18}F. Initial experience suggests that these novel tracers can detect prostate cancer relapses and

metastases with high contrast by binding to the extracellular domain of PSMA, followed by internalization (20, 21). However, these promising agents do not detect all recurrences.

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 (22, 23). 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 (24). However, recent work indicates that ^{18}F-FACBC uptake in prostate cancer is similar to that in BPH nodules (25).

In addition, prostate-specific membrane antigen (PSMA) recently has received increased attention (26). 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 (27). It therefore provides a promising target for prostate cancer-specific imaging (28). Recently methods have been developed to label PSMA ligands with ^{68}Ga enabling their use for PET imaging and therapy (29). 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 (30). 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).

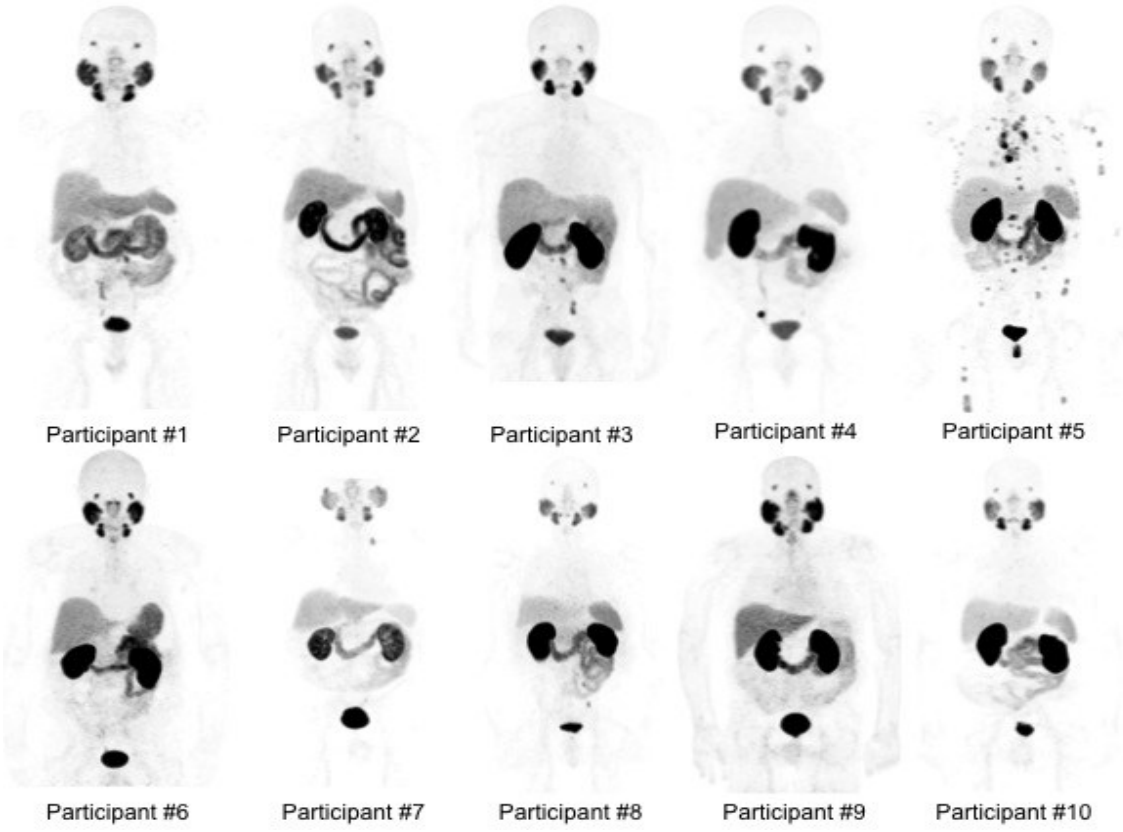


Figure 1: Maximum intensity projection (MIP) images from 10 participants in the pilot study conducted at Stanford University.

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 (31, 32). Therefore, we propose the following aim: to evaluate ^{68}Ga-PSMA-11 PET/CT for detection of recurrent prostate cancer after initial therapy in patients with elevated PSA.

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 52–212 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 (30). 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 (32). 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.

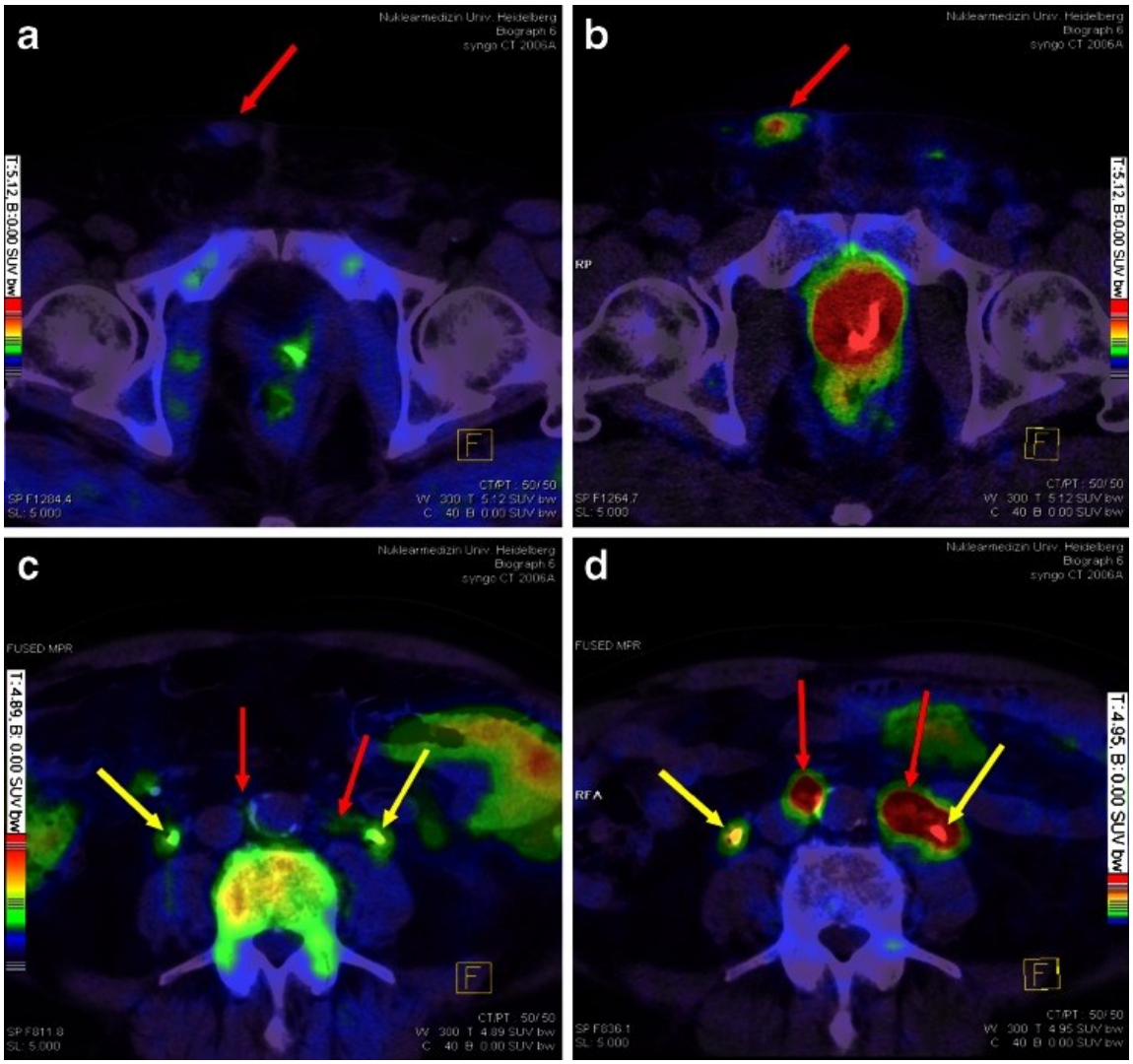


Figure 2: Red arrows point to a nodular pelvic wall metastasis (a, b, histologically-confirmed) and to small lymph nodes (c, d) which present with clearly pathological tracer uptake in ^{68}Ga-PSMA-11 PET/CT (b and d) only. Yellow arrows point to both catheterized ureters (c, d). Patient presented with 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 evaluated the first 32 participants enrolled in the study (33). Excluding one patient with a very high PSA of 1170 ng/mL, the mean PSA at time of scan was 7.3 ng/mL. ^{68}Ga-PSMA-11 PET detected sites of recurrence in 24/32 (75 %) patients, including 8/12 (66.7%) patients with PSA below 1 ng/mL, and the lowest PSA value associated with a positive scan was 0.21 ng/mL. An example is shown in Figure 3.

Figure 3: 73 year-old man with rising PSA (0.9 ng/dl) after initiat treatment of prostate cancer. ^{68}Ga-PSMA-11 PET identifies recurrent prostate cancer in a left pelvic lymph node.

2.5 Study Design

This is a phase 2-3 study with a total of 200 participants with biochemically recurrent prostate cancer. Eligible participants will undergo baseline assessments at enrollment. Study participants will receive ^{68}Ga-PSMA-11 and undergo a PET/CT. All patients will first be seen by a Stanford Cancer Institute physician and then referred 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, blood pressure, respiratory rate, pulse oxymetry) 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. A dose of 20 mg of furosemide is recommended to be injected together with, shortly before, or after administration of the radiotracer in order to minimize PET scatter artifacts from excreted radiotracer accumulation in the kidney and urinary bladder that can occur with ^{68}Ga-PSMA-11. However, this is not needed if the scanner can reduce such artifacts during image reconstruction
6. Participant will void immediately prior to the scan
7. Approximately 50 to 100 minutes later, a low-dose CT will be obtained from vertex to mid-thighs; this will use 120 kV and dose modulation based on body habitus, ranging 10 to 105 mA. This will be followed by a static PET emission scan over the same area.
8. If participant agrees, immediately after first scan and without reinjecting ^{68}Ga-PSMA-11, a second PET/CT will be acquired to compare standard vs digital PET/CT. The CT will be done for attenuation correction only.
9. Vital signs (heart rate, blood pressure, respiratory rate, pulse oxymetry) will be recorded again at the completion of the study.
10. Participants be dismissed.
11. Participants will be contacted at 24 to 72 hours following the scan in order to capture potential late occurring Adverse Events.
12. Clinical follow-up of participant at 3 to 12 months following the scan in order to analyze secondary endpoints.

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

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

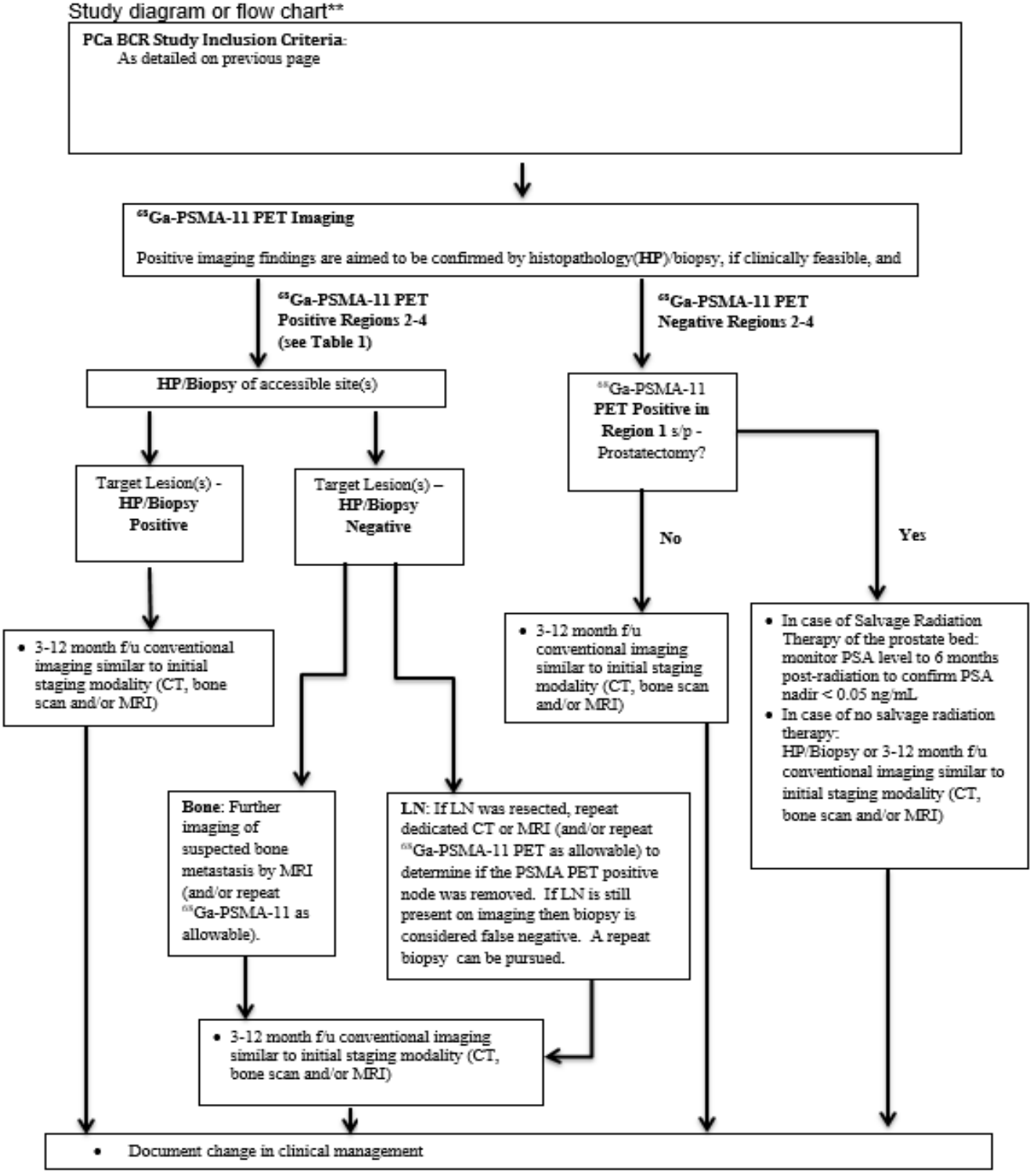
3.1 Inclusion Criteria

- ≥ 18 years-old
- Histopathological-proven prostate adenocarcinoma
- Rising PSA after definitive therapy with prostatectomy or radiation therapy (external beam or brachytherapy)
    a. Post radical prostatectomy (RP) – AUA recommendation (34)
        i. PSA greater than 0.2 ng/mL measured after at least 6 weeks from radical prostatectomy
        ii. Confirmatory persistent PSA greater than 0.2 ng/mL (total of two PSA measurements greater than 0.2 ng/mL)
    b. Post-radiation therapy –ASTRO-Phoenix consensus definition (35)
        i. A rise of PSA measurement of 2 or more ng/mL over the nadir
- Able to provide written consent
- Karnofsky performance status of ≥ 50 (or ECOG/WHO equivalent)

3.2 Exclusion Criteria

- Investigational therapy for prostate cancer.
- Unable to lie flat, still or tolerate the study scan.
- Prior history of any other malignancy within the last 2 years, other than skin basal cell or cutaneous superficial squamous cell carcinoma that has not metastasized and superficial bladder cancer.

Study diagram or flow chart**



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

The administered dosage 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) (36-39).

4.2 Source of the Study Agent

Molecular Imaging Program at Stanford
Satellite Radiochemistry Facility
300 Pasteur Dr, C21
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/CT

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

Whole-body (skull base to mid-thighs) PET/CT images will be obtained using the GE PET/CT 600 or 690 scanners. In brief, PET/CT images will be acquired in 3D mode at 50 to 100 minutes after injection of 3 to 7 mCi of ^{68}Ga-PSMA-11.

The PET emission scan is corrected using segmented attenuation data of the CT scan. PET images are reconstructed using ordered subset expectation maximization (OSEM) with 2 iterations and 32 subsets for the Discovery 600 scanner and with 2 iterations and 24 subsets for the Discovery 690 scanner. These are the vendor-recommended reconstruction parameters. Images will be reviewed and analyzed using Advantage Workstation version 4.6 (GE Healthcare).

5.3 Details of processing/analysis

The lesions will be analyzed by Nuclear Medicine physicians blinded to the diagnosis and results of the other scan, in a randomized order to avoid bias. ^{68}Ga-PSMA-11 PET data 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.

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 - 48 Hours Post-Scan	3-12 Months Post-Scan	12 Months (End-of-Study)
Informed consent	X				
Demographics	X				
Medical history	X				
^{68}Ga-PSMA-11		X			
Follow-up Call to Participant			X		
Clinical Follow-up				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 PET/CT. The effective dose from one typical maximum of 259 MBq (range: 3-7 mCi) administration of ^{68}Ga-PSMA is 6.68 mSv. The effective dose from one CT attenuation scan is 3 mSv. Therefore, the total effective dose from the ^{68}Ga-PSMA PET/CT scan is 9.68 mSv, approximately equal to 19.4% of the limit that radiation workers (for example, 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 results in death) using the Adverse Events Communication Form. If the Principal Investigator determines the unanticipated adverse device 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. MEASUREMENTS

10.1 Outcome Measures

The principal goal of this study is to compare, in the setting of suspected prostate cancer recurrence, the diagnostic performance of ^{68}Ga-PSMA-11 PET/CT in cases where conventional imaging for detecting recurrent prostate cancer is likely to have false negatives. Sites of suspected disease will be evaluated by ^{68}Ga-PSMA-11 PET/CT and conventional imaging by region for all patients. Specifically, it is hypothesized that the diagnostic performance of the ^{68}Ga-PSMA-11 PET/CT will be superior to anatomical imaging, and that ^{68}Ga-PSMA-11 PET/CT will provide complementary information.

10.1.1 Primary Outcome

Primary Outcome Title: Confirmation of Prostate Cancer Recurrence

Description: Prostate cancer patients with suspected prostate cancer recurrence will be evaluated with ^{68}Ga-PSMA-11 PET/CT and conventional imaging. The outcome will be reported as the percentage of participants for whom tumor lesions are identified by ^{68}Ga-PSMA-11 PET/CT, and for whom tumor lesions are identified by histopathology/biopsy and/or conventional imaging follow-up. The outcome is reported as percentages without dispersion.

Time Frame: 1 year

10.1.2 Secondary Outcomes

Secondary Outcome Title: ^{68}Ga-PSMA-11 PET/CT Sensitivity and Specificity by Participant

Description: The sensitivity and specificity of ^{68}Ga-PSMA-11 PET/CT for detection of tumor by participant will be determined, as confirmed by conventional imaging follow-up and/or histopathology/biopsy, within the following 1 year. The sensitivity and specificity of ^{68}Ga-PSMA-11 PET/CT for detection of tumor lesions is reported with the 95% confidence interval.

Time Frame: 12 months

Secondary Outcome Title: ^{68}Ga-PSMA-11 PET/CT Sensitivity and Specificity by Region

Description: The sensitivity and specificity of ^{68}Ga-PSMA-11 PET/CT for tumor detection by location will be determined, as confirmed by conventional imaging follow-up and/or histopathology/biopsy, within the following 1 year. The regions evaluated will be the prostate bed; pelvis outside of prostate bed including lymph nodes; extrapelvic soft tissue; lymph nodes; and organ metastases (non bone); and bone metastases. The

sensitivity and specificity of ^{68}Ga-PSMA-11 PET/CT for detection at the specified tumor locations is reported with the 95% confidence interval.

Time Frame: 12 months

Secondary Outcome Title: ^{68}Ga-PSMA-11 PET/CT Predictive Value by Participant

Description: The predictive value of ^{68}Ga-PSMA-11 PET/CT for detection of tumor, as confirmed by conventional imaging follow-up and/or histopathology/biopsy, within the following 1 year, is assessed by participant. Positive predictive value (PPV) is the probability that participants identified by ^{68}Ga-PSMA-11 PET/CT as having prostate cancer recurrence, do have prostate cancer recurrence. Negative predictive value (NPV) is the probability that participants not identified by ^{68}Ga-PSMA-11 PET/CT as having prostate cancer recurrence, do not have prostate cancer recurrence. The outcome is reported as the PPV and the NPV of ^{68}Ga-PSMA-11 PET/CT for confirmation of prostate cancer recurrence by participant, with 95% confidence interval.

Time Frame: 12 months

Secondary Outcome Title: ^{68}Ga-PSMA-11 PET/CT Predictive Value by Region

Description: The predictive value of ^{68}Ga-PSMA-11 PET/CT for detection of tumor location, as confirmed by conventional imaging follow-up and/or histopathology/biopsy, within the following 1 year, is assessed by region [prostate bed; pelvis outside of prostate bed including lymph nodes; extrapelvic soft tissue; lymph nodes; and organ metastases (non bone); and bone metastases]. Negative predictive value (NPV) is the probability that participants not identified by ^{68}Ga-PSMA-11 PET/CT as having prostate cancer recurrence, do not have prostate cancer recurrence. The outcome is reported as the PPV and the NPV of ^{68}Ga-PSMA-11 PET/CT for confirmation of prostate cancer recurrence by region, with 95% confidence interval.

Time Frame: 12 months

Secondary Outcome Title: ^{68}Ga-PSMA-11 PET/CT Per-patient Tumor Detection Rates

Description: ^{68}Ga-PSMA-11 PET/CT tumor detection rates by patient, stratified by PSA value in ng/mL (0.2 to < 0.5; 0.5 to < 1.0; 1.0 to < 2.0; 2.0 to < 5.0; ≥ 5.0), are reported with mean ± SD and 95% confidence interval.

Time Frame: 12 months

10.2 Measurement Methods

Visually PET positive lymph nodes will be considered greater than blood pool (adjacent or mediastinal blood pool); PET positive bone lesions will be considered greater than physiologic bone marrow; PET positive prostate, prostate bed and visceral lesions will be considered greater than physiologic background activity of the involvement organ or anatomic site.

Sites of suspected metastatic disease will be graded as positive or negative on two separate analysis, for a more sensitive or specific visual read respectively.

10.3 Primary Endpoint

The primary endpoint is sensitivity and PPV on a per-patient and per-region-basis (Table 1) of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy.

Table 1: Region Definition

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

10.4 Secondary endpoints:

1. PPV and negative predictive value (NPV) on a per-patient and per-region-basis (Table 1) of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy and conventional imaging follow-up.
2. Sensitivity and specificity on a per-patient basis of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy and conventional imaging follow-up.
3. Detection rates on a per-patient basis of ^{68}Ga-PSMA-11 PET stratified by PSA value in ng/mL (0.2 to < 0.5; 0.5 to < 1.0; 1.0 to < 2.0; 2.0 to < 5.0; ≥ 5.0).

10.5 Exploratory Endpoints

1. Impact of ^{68}Ga-PSMA-11 PET on clinical management in patients with recurrence of prostate cancer.
2. Inter-reader reproducibility

10.6 Measurement Time Points

Uptake will be evaluated after the scan completion.

11. STATISTICAL CONSIDERATIONS

11.1 Statistical Design

Prospective single center, single-arm study. Patients will be scanned with ^{68}Ga-PSMA-11 PET/MRI. MRI and PET/MRI scans will each be evaluated separately by 3 readers.

11.2 Randomization

No randomization will be done.

11.3 Key variables

11.3.1 Analysis Population

All lesions identified by ^{68}Ga-PSMA-11 PET/CT.

11.3.2 Analysis Plan

We will calculate point estimates and 95% confidence intervals for:

1. Percentage of patients who had true lesions.
2. Sensitivity and specificity of ^{68}Ga-PSMA-11 PET/CT.

11.4 Sample Size

We expect to recruit 200 patients over the course of this trial. The number of lesions cannot be predicted at this time, however, if our expectation of a 30% discovery rate is correct, the resulting confidence interval would be roughly ± 7 percentage points, and confidence intervals for specificity/sensitivity would be roughly ± 10 percentage points.

11.5 Accrual estimates

We expect the accrual of 40 patients each year for 5 years.

Inclusion/Exclusion Criteria Checklist

Protocol Title:	^{68}Ga PSMA-11 PET/CT for detection of recurrent prostate cancer after initial therapy in patients with elevated PSA and non-contributory bone scintigraphy, computed tomography (CT) or magnetic resonance imaging (MRI)
Protocol Number:	**IRB-35932 / PROS0076**
Principal Investigator:	**Andrei Iagaru, MD**

Inclusion Criteria – Yes must be checked to be eligible (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation**
1. ≥ 18 year-old	☐	☐	☐
2. Histologically-proven prostate adenocarcinoma			
3. Rising PSA after definitive therapy with prostatectomy or radiation therapy (external beam or brachytherapy) a. Post radical prostatectomy (RP) – AUA recommendation i. PSA greater than 0.2 ng/mL measured after at least 6 weeks from radical prostatectomy ii. Confirmatory persistent PSA greater than 0.2 ng/mL (total of two PSA measurements greater than 0.2 ng/mL) b. Post-radiation therapy –ASTRO-Phoenix consensus definition i. A rise of PSA measurement of 2 or more ng/mL over the nadir	☐	☐	☐
4. Able to provide written consent	☐	☐	☐
5. Karnofsky performance status of ≥50 (or ECOG/WHO equivalent)	☐	☐	☐

Exclusion Criteria –No must be checked to be eligible (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation**
1. Investigational therapy for prostate cancer	☐	☐	☐
2. Unable to lie flat, still or tolerate the study scan	☐	☐	☐
3. Prior history of any other malignancy within the last 2 years, other than skin basal cell or cutaneous superficial squamous cell carcinoma that has not metastasized and superficial bladder cancer.	☐	☐	☐

*****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:	

REFERENCES:

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA: A Cancer Journal for Clinicians. 2015;65(1):5-29.
2. Roscigno M, Sangalli M, Mazzoccoli B, Scattoni V, Da Pozzo L, Rigatti P. Medical therapy of prostate cancer. A review. Minerva urologica e nefrologica. 2005;57(2):71-84.
3. Oh WK, Kantoff PW. Treatment of locally advanced prostate cancer: is chemotherapy the next step? Journal of clinical oncology. 1999;17(11):3664-75.
4. Jani AB. Management strategies for locally advanced prostate cancer. Drugs & aging. 2006;23(2):119-29.
5. Isbarn H, Wanner M, Salomon G, et al. Long-term data on the survival of patients with prostate cancer treated with radical prostatectomy in the prostate-specific antigen era. BJU International. 2010;106(1):37-43.
6. Van Poppel H, Vekemans K, Da Pozzo L, et al. Radical prostatectomy for locally advanced prostate cancer: Results of a feasibility study (EORTC 30001). European Journal of Cancer. 2006;42(8):1062-7.
7. Bott SRJ. Management of recurrent disease after radical prostatectomy. Prostate Cancer & Prostatic Diseases. 2004;7(3):211-6.
8. Panebianco V, Sciarra A, Lisi D, et al. Prostate cancer: 1HMRS-DCEMR at 3 T versus [(18)F]choline PET/CT in the detection of local prostate cancer recurrence in men with biochemical progression after radical retropubic prostatectomy (RRP). European Journal of Radiology. 2012;81(4):700-8.
9. Beer AJ, Eiber M, Souvatzoglou M, Schwaiger M, Krause BJ. Radionuclide and hybrid imaging of recurrent prostate cancer. Lancet Oncol. 2011;12(2):181-91.
10. Oyen RH, Poppel HPV, Ameye FE, Voorde WAVd, Baert AL, Baert LV. Lymph node staging of localized prostatic carcinoma with CT and CT-guided fine-needle aspiration biopsy: prospective study of 285 patients. Radiology. 1994;190(2):315-22.
11. Harisinghani MG, Barentsz J, Hahn PF, et al. Noninvasive Detection of Clinically Occult Lymph-Node Metastases in Prostate Cancer. New England Journal of Medicine. 2003;348(25):2491-9.
12. Iagaru A, Young P, Mittra E, Dick DW, Herfkens R, Gambhir SS. Pilot Prospective Evaluation of 99mTc-MDP Scintigraphy, 18F NaF PET/CT, 18F FDG PET/CT and Whole-Body MRI for Detection of Skeletal Metastases. Clinical Nuclear Medicine. 2013;38(7):e290-e6.
13. Iagaru A, Mittra E, Dick D, Gambhir S. Prospective Evaluation of 99mTc MDP Scintigraphy, 18F NaF PET/CT, and 18F FDG PET/CT for Detection of Skeletal Metastases.

Mol Imaging Biol. 2012;14(2):252-9.
14. Sandblom G, Sörensen J, Lundin N, Häggman M, Malmström P-U. Positron emission tomography with C11-acetate for tumor detection and localization in patients with prostate-specific antigen relapse after radical prostatectomy. Urology. 2006;67(5):996-1000.
15. Oyama N, Miller TR, Dehdashti F, et al. 11C-Acetate PET Imaging of Prostate Cancer: Detection of Recurrent Disease at PSA Relapse. Journal of Nuclear Medicine. 2003;44(4):549-55.
16. Wachter S, Tomek S, Kurtaran A, et al. 11C-Acetate Positron Emission Tomography Imaging and Image Fusion With Computed Tomography and Magnetic Resonance Imaging in Patients With Recurrent Prostate Cancer. Journal of clinical oncology. 2006;24(16):2513-9.
17. Rietbergen DDD, van der Hiel B, Vogel W, Stokkel MPM. Mediastinal lymph node uptake in patients with prostate carcinoma on F18-choline PET/CT. Nuclear medicine communications. 2011;32(12):1143-7.
18. Nanni C, Schiavina R, Boschi S, et al. Comparison of 18F-FACBC and 11C-choline PET/CT in patients with radically treated prostate cancer and biochemical relapse: preliminary results. Eur J Nucl Med Mol Imaging. 2013;40 Suppl 1:S11-7.
19. Turkbey B, Mena E, Shih J, et al. Localized prostate cancer detection with 18F FACBC PET/CT: comparison with MR imaging and histopathologic analysis. Radiology. 2014;270(3):849-56.
20. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of Hybrid 68Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. Journal of Nuclear Medicine. 2015;56(5):668-74.
21. Rowe SP, Gage KL, Faraj SF, et al. 18F-DCFBC PET/CT for PSMA-based Detection and Characterization of Primary Prostate Cancer. Journal of Nuclear Medicine. 2015.
22. Heinisch M, Dirisamer A, Loidl W, et al. Positron emission tomography/computed tomography with F-18-fluorocholine for restaging of prostate cancer patients: meaningful at PSA < 5 ng/ml?
23. Vees H, Buchegger F, Albrecht S, et al. 18F-choline and/or 11C-acetate positron emission tomography: detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1 ng/mL) after radical prostatectomy.
24. Nanni C, Schiavina R, Boschi S, et al. Comparison of 18F-FACBC and 11C-choline PET/CT in patients with radically treated prostate cancer and biochemical relapse: preliminary results.
25. Turkbey B, Mena E, Shih J, et al. Localized prostate cancer detection with 18F FACBC

PET/CT: comparison with MR imaging and histopathologic analysis.
26. Schäffer M, Bauder Wüst U, Leotta K, et al. A dimerized urea-based inhibitor of the prostate-specific membrane antigen for 68Ga-PET imaging of prostate cancer.
27. Sweat SD, Pacelli A, Murphy GP, Bostwick DG. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases.
28. Eder M, Eisenhut M, Babich J, Haberkorn U. PSMA as a target for radiolabelled small molecules.
29. Hillier SM, Maresca KP, Femia FJ, et al. Preclinical Evaluation of Novel Glutamate-Urea-Lysine Analogues That Target Prostate-Specific Membrane Antigen as Molecular Imaging Pharmaceuticals for Prostate Cancer. Cancer Research. 2009;69(17):6932-40.
30. Afshar Oromieh A, Malcher A, Eder M, et al. PET imaging with a [68Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions.
31. Afshar Oromieh A, Haberkorn U, Eder M, Eisenhut M, Zechmann CM. [68Ga]Gallium-labelled PSMA ligand as superior PET tracer for the diagnosis of prostate cancer: comparison with 18F-FECH.
32. Afshar Oromieh A, Zechmann C, Malcher A, et al. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer.
33. Park S, HATAMI N, Baratto L, Yohannan T, Davidzon G, Iagaru A. Dual-Time 68Ga-PSMA-11 Imaging for Biochemically Recurrent Prostate Cancer Using LYSO and SiPM-Based Detectors PET/CT. Journal of Nuclear Medicine. 2018;59(supplement 1):431.
34. Cookson MS, Aus G, Burnett AL, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. The Journal of urology. 2007;177(2):540-5.
35. Roach M, 3rd, Hanks G, Thames H, Jr., et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. International journal of radiation oncology, biology, physics. 2006;65(4):965-74.
36. Hartmann H, Zöphel K, Freudenberg R, et al. [Radiation exposure of patients during 68Ga-DOTATOC PET/CT examinations]. Nuclear-Medizin. 2009;48(5):201-7.
37. Pettinato C, Sarnelli A, Di Donna M, et al. 68Ga-DOTANOC: biodistribution and dosimetry in patients affected by neuroendocrine tumors. European journal of nuclear medicine

and molecular imaging. 2008;35(1):72-9.
38. Sandström M, Velikyan I, Garske-Román U, et al. Comparative Biodistribution and Radiation Dosimetry of 68Ga-DOTATOC and 68Ga-DOTATATE in Patients with Neuroendocrine Tumors. The Journal of nuclear medicine. 2013;54(10):1755-9.
39. Kim J, Lee J, Kang K, et al. Whole-body distribution and radiation dosimetry of (68)Ga-NOTA-RGD, a positron emission tomography agent for angiogenesis imaging. Cancer biotherapy and radiopharmaceuticals. 2012;27(1):65-71.