UTSouthwestern
Harold C. Simmons
Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

STU-2019-1198

The Role of 68Gallium PSMA-11 in Enhancing Diagnosis of Primary and Metastatic Prostate Cancer

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Study Drug/Treatment: 68Ga Prostate Specific Angtigen-11

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Amendment/Version # 3

STU-2019-1198

The Role of 68Gallium PSMA-11 in Enhancing Diagnosis of Primary and Metastatic Prostate

Principal Investigator (PI) Name: **Neil Rofsky, MD**

PI Signature: _____

Date: _____

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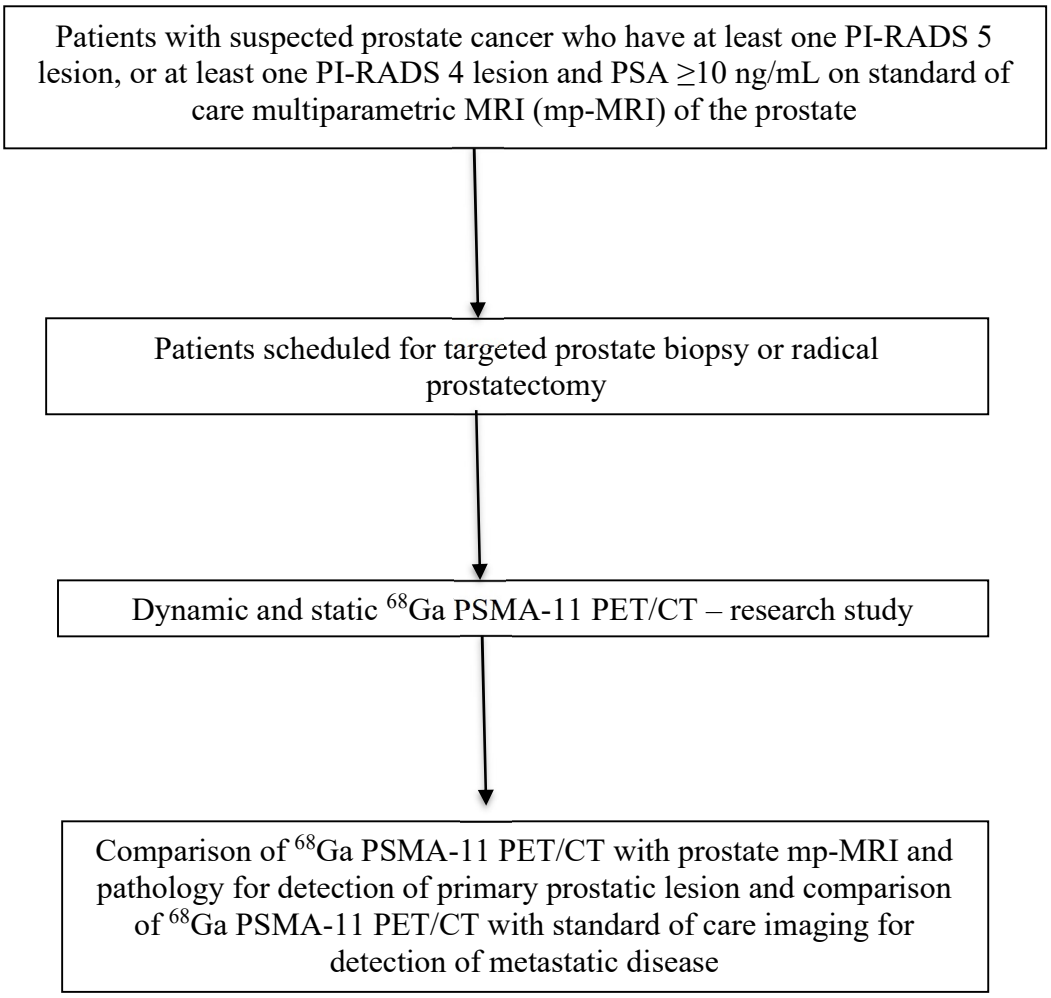
LIST OF ABBREVIATIONS (EXAMPLES)

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IDE	Investigational Device Exemption
IHC	Immunohistochemistry
IND	Investigational New Drug
IV (or iv)	Intravenously
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic Complete Response
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
p.o.	peros/by mouth/orally
PR	Partial Response
RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease

SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	The Role of ^{68}Ga PSMA-11 in Enhancing Diagnosis of Primary and Metastatic Prostate Cancer
Short Title	^{68}Ga PSMA-11 PET/CT in Prostate Cancer
Protocol Number	STU-2019-1198
Phase	Phase 2
Methodology	Unblinded single arm imaging study
Study Duration	2 years
Study Center(s)	Single-center
Objectives	To assess the ability of 68Ga PSMA-11 PET/CT to increase diagnostic accuracy in localizing primary and metastatic lesions in patients with suspected prostate cancer and elevated PI-RADS scores and PSA.
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	Patients with suspected prostate cancer who have at least one PI-RADS 5 lesion, or at least one PI-RADS 4 lesion and PSA ≥10 ng/mL on standard conventional imaging multiparametric MRI (mp-MRI) of the prostate and scheduled for biopsy or radical prostatectomy.
Study Product(s), Dose, Route, Regimen	^{68}Ga Prostate Specific Membrane Antigen-11, single intravenous injection, 1.8 – 2.2 MBq/kg body weight
Duration of administration	Single intravenous administration
Reference therapy	Imaging study only
Statistical Methodology	Descriptive statistics only

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

In developed countries, prostate cancer is the most common malignancy in men and the third leading cause of death in men [1, 2]. Despite being a common cancer, it has proven challenging to diagnose accurately both primary and metastatic lesions. There are numerous reasons for this challenge including the insensitivity of serum prostate specific antigen(PSA) in distinguishing benign from malignant disease, sampling errors in unguided biopsies of the prostate, and the multifocal nature of prostate cancer lesions within the prostate [3].

In the evaluation of primary prostate cancer, the use of multi parametric MRI (mp-MRI) has increased the detection of primary prostate cancer, but there is still a significant number of undetected lesions using this technique. A recent large study [3], which correlated pre-prostatectomy mp-MRI imaging with post prostatectomy whole mount pathology (WMP) of the resected gland, reported that less than half of all individual prostate cancer lesions were identified. These tumors were most commonly small lesions (<1 cm), multifocal lesions, lesions associated with Gleason score < 3+3, and with Prostate Imaging –Reporting and Data System (PI-RADS) v2.1 score < 4. However, some of these undetected lesions have elevated PSA and Gleason scores ≥ 7, making more aggressive biologic behavior likely [3].

In addition, accurate localization of metastatic lesions outside the prostate with standard of care imaging, such as magnetic resonance imaging (MRI) and computed tomography (CT) of the pelvis, lack sensitivity as they are dependent upon size criteria and may not detect disease in smaller nodes [4]. Planar bone scintigraphy, standard of care in high-grade tumors, may also under identify small lesions and may lack specificity due to uptake in additional common benign disease [5]. For these reasons, it is desirable to pursue additional imaging with greater sensitivity and specificity for detecting primary tumors as well as staging for metastatic disease [6].

1.2 Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities

In the last several years, molecular imaging using a variety of radiopharmaceuticals has been used to enhance the detection of both primary and metastatic lesions, with varying degrees of sensitivity. Some of the most promising of these are radio-ligands that target prostate specific membrane antigen (PSMA), a glycoprotein membrane antigen that is over expressed in the majority of prostate cancers. One of these ligands is ^{68}Ga labelled (Glu-NH-CO-NH-Lys(AHX)-HBED-CC;HBED=N,N'-bis[2-hydroxy-5-(carboxyethyl)benzy] ethylenediamine-N,N'-diacetic acid) (^{68}Ga PSMA-11) which can be imaged using positron emission tomography with computed tomography (PET/CT) [1]. ^{68}Ga PSMA-11 PET/CT has been used extensively to evaluate patients with prostate cancer outside of the United States. It has been found useful in the diagnosis of primary tumors [5, 7] and metastatic lesions [1, 8-10]. It has been useful in the setting of biochemical relapse, when PSA begin to rise, but is still relatively low, following definitive therapy [11, 12]. According to clinicaltrials.gov, there are currently (June 2019) 68 ongoing trials using ^{68}Ga PSMA-11 in the United States and other countries.

The toxicity of the precursor PSMA-11 has been reported to be below the no-observed-adverse-effect-level (NOEL). 86 µg PSMA-11 per kg body weight administered i.v. in one species (female and male rat) in the single-dose acute toxicity was below the NOEL. Based on the referenced study, a safety factor of 1000 can be assumed for a maximum human dose of PSMA-11 of 6.3 nmol or 6 µg per injection for a standardized patient of 70 kg body weight at a maximal concentration of 0.6 µg/mL (AURIGON 770.321.4369) [15].

1.3 Other Agents

None.

1.4 Rationale

A recent case report has documented that ^{68}Ga PSMA-11 PET/CT may identify a prostate primary lesion even when mp-MRI does not [13]. In addition, mp- MRI may detect only a single lesion with PI-RADS v 2.1 ≥4 but prostate cancer is often multifocal [3] and with the addition of ^{68}Ga PSMA-11 PET/CT, those additional prostatic lesions might be identified. Several studies have demonstrated that early dynamic PET/CT imaging immediately after injection of ^{68}Ga PMSA-11 can enhance primary prostate cancer detection as tumor uptake begins rapidly after injection and before the urinary bladder begins to fill with excreted tracer [7, 14].

In addition to identifying primary prostatic lesions, it is possible that ^{68}Ga PMSA-11 PET/CT may be able to detect more metastatic disease than that detected on current standard of care staging imaging for patients with elevated PI-RADS scores and PSA values. ^{68}Ga PMSA-11 PET/CT is reported to be able to detect small suspicious nodes and extra prostatic lesions due to its greater sensitivity and specificity compared to a variety of other imaging modalities [4, 8, 12].

The purpose of the proposed research is to evaluate the added value of ^{68}Ga PSMA-11 PET/CT in relation to detect additional primary prostate cancer lesions compared to mp-MRI in a group of patients with elevated PI-RADS scores and PSA. We propose that the addition of early dynamic ^{68}Ga PMSA-11 PET/CT imaging to the more usual delayed imaging will enhance detection of primary lesions and additional lesions not detected on the mp-MRI. In addition, the dynamic imaging will allow us to evaluate the kinetics of uptake in the prostate gland. It is possible that even in the absence of focal uptake, hyperemia of the gland could indicate the presence of an occult primary.

A second purpose of this research is to examine the value of ^{68}Ga PSMA-11 PET/CT in this same group of patients in detecting metastatic disease at initial staging in comparison with current standard of care imaging such as CT and MRI.

1.5 Correlative Studies

2.0 N/ASTUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To assess whether ^{68}Ga PSMA-11 PET/CT can detect additional primary prostate cancer lesions through use of early dynamic PET/CT imaging in comparison to mp-MRI in patients with PI-RADS v2.1 score 5 (with any PSA), or score 4 and PSA ≥ 10 ng/mL.

2.2 Secondary Objectives

2.2.1 To assess whether ^{68}Ga PSMA-11 PET/CT can detect additional sites of metastatic disease at staging in comparison to standard of care imaging in patients with PI-RADS v2.1 score 5 (with any PSA), or score 4 and PSA ≥ 10 ng/mL

2.3 Exploratory Objectives

None

2.4 Endpoints

The primary endpoint is to determine per lesion sensitivity of ^{68}Ga PSMA-11 for the detection of prostatic lesions in patients with elevated PSA and abnormal mp-MRI of the prostate (as defined as at least one lesion with PI-RADS v2.1 score 5 with any PSA or score 4 and PSA ≥10 ng/mL). A second endpoint will be to determine per person sensitivity of ^{68}Ga PSMA-11 for the detection of metastatic disease, compared to standard of care imaging.

3.0 Subject ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Patients with suspected prostate cancer (e.g., abnormal digital rectal exam, elevated and/or rising PSA) as determined by referring physician

3.1.2 Patients must have had a diagnostic, standard of care mp-MRI of the prostate with at least one lesion with a PI-RADS v2.1 score ≥ 4

3.1.3 In men with PI-RADS v2.1 score 4, PSA should be ≥ 10 ng/mL. In men with at least one PI-RADS v2.1 score 5 lesion, there is no restriction on PSA level.

3.1.4 Patients must be scheduled for biopsy or radical prostatectomy

3.1.5 Patients must be older than 18 years of age

3.1.6 Patients should not have had any type of curative or palliative therapy for prostate cancer before enrolling in the study

3.1.7 Patients must be medically stable as judged by the patient's physician

3.1.8 Patients must be able to lie still for a total of 60 minutes for the PET/CT scans

3.1.9 Ability to understand and the willingness to sign a written informed consent

3.2 Exclusion Criteria

3.2.1 Patients who have had a prior prostatectomy or radiotherapy for prostate cancer cannot participate in the study

3.2.2 Patients who have had a prior biopsy for prostate cancer cannot participate in the study

3.2.3 Patients who have been treated for cancers other than skin cancers

3.2.4 Subjects may not be receiving any other investigational agents for the treatment of the cancer under study

3.2.5 Patients may not weigh more than the maximum weight limit for the PET/CT scanner table (>200kg or 440 lbs)

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to ^{68}Ga PSMA-11 or other agents used in the study such as gadolinium-based intravenous contrast agent used during the mp-MRI

3.2.7 Prior TURP/BPH procedures, including steam/laser therapies.

4.0 TREATMENT PLAN

4.1 Injection of ^{68}Ga PSMA-11

This is a nontherapeutic imaging only study. There will be a single IV injection of 1.8 – 2.2 MBq (0.049-0.059 mCi) per kilogram of body weight of ^{68}Ga PSMA-11 [15]. Injections will be performed in the PET/CT Imaging Services located on the 2nd floor of the Clements Building at UT Southwestern Medical Center.

4.2 Scan Acquisition

Patients will be scanned on a 128 slice PET/CT scanner. The patient will be positioned supine, with arms elevated above the head as tolerated by the patient. Data acquisition will occur as 2 discrete components: 1) a dynamic part (dPET/CT studies) and the static part (whole-body PET/CT). With the patient on the scanning table, the patient will be injected with ^{68}Ga PSMA-11 and dPET/CT scanning will be performed over the pelvic area for 30 minutes [11, 12, 16]. The dPET/CT will be obtained in list mode with dynamic frames acquired at 10 x 30 seconds, 5 x 60 seconds, 5 x 120 seconds and 2 x 300 seconds. At 60 minutes post injection, a standard whole body PET scan with images from vertex of the skull to the feet will be acquired at 2-3 minutes per bed step, adjusted for body weight, along with CT images over the same range. The manufacturer's CT dose exposure limit software will be utilized. CT data will be used for attenuation correction and for anatomic localization of uptake sites [15]. The CT data will be reconstructed with soft tissue (B40f) and bone (B80) kernels.

4.3 Imaging Analysis

For the dynamic scan, all frames will be summed to produce a single image over the pelvis. This image will be visually evaluated for focal uptake in and around the prostate gland. In addition, the dynamic image frames will also be used to construct time activity curves comparing post injection time vs standard uptake value (SUV) of ^{68}Ga PSMA-11 uptake. These curves will be constructed with volumes of interest in the prostate as a whole, in any visible focal prostate lesions and over the common left iliac artery to provide an arterial input curve. If metastatic lesions are detected on this scan, separate time activity curves will be calculated as well.

Whole body images will be visually and quantitatively evaluated independently by two experienced PET/CT readers. The readers will first assess whether the primary tumor is visually distinguishable from the surrounding prostate tissue. A prostate tumor will be judged positive if the focal tracer uptake is higher than that of the surrounding prostate tissue. For calculations of SUV, a VOI will be drawn around areas of focal uptake within the prostate using iso-contour (SUVmax). The same size VOI will be drawn in the region of the uninvolved prostate. If no focal uptake is seen in the prostate, a VOI will be drawn around the prostate.

Comparisons will be made between the interpretations provided by the two PET/CT readers and the degree of agreement will be calculated. Mean and maximum SUVs will

be obtained on all areas of interest. Anatomic measurements of suspicious lymph nodes will be made in the short axis.

To evaluate focal uptake in lymph nodes and distant metastatic disease, VOIs will be drawn around each lesion. SUV maximum and mean will be recorded for all lesions. In addition, VOIs will be drawn around normal uptake in the prostate and a 2 cubic centimeter VOI will be drawn in the gluteal muscle, for use as normal background [7]. A lesion will be considered positive when the uptake exceeds normal background.

Because of the small number of subjects, descriptive statistics will used, such as percentage of times a focus of uptake in the prostate can be seen on the PET/CT and whether this focus corresponds to any detectable abnormality on review of mp-MRI of the prostate. With regard to lesions outside the prostate, comparison will be made with the results from the ^{68}Ga PSMA-11 scan and possible lesions seen on conventional imaging, such as pelvic CT or MRI or bone scintigraphy.

If possible, biopsy confirmation of sites of abnormal focal ^{68}Ga PSMA-11 uptake will be obtained per standard of care. If patient undergoes surgery without biopsy, findings of imaging will be correlated with whole mount pathology (WMP) of the resected gland with final pathology on the surgical specimen. For surgical patients, customized molds will be created based on MRI data to optimize co-registration of cross-sectional imaging and pathology data, as previously reported by our group [17]. If a patient undergoes radiation therapy or other ablation treatment without biopsy, post treatment conventional imaging will be performed and results will be compared for regression in size

4.4 Concomitant Medications/Treatments

Patients should not be receiving any treatment for prostate cancer, including anti androgen therapy as this can affect ^{68}Ga PSMA-11 uptake.

4.5 Other Modalities or Procedures

The initial mp-MRI of the prostate is standard of care and not part of the research protocol. Per current guidelines [18], cross sectional imaging (CT or MRI) is also considered standard of care in men with unfavorable intermediate or high risk disease.

4.6 Duration of Follow Up

2 years

4.7 Removal of Subjects from Protocol

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for treatment discontinuation and the date of discontinuation. The subject should be followed-up per protocol.

4.8 Subject Replacement

If a subject is removed from the study for any reason, he may be replaced.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 3 months prior to registration unless otherwise stated. The screening procedures include:

5.1.1 *Informed Consent*

Informed consent will be obtained from each research participant by the investigator or the study coordinator. No participant will be allowed to participate without a signed, IRB consent form

5.1.2 *Medical history*

Review of complete medical and surgical history up to 60 days available in the electronic medical record system at UT Southwestern Medical Center

5.1.3 *Demographics*

Age, gender, race, ethnicity

5.1.4 *Review subject eligibility criteria*

5.1.5 *Review previous and concomitant medications*

5.1.6 *Physical exam including vital signs, height and weight*

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 *Adverse event assessment*

Baseline adverse events will be assessed. See section 7 for Adverse Event monitoring and reporting.

5.1.8 *Blood draw for correlative studies*

N/A

5.1.9 *Serum chemistries*

None is needed for ^{68}Ga PSMA-11 PET/CT.

5.2 Procedures During Treatment

There is no planned treatment. The subjects will come to PET/CT imaging suite and an intravenous catheter will be placed. The subject will have height and weight measured in order to calculate dose of ^{68}Ga PSMA-11 to be injected.

5.3 Follow-up Procedures

Follow-up of patient's clinical condition, pathology, laboratory values and imaging studies related to the study disease will occur for 2 years to correlate with the imaging results. Adverse events will be evaluated up to 24 hours. Due to the drug's short half-life of 68 min and the toxicological profile, no long-term toxicities are anticipated.

5.4 Time and Events Table

Event	Visit 1: screening	Visit 2: ^{68}GA PSMA-11 PET/CT	Follow-up
Informed Consent	X		
Demographics	X		
Clinical history	X		
Height/weight	X	X	
Physical exam	X		
Survival/patient status			X
Review pathology records			X
^{68} Ga PSMA-11 PET/CT		X	
Other radiologic studies (CT or MRI)	X		X
Adverse event evaluation*			X

*Adverse event evaluation up to 24 hours post injection.

5.5 Removal of Subjects from Study

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Subject withdraws consent (termination of treatment and follow-up);

5.5.3 Subject is unable to comply with protocol requirements;

5.5.4 Subject experiences toxicity that makes continuation in the protocol unsafe;

5.5.6 Treating physician determines that continuation on the study would not be in the subject's best interest;

5.5.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.5.9 Lost to follow-up. If a research subject cannot be located to document disease state after a period of 2 years, the subject may be considered "lost to follow-up". All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

6.0 Measurement of Effect

This is a non-therapeutic, exploratory protocol. The protocol focuses on exploring the ability of ^{68}Ga PSMA-11 to demonstrate primary and metastatic disease in patients with suspected prostate cancer.

6.1 Safety/tolerability

As with all PET/CT imaging agents, ^{68}Ga PSMA-11 is a radiopharmaceutical that decays with positron emission, a form of radiation. This poses a radiation risk but this risk is extremely small at the dose administered in this study. The organ and total body doses associated with ^{68}Ga PSMA-11 are comparable to or lower than those associated with other widely used clinical nuclear medicine procedures.
The radiation absorbed effective dose from the intravenously injected ^{68}Ga PMSA-11 is estimated to be 237 mRem (2.37mSv) [19].
Risks of PET/CT studies include those due to IV line placement. These risks include bleeding or possible hematoma at the site of the injection. A physician will be available to document the adequacy of the venous line and to provide assistance in case of inadvertent tracer extravasations or hematoma formation.
All adverse events occurring within a 24 hour period post ^{68}Ga PSMA-11 infusion will be recorded. The adverse events to be specifically monitored during the infusion include localized discomfort at the IV injection site, pain, respiratory difficulties, flushing, dizziness, pruritus/rash, and any other symptoms that could be secondary to an anaphylactic reaction. The subject will be instructed to report any subjective symptoms or sensory changes noted.

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

There is no experimental therapy. This is an imaging only study.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

7.1.1 Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they

can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through 24 hours post treatment will be considered acute adverse events.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization[1,2] or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE

truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

7.1.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.2 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC and/or HRPP

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *may NOT be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 24 hours[1] of the last dose of protocol treatment. Any event that occurs more than 24 hours after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported as indicated in the sections below.

[1] Revised to 24 hours due to the drugs short half-life of 68 min.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

7.2.1 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

All SAE/UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SCCC DSMC within 5 business days of the PI or delegated study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events.

The UTSW study team is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE/UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs/UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

The following instructions section may be modified as needed to ensure clear guidance for institutions participating in the trial who will not report directly to the UTSW Institutional Review Board. If needed, this reporting may be facilitated by the UTSW study team for example.

Telephone reports to: Neil M. Rofsky MD, 214-648-7702 Neil.rofsky@utsouthwestern.edu
Written reports to: Neil Rofsky MD Email: Neil.rofsky@utsouthwestern.edu

Fax: 214-648-7782

UTSW SCCC Data Safety Monitoring Committee Coordinator
Email: SCCDSMC@utsouthwestern.edu
Fax: 214-648-5949 or deliver to BLB.306

UTSW Institutional Review Board (IRB)
Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP/IRB

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW IRB within 5 working days of PI awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of PI awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combined.pdf.

7.3 Unblinding Procedures

The proposed study is not blinded.

8.0 DRUG/TREATMENT INFORMATION

8.1 ^{68}Ga labelled (^{68}Ga labelled (Glu-NH-CO-NH-Lys(AHX)-HBED-CC; HBED=*N,N'*-bis[2-hydroxy-5-(carboxyethyl)benzy]ethylenediamine-*N,N'*-diacetic acid))

- Other names for the drug(s): ^{68}Ga PSMA-11
- Classification - type of agent: radiopharmaceutical for imaging purposes
- Mode of action: Binds to the prostate specific antigen, a cell surface protein which is over expressed in the majority of prostate cancers.
- Storage and stability: The drug solution is stored at room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial and has an expiration time of 4 hours.
- Protocol dose: 1.8- 2.2. MBq/kg of body weight
- Preparation: Provided as unit dose by the UTSW cyclotron facility to inject into patients. ^{68}Ga PSMA-11 is administered to subjects by intravenous injection. The drug solution is stored at room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial and has an expiration time of 4 hours
- Route of administration for this study: intravenous
- Incompatibilities: none known
- Availability: Produced at the UTSW Cyclotron facility under an FDA IND
- Side effects: none known

8.1.1 Return and Retention of Study Drug

Any unused 68Ga PSMA-11 will be stored at the UTSW Cyclotron Facility for up to 1 year in the event that additional testing for quality control is required.

9.0 CORRELATIVES/SPECIAL STUDIES

Standard of care imaging tests will be performed by the treating physician as detailed above.

Tissue obtained at the time of prostatectomy or biopsy will be reviewed for correlation with imaging tests.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a prospective, unblended single arm, single institution phase II pilot study to explore use of ^{68}Ga PSMA-11 PET/CT in aiding diagnosis of primary prostate cancer and prostate cancer metastases compared to current conventional imaging.

10.2 Sample Size and Accrual

This pilot study will generate preliminary data regarding improved diagnosis with ^{68}Ga PSMA-11 to support a larger future study of using hybrid PET/MRI in diagnosis of prostate cancer.
It is anticipated that up to 20 patient will be enrolled. As this is a pilot study, nor formal sample size calculations are required.

10.3 Data Analyses

Because of the small number of subjects, descriptive statistics will be used, such as percentage of times a focus of uptake in the prostate can be seen on the PET/CT and whether this focus corresponds to any detectable abnormality on review of mp-MRI of the prostate. To be specific, we will summarize percent of incidences when 1) PET/CT is concordant with mp-MRI, 2) uptake seen on PET/CT but normal on mp-MRI and 3) no uptake on PET/CT but abnormal seen on mp-MRI. This will be displayed in a two-by-two contingency table.

Comparison will also be made to pathologic specimens from biopsy and/or prostatectomy (as reference standard) to correlate whether abnormal foci of tracer uptake correspond to sites of tumor. The per-lesion diagnostic performance of PET/CT (sensitivity and false positives) will be reported. This will be displayed in a two-by-two contingency table.

With regard to lesions outside the prostate, comparison will be made of the results from the ^{68}Ga PSMA-11 scan and possible lesions seen on conventional imaging, such as pelvic CT or MRI or bone scintigraphy. To be specific, we will summarize percent of incidences when 1) PET/CT is concordant with pelvic CT/MR/BS, 2) uptake seen on PET/CT but normal on pelvic CT/MR/BS and 3) no uptake on PET/CT but lesion seen on pelvic CT/MR/BS. This will be displayed in a two-by-two contingency table.

If possible, biopsy confirmation of sites of abnormal focal ^{68}Ga PSMA-11 uptake outside the prostate gland will be obtained. If biopsy is not possible due to position or size of suspected lesion, post treatment conventional imaging will be performed and results will be compared for regression in size. The per-site diagnostic performance of PET/CT (sensitivity and false positives) will be reported. This will be displayed in a two-by-two contingency table.

Agreement between two readers in continuous measurements (mean and max SUV) will be assess by intraclass correlation coefficients (ICC) and Bland-Altman plots per area of interest. Agreement between two readers in discrete measurements (visual distinguishability of primary tumor, additional primary lesion, sites of metastasis) will be assessed by Cohen’s kappa.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy

on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.3 Required Documentation (for multi-site studies)

This is a single site imaging study.

11.4 Registration/Randomization Procedures

All subjects must be registered with the UTSW Radiology Clinical Research Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the PI or Study Coordinator. To register a subject, call 214-645-1568 Monday through Friday, 9:00AM-5:00PM.

Subjects will be registered after PI has confirmed eligibility and study number will be generated in Velos.

11.5 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT and/or the CRO Multi-Center IIT Monitor. This review includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring

Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

11.6 Adherence to the Protocol

Except for an emergency situation, in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

➢ **Reporting requirement**: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation.

11.6.2 Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others

➢ **Reporting requirement**: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

11.6.3 Major Deviations (also called **violations**): include any departure from IRB-approved research that:

- Harmed or placed subject(s) or others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

11.6.4 Minor Deviations: include any departure from IRB-approved research that:

- Did not harm or place subject(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

11.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically,

monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

12.0 REFERENCES

1. Perera, M., et al., *Sensitivity, Specificity, and Predictors of Positive (68)Ga-Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer: A Systematic Review and Meta-analysis.* Eur Urol, 2016. **70**(6): p. 926-937.

2. Torre, L.A., et al., *Global Cancer Incidence and Mortality Rates and Trends--An Update.* Cancer Epidemiol Biomarkers Prev, 2016. **25**(1): p. 16-27.

3. Johnson, D.C., et al., *Detection of Individual Prostate Cancer Foci via Multiparametric Magnetic Resonance Imaging.* Eur Urol, 2019. **75**(5): p. 712-720.

4. Hovels, A.M., et al., *The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis.* Clin Radiol, 2008. **63**(4): p. 387-95.

5. Suh, C.H., et al., *Yield of bone scintigraphy for the detection of metastatic disease in treatment-naive prostate cancer: a systematic review and meta-analysis.* Clin Radiol, 2018. **73**(2): p. 158-167.

6. Yaxley, J.W., et al., *Risk of metastatic disease on (68) Ga-PSMA PET/CT scan for primary staging of 1253 men at the diagnosis of prostate cancer.* BJU Int, 2019.

7. Uprimny, C., et al., *(68)Ga-PSMA-11 PET/CT in primary staging of prostate cancer: PSA and Gleason score predict the intensity of tracer accumulation in the primary tumour.* Eur J Nucl Med Mol Imaging, 2017. **44(**6): p. 941-949.

8. Chaloupka, M., et al., (*68)Gallium-Prostate-Specific Membrane Antigen PET/Computed Tomography for Primary and Secondary Staging in Prostate Cancer.* Urol Clin North Am, 2017. **44**(4): p. 557-563.

9. Lengana, T., et al., *(68)Ga-PSMA PET/CT Replacing Bone Scan in the Initial Staging of Skeletal Metastasis in Prostate Cancer: A Fait Accompli?* Clin Genitourin Cancer, 2018. **16**(5): p. 392-401.

10. Pyka, T., et al., *Comparison of bone scintigraphy and 68Ga-PSMA PET for skeletal staging in prostate cancer.* European Journal of Nuclear Medicine and Molecular Imaging, 2016. **43**(12): p. 2114-2121.

11. Ceci, F., et al., *(68)Ga-PSMA PET/CT for restaging recurrent prostate cancer: which factors are associated with PET/CT detection rate?* Eur J Nucl Med Mol Imaging, 2015. **42**(8): p. 1284-94.

12. Emmett, L., et al., *A Prospective, Multi-site, International Comparison of F-18 fluoro-methyl-choline, multi-parametric magnetic resonance and Ga-68 HBED-CC (PSMA-11) in men with High-Risk Features and Biochemical Failure after Radical Prostatectomy: Clinical Performance and Patient Outcomes.* J Nucl Med, 2018.

13. Muehlematter, U.J., et al., *68Ga-PSMA PET/MR-Positive, Histopathology-Proven Prostate Cancer in a Patient With Negative Multiparametric Prostate MRI.* Clin Nucl Med, 2018. **43**(8): p. e282-e284.

14. Perveen, G., et al., *Role of Early Dynamic Positron Emission Tomography/Computed Tomography with 68Ga-prostate-specific Membrane Antigen-HBED-CC in Patients with Adenocarcinoma Prostate: Initial Results.* Indian J Nucl Med, 2018. **33**(2): p. 112-117.

15. Fendler, W.P., et al., *(68)Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0.* Eur J Nucl Med Mol Imaging, 2017. **44**(6): p. 1014-1024.

16. Sachpekidis, C., et al., *68Ga-PSMA-11 Dynamic PET/CT Imaging in Primary Prostate Cancer.* Clin Nucl Med, 2016. **41**(11): p. e473-e479.

17. Costa, D.N., et al., *Improved Magnetic Resonance Imaging-Pathology Correlation With Imaging-Derived, 3D-Printed, Patient-Specific Whole-Mount Molds of the Prostate.* Invest Radiol, 2017. **52**(9): p. 507-513.

18. Sanda, M.G., et al., *Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options.* Journal of Urology, 2018. **199**(3): p. 683-690.

19. Pfob, C.H., et al., *Biodistribution and radiation dosimetry of (68)Ga-PSMA HBED CC-a PSMA specific probe for PET imaging of prostate cancer.* Eur J Nucl Med Mol Imaging, 2016. **43**(11): p. 1962-70.