Official Title: PSMA-PET/MRI for Radiation Treatment Planning in Patients with Locally Metastatic Prostate Cancer: A Pilot Study

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Title: **PSMA-PET/MRI for Radiation Treatment Planning in Patients with Locally Metastatic Prostate Cancer: A Pilot Study**

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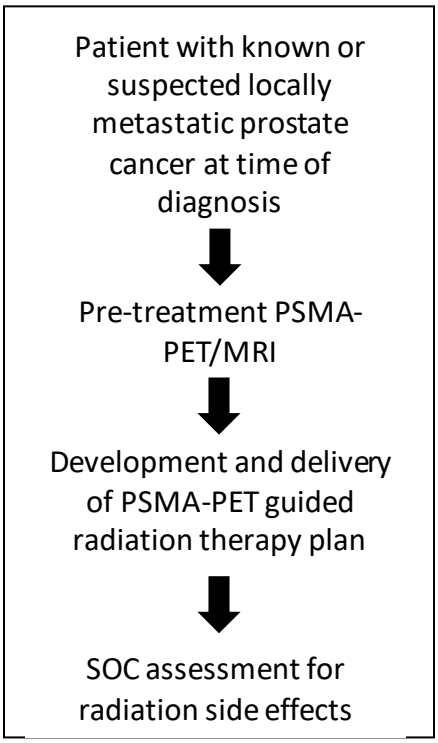
Introduction and Study Rationale

6.0 Overview and Schema

There is great need for more accurate staging of extraprostatic disease at the time of initial diagnosis to guide therapy and thereby reduce the rates of biochemical recurrence and death from prostate cancer. We propose to develop an optimized simultaneous PET/MRI protocol for local, regional and whole body pre-therapeutic initial staging of locally metastatic prostate cancer in a single imaging session using the amino acid PET tracer, [^{68}Ga]PSMA-11. Despite advances in the diagnosis and treatment of prostate cancer, the pretreatment staging of men with prostate carcinoma (PCa) is currently problematic. Conventional imaging is falsely negative for regional lymph node metastases in a substantial fraction of men. To address this unmet need, we will determine utility of positron emission tomography (PET) using ^{68}Ga-labeled PSMA-11 combined with simultaneous PET/MRI (PSMA-PET/MRI) in men with oligometastatic prostate cancer to detect regional metastases and plan radiation therapy to boost dose to lymph node metastases not identified with CT and/or MRI alone. Although not the aim of the current study, this could lead to a larger study to evaluate efficacy and outcomes in men undergoing PSMA-PET/MRI based radiotherapy planning when compared to standard-of-care pelvic radiotherapy. We will compare MRI alone to simultaneous PSMA-PET/MRI in terms of lesion detection in pelvic nodal stations. Subsequently, patient-specific radiation therapy plans will be developed utilizing the results of the PSMA-PET/MRI and additional radiation will be delivered to suspicious pelvic lymph nodes and clinical toxicity will be evaluated to ensure no additional adverse events occur due to the additional radiation delivered. If this preliminary study suggests a benefit of PSMA-PET/MRI in the pretreatment setting, additional larger studies will be designed based on these results.



This clinical feasibility study will investigate the use of PSMA-PET/MRI to guide radiation treatment planning and delivery in patients with known or suspected locally metastatic prostate cancer at the time of diagnosis. The patients will undergo a single PSMA-PET/MRI (or PET/CT in some circumstances) prior to initiation of treatment. Following development of a PSMA-PET guided radiation treatment plan, therapeutic radiation will be delivered per standard-of-care parameters and assessments of feasibility and tolerability will be performed. A total of 10 patients will be enrolled in this study. If the PET/MRI demonstrates a suspicious finding that may make a patient ineligible for radiation therapy, the treating clinician (including urology and radiation oncology) will be alerted, and the decision to pursue biopsy and/or alter the patient's treatment plan will be based on standard of care imaging and consensus after presenting the case at the GU tumor board.

6.1 Background and Rationale

Prostate cancer will affect approximately one in ten men in their lifetime with approximately 161,360 new cases and 26,730 deaths in 2017.[1] Prostate cancer represents approximately 19% of all new cancer cases

in males in the United States with over 3 million men currently living with prostate cancer in the United States.[1] There is a substantial minority of patients with high-risk prostate adenocarcinoma that are at significant risk for regional nodal and distant metastases at the time of diagnosis. In contrast to localized disease, the 5-year survival for patients with distant metastatic disease is 29%.

There is great need for more accurate staging of extraprostatic disease at the time of initial diagnosis to guide therapy and thereby reduce the rates of biochemical recurrence and death from prostate cancer. To address this unmet need, we will determine utility of positron emission tomography (PET) using 68Ga-labeled PSMA-11 combined with simultaneous PET/MRI (PSMA-PET/MRI) in men with oligometastatic prostate cancer to detect regional metastases and plan radiation therapy to boost dose to lymph node metastases not identified with CT and/or MRI alone. Although not the aim of the current study, this could lead to a larger study to evaluate efficacy and outcomes in men undergoing PSMA-PET/MRI based radiotherapy planning when compared to standard-of-care pelvic radiotherapy.

The utility of conventional anatomic imaging for staging is limited. Disease control outcomes for men with high-risk prostate cancer remain suboptimal, with 10-year biochemical failure rates on the order of 25%-40% in modern trials of dose-escalated radiotherapy and long-term androgen suppression.[2, 3] Additionally, the 5-year disease-free survival rate drops from 85% of patients with no nodal metastases to 50% in those patients with nodal metastases. This is thought to be due to lack of detection of small volume metastatic disease and small volume locoregionally invasive disease not identified on conventional pretreatment imaging.

Prostate MRI is essential for cancer staging within the gland, but limited in detection of nodal metastases. While prostate MRI is valuable for the staging of the known cancer, its sensitivity and specificity for the detection of pelvic lymph node metastases is limited by RECIST 1.1 criteria and nodal morphology. Molecular imaging has great potential to supplement MRI and increase diagnostic accuracy, and simultaneous PET/MRI can provide both dedicated pelvic PET and MRI imaging for regional staging as well as whole body staging in a single imaging session.

PSMA PET ligands show great promise for detection of both intraprostatic and extraprostatic disease. Prostate specific membrane antigen (PSMA) is a transmembrane cellular receptor that is overexpressed in prostate cancer cells. Recently, small molecules have been developed that bind to the extracellular component of the transmembrane PSMA receptor. These agents have been tagged with both ^{18}F and ^{68}Ga for imaging and ^{90}Y and ^{177}Lu for therapeutic purposes. Restaging accuracy of fluciclovine and PSMA-PET/CT are superior to choline compounds, particularly at low PSA levels, and a single 10 patient case series suggests superiority of PSMA PET over fluciclovine.[4, 5] A limitation of PSMA ligands is that approximately 10% of prostate carcinoma and nodal metastases are PSMA negative.[1-4]

PET imaging has been shown to alter radiation treatment planning in patients with recurrent prostate cancer. The concept of PET guided radiation therapy is well-established and utilizes standardized uptake values (SUV) within lesions to automatically segment target volumes.[6-8] The technique has been evaluated previously in recurrent prostate cancer with use of [11C]choline and [18F]fluorocholine PET/CT with increases in detected gross tumor volume.[9, 10] PSMA-PET/CT has been demonstrated to be superior to [11C]choline PET/CT in recurrent prostate cancer in both sensitivity and specificity and has been shown to alter radiation therapy management in a substantial fraction of patients.[11-14] Therefore, we expect that PSMA-PET/MRI will be valuable in the initial staging and radiation treatment planning in patients with oligometastatic prostate cancer and that target lesion segmentation is feasible utilizing SUV thresholding.

PET/MRI is likely the optimal modality to image patients for pretreatment staging of prostate carcinoma. In one study, a patient can undergo a multiparametric prostate MRI for characterization of the primary lesion and the extent of regional extraprostatic disease along with a molecular imaging study to improve the accuracy of regional staging and provide whole body staging. In addition, simultaneous acquisition of PET and MRI data allows for more accurate coregistration of MRI and PET data which may be difficult to achieve with software fusion, a key to detecting non-enlarged lymph nodes and other small lesions.

6.2 Study Objectives

Specific Aim #1: Determine the concordance of imaging findings for PSMA-PET/MRI and MRI of the pelvis and prostate gland.

Hypothesis #1: PSMA-PET/MRI will identify more regional lymph node metastases than MRI alone.

There have been numerous prior studies demonstrating the value of MRI for the locoregional staging for PCa. We expect the simultaneous acquisition of MRI and PSMA PET data to provide valuable preoperative staging information, with PSMA PET detecting metastatic disease in subcentimeter pelvic lymph nodes not identified with MRI alone. Additionally, PSMA-PET/MRI provides whole body staging in regions not evaluated by pelvic MRI and may detect additional distant metastases.

Specific Aim #2: Establish feasibility and assess acute toxicity of PSMA-PET/MRI directed pelvic radiotherapy.

Hypothesis #2: PSMA-PET/MRI directed radiation therapy will be feasible in the vast majority of patients (>90%) and can be safely administered without increased acute radiation toxicities.

The primary goal of Specific Aim 2 is to provide preliminary information to confirm the feasibility of radiation dose escalation to the suspicious LNs identified on PSMA-PET/MRI. If results from this trial are supportive, this will lead to a larger clinical trial evaluating efficacy and disease outcomes between patients who have undergone PSMA-PET/MRI directed radiotherapy versus standard-of-care pelvic radiotherapy.

6.3 Investigational Plan

6.3.1 Study Design

- Prospective IRB-approved study enrolling 10 patients with locally metastatic prostate cancer for pretreatment PSMA-PET/MRI prior to the initiation of treatment
- All patients will undergo standard-of-care clinical evaluation and imaging workup with nuclear medicine bone scan and either CT of the abdomen and pelvis or MRI pelvis
- Patients will undergo standard-of-care androgen deprivation therapy following PSMA-PET/MRI and prior to radiation therapy
- If study PET/MRI demonstrates a suspicious finding that may preclude a patient radiation therapy, the treatment team will be alerted to potentially investigate the finding further (i.e. additional imaging or biopsy)
- Acute radiation toxicities will be assessed at standard-of-care intervals

6.3.2 **Study Population**

- Men with treatment-naïve prostate cancer with metastatic disease localized to the pelvis

6.3.3 **Inclusion Criteria**

- Biopsy-proven treatment-naïve prostate adenocarcinoma with pelvic metastases known to suspected on standard-of-care staging imaging or a nomogram-based risk of lymph node metastases greater than or equal to 20%
- Eligibility and plan to undergo definitive radiation therapy for prostate cancer per established standard-of-care radiation oncology clinical guidelines
- Be at least 18 years of age.

6.3.4 **Exclusion Criteria**

- Inability to tolerate or undergo PET/MRI or PET/CT
- Previous or current hematologic or lymphatic disorder (including leukemia, lymphoma, Castleman's disease, etc.)
- Recurrent prostate adenocarcinoma
- Known distant metastatic disease
- Current or prior treatment for prostate cancer

6.3.5 **Withdrawal Criteria**

- Given that enrollment in this study will involve a single imaging exam, no withdrawal criteria will be used

6.3.6 **Replacement of Patients**

- Given that enrollment in this study will involve a single imaging exam, no replacement of patients will be used

6.3.7 **Study Duration**

- Study enrollment and imaging will take place over 24 months

6.3.8 **Safety Monitoring**

6.3.8.1 **Data and Safety Monitoring Plan**

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document. PET/MRI scans will be loaded into a separate password-protected image storage system that will not appear on the PACS utilized in clinical practice.

6.3.9 **Ethical Considerations**

Given that the study involves a single imaging session with PET/MRI and the expected age of the enrolled adult patients, ethical concerns regarding additional radiation exposure are minimal.

The only ethical consideration was the availability of the results of the study PET/MRI to the clinicians. Although the PET radiopharmaceutical used ([^{68}Ga]PSMA-11) is not currently FDA-approved, it has been extensively studied and used in Europe with excellent correlation between radiotracer activity and metastatic disease. Therefore, a suspicious lesion on the study PET/MRI is expected to correlate with metastatic disease. Therefore, if the PET/MRI demonstrates a suspicious finding, the treating clinician (including urology and radiation oncology) will be alerted, and the decision to pursue biopsy and/or alter the patients treatment plan will be based on standard of care imaging and consensus after presenting the case at the GU tumor board.

6.4 Study Procedures

6.4.1 Informed Consent Procedure

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

6.4.2 Patient Registration

Enrollment in the study will be available after the patient has been seen by their treating physician at UAB. The majority of these patients are expected to be seen by Radiation Oncology in either their own clinic or as part of multidisciplinary Urology clinic. However, all patients that meet enrollment criteria are eligible. Registration in the study will be performed by a research coordinator from the UAB Department of Radiology. Participation in the study is voluntary and choosing not to participate will not affect patient care in any way.

6.4.3 Initiation of Study

The PET tracer [^{68}Ga]PSMA-11 is made on site in the UAB Radiopharmacy by a licensed Radiopharmacist. [^{68}Ga]PSMA-11 is an investigational new drug (IND) and the study will be initiated only after approval of UAB Radiation Safety Committee, UAB IRB and FDA.

6.4.4 Drug Information

[^{68}Ga]PSMA-11 is an investigational PET radiopharmaceutical that has been used extensively in clinical trials for patients with newly diagnosed and biochemically recurrent prostate cancer. The radiopharmaceutical targets the PSMA transmembrane protein, which is overexpressed in prostate cancer cells. The target dosage of radiopharmaceutical administered to the patient is 185 MBq (5 mCi) ±10% given intravenously. This results in an effective dose of approximately 3 mSv to the patient, which is equal to 1 years of natural background radiation exposure (3 mSv/yr).

6.4.5 Patient Assessment

Identification and workup of patients prior to potential enrollment in the study will follow standard-of-care procedures per the treating physician (urology, radiation oncology, etc.). For initial staging of prostate cancer, this will include a nuclear medicine bone scan and either a CT abdomen and pelvis or MRI of the pelvis per NCCN guidelines. If a patient is determined to be eligible for the study, the research coordinator in this study will be asked to come to the clinic to discuss potential enrollment in the study.

6.4.6 **Imaging Information**

6.4.6.1 **[^{68}Ga]PSMA-11 PET Preparation and Injection**

The injected dose of PSMA will be 185 MBq (5 mCi) followed by an uptake interval of 50-100 minutes.[5] The patient will be instructed to avoid strenuous exercise for 24 hours prior to injection and to avoid caloric intake for 4 hours prior to injection.

6.4.6.2 **[^{68}Ga]PSMA-11 PET/MRI and PET/CT Protocol**

Whole body imaging

Positron Emission Tomography Acquisition: The patient will be placed on the PET/MRI scanner in the supine position. Initial localizer images will be obtained. Subsequently, static whole body images will be acquired from pelvis to skull base utilizing approximately eight 14 cm detector beds for 5 minute acquisitions per bed position. Correction for randoms, scatter, attenuation and reconstructions will be performed per the manufacturer's recommendations.

Whole Body MRI: Sequences performed will include MR attenuation correction (MRAC), axial and coronal T2 single shot fast spin echo, sagittal T1 turbo spin echo for skeletal evaluation, and whole body Dixon-derived sequences.

Following whole body PET imaging, a routine noncontrast MRI of the prostate gland will be performed at UAB in the PET/MRI scanner per institutional protocol, which includes high b-value diffusion-weighted imaging (b2000) and small field-of-view T2 imaging. Dynamic-contrast enhanced and post-contrast T1 images will be omitted from the protocol to reduce scan time and due to less impact on scan interpretation for patients presenting for staging of known prostate cancer. An additional static pelvic PET acquisition will be performed concurrently.

PET/CT Acquisition: If a patient is unable to undergo PET/MRI secondary to technical failure of the PET/MRI scanner, MRI-incompatible metallic implant, or severe claustrophobia, a PET/CT may be performed instead at the Primary Investigator's discretion. The patient will be placed on the PET/CT scanner in the supine position. Initial localizer images will be obtained. Subsequently, static whole body images will be acquired from pelvis to skull base utilizing approximately eight 14 cm detector beds for 5 minute acquisitions per bed position. Correction for randoms, scatter, attenuation and reconstructions will be performed per the manufacturer's recommendations.

6.4.6.3 **PET/MRI Imaging Interpretation and Storage**

Images from the PET/MRI will be stored and reviewed using a commercially available software package (MIM Encore, Cleveland, OH) and not be available for viewing in the institutional PACS or patient's medical record. This is in an effort to blind the treating physicians from making clinical decisions on an experimental imaging technique. The prostate MRI images will be sent to clinical PACS and the medical record as part of standard-of-care imaging and can be used in the clinical-decision making process. No formal interpretation will be generated for the [^{68}Ga]PSMA-PET portion of the PET/MRI study, but the prostate MRI will have a clinical interpretation by a dedicated abdominal radiologist who will also be blinded to the patient enrollment in the study. Dedicated study readers from both abdominal imaging and molecular imaging will interpret first the prostate MRI alone, and then the fused PET/MRI to assess potential added value from the PET/MRI. The study readers will be blinded to the results of any additional standard-of-care

imaging and clinical evaluation and will only have knowledge that the patient has biopsy-proven prostate cancer.

Assessment of the prostate MR primary lesion location, extracapsular extension (ECE), seminal vesicle invasion (SVI), and metastatic disease will be evaluated utilizing a Likert scale from 1-5 to indicate reader confidence utilizing PI-RADS v2.0 criteria. The PSMA-PET/MRI will be evaluated with the same 1-5 Likert scale utilizing the PSMA-RADS v1.0 criteria.[16] The number of pelvic nodal metastases detected at each lymph node station will be recorded. Exams will be interpreted by three radiologists/nuclear medicine physicians to evaluate interreader agreement with disputes resolved by consensus.

MRI Data Analysis: The MRI images will be qualitatively analyzed.

Qualitative analysis: A visual evaluation of the pelvic lymph nodes with suspected metastatic disease will be performed. The number of positive metastatic lymph nodes and their nodal stations will be recorded. Nodal stations that will be examined include right and left common iliac, internal iliac, external iliac, obturator, inguinal, and retroperitoneal (total of 11 stations per patients).

MRI Images
1 = Normal lymph nodes
2 = Mild prominence not meeting RECIST criteria for adenopathy (low suspicion)
3 = Borderline enlarged by RECIST criteria (intermediate suspicion)
4 = Definitely abnormal size or morphology, probable metastasis (high suspicion)
5 = Markedly abnormal size and morphology, definite metastasis (very high suspicion)

Note: In cases of nonhomogenous intensity on MRI images, the grade will be determined on the basis of the most suspicious area.

PET Data Analysis: The PET images will be qualitatively and quantitatively assessed. The scoring will be based primarily on the PET data, but the reader will have access to the MRI data for anatomic correlation and characterization of lymph node morphology. For PET data analysis, a lymph node positive based on MRI criteria but negative based on PSMA-PET criteria will be scored as negative.

Qualitative analysis: A visual evaluation of the pelvic lymph nodes with suspected metastatic disease will be performed utilizing PSMA-RADS version 1.0 criteria (Table 1). The number of positive metastatic lymph nodes and their nodal stations will be recorded.

Quantitative analysis: Nodes scored as intermediate or higher suspicion based on MRI and/or PET will undergo further quantitative analysis.

Standardized uptake values (SUVs): The maximum SUV will be measured. Additionally, the mean SUV and metabolic tumor volume will be measured based on a 40% isocontour.

TABLE 1

Summary of PSMA-RADS Version 1.0 for Reporting Findings on PSMA-Targeted PET Imaging

Category	Findings
PSMA-RADS-1 (benign)	
PSMA-RADS-1A	Benign lesion characterized by biopsy or pathognomonic finding on anatomic imaging and without abnormal uptake.
PSMA-RADS-1B	Benign lesion characterized by biopsy or pathognomonic finding on anatomic imaging and with focal radiotracer uptake.
PSMA-RADS-2 (likely benign)	Equivocal (focal, but low level such as blood pool) uptake in soft-tissue site atypical of PCa involvement (e.g., axillary or hilar lymph nodes); equivocal uptake in bone lesion atypical of PCa involvement (e.g., uptake fused to bone lesion and strongly suspected of being degenerative or another benign etiology.
PSMA-RADS-3 (equivocal*)	
PSMA-RADS-3A	Equivocal uptake in soft-tissue site typical of PCa involvement (e.g., pelvic or retroperitoneal lymph nodes). If targetable for biopsy (up to and including excision), biopsy may help confirm diagnosis. Alternatively, follow-up imaging (either anatomic or PSMA-targeted PET/CT) showing progression can confirm diagnosis. We recommend initial follow-up period of 3–6 mo.
PSMA-RADS-3B	Equivocal uptake in bone lesion not definitive but also not atypical of PCa on anatomic imaging (i.e., pure marrow-based lesion with little if any surrounding bony reaction, lytic or infiltrative lesion, or classic osteoblastic lesion). Comparison to bone scan, $Na^{18}F$ PET, or tumor-protocol MR images may be helpful, and bone biopsy may have a role. Alternatively, follow-up imaging (either anatomic or PSMA-targeted PET/CT) with evidence of progression may confirm diagnosis. We recommend initial follow-up period of 3–6 mo.
PSMA-RADS-3C	Intense uptake in site highly atypical of all but advanced stages of PCa. Likelihood of nonprostatic malignancy or other benign tumor is high. Biopsy to confirm diagnosis histologically is often preferred, although organ-specific follow-up imaging may be done (e.g., liver-protocol MRI to evaluate possible primary hepatocellular carcinoma).
PSMA-RADS-3D	Lesion suggestive of malignancy on anatomic imaging but lacking uptake. Differential considerations include nonprostatic malignancy, neuroendocrine PCa, and an uncommon case of prostate adenocarcinoma that fails to express PSMA. Biopsy to confirm diagnosis histologically is often preferred, although organ-specific follow-up imaging may be done.
PSMA-RADS-4 (PCa highly likely)	Intense uptake in site typical of PCa but lacking definitive findings on conventional imaging. Given the high specificity of PSMA agents in all reported series, it is unlikely that biopsy confirmation will be needed, although obtaining tissue for genomic analysis or other purposes may be useful.
PSMA-RADS-5 (PCa almost certainly present)	Intense uptake in site typical of PCa and having corresponding findings on conventional imaging. Given the high specificity of PSMA agents in all reported series, it is unlikely that biopsy confirmation will be needed, although obtaining tissue for genomic analysis or other purposes may be useful.

6.4.7 **Safety Monitoring**

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

6.4.8 **Patient Follow-Up**

Patients will be called within 24 hours of [^{68}Ga]PSMA-11 administration to ensure no adverse events have occurred. Patients will be seen in the clinic if there are any concerning study related adverse events requiring further evaluation.

6.5 Radiation Treatment Planning and Delivery

6.5.1 **RADIOTHERAPY SIMULATION**

CT simulation for radiotherapy planning will be performed within 8 weeks of the initiation of neoadjuvant androgen suppression (per standard-of-care clinical guidelines) and within 10 weeks of the PSMA staging scan. Patients will be asked to have an empty rectum and full bladder at time of simulation. Bowel regimen will consist of two 17g doses of polyethylene glycol laxative and two 125mg doses of simethicone the day prior to simulation. Patients will be asked to drink 24 ounces of water 30 minutes prior to simulation in order to ensure bladder fullness. A custom molded foam form will be created to aid patient immobilization. A retrograde urethrogram will be performed to improve visualization of the prostate apex [6]. The CT scan will extend from the L1/L2 to mid-femur and will utilize ≤3mm slice thickness. Intravenous iohexol contrast will be utilized to improve visualization of lymph nodes. All CT simulation parameters and patient preparation is per standard-of-care clinical guidelines.

6.5.2 **RADIOTHERAPY TARGET VOLUME DELINEATION (Figure 1)**

Varian Eclipse software (Varian Medical Systems LLC, Palo Alto, CA, USA) will be used for radiotherapy target delineation and treatment planning. For all patients we will initially define traditional standard-of-care clinical target volumes for the treatment of high risk prostate cancer:

$\underline{CTV_{P+SV}}$ will contain the entire prostate gland and portion of the seminal vesicles at risk for tumor involvement. At least the proximal 1cm of the seminal vesicles. In cases where gross seminal vesicle invasion is identified the entire seminal vesicles will be included.
$\underline{CTV_{eLN}}$ will contain the elective lymph node target volumes. Elective nodal regions will be delineated in accordance with published consensus guidelines[7] and will include the obturator, internal iliac, external iliac, and distal common iliac chains.

Next, the PSMA PET scan will be rigidly co-registered to radiation simulation CT scan. Rigid co-registration is preferred for two specific reasons: (1) we recognize that 8-10 weeks of androgen suppression between PSMA-PET/MRI and radiotherapy simulation may lead to in changes in LN size that may lead to error in deformable registration, and (2) prior experience with PSMA-PET/MRI co-

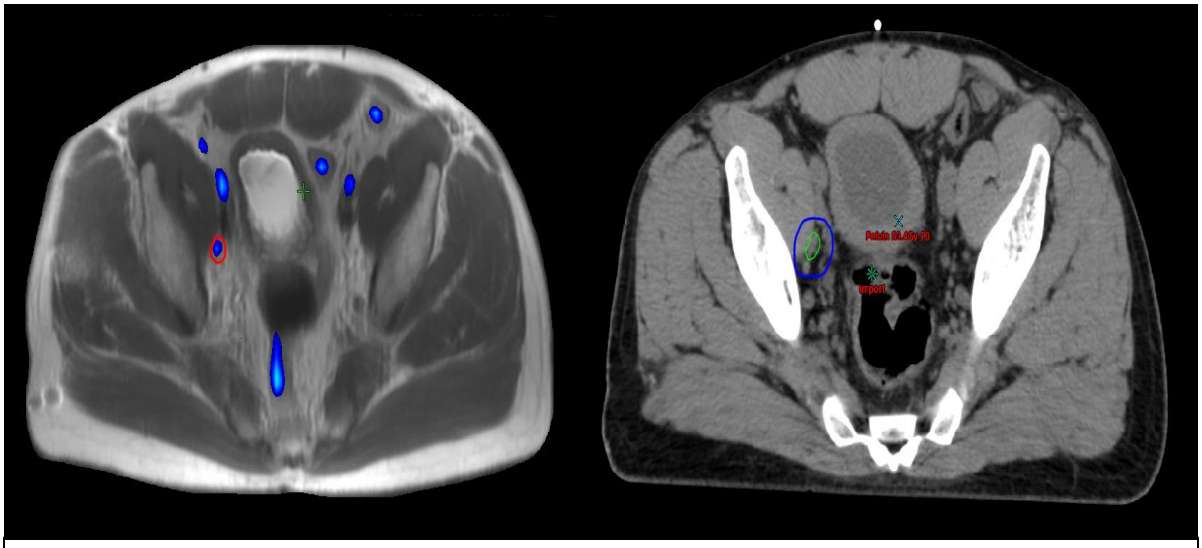


Figure 1: Example of fluciclovine-PET/MRI directed radiotherapy treatment planning. Left image shows the [^{18}F]fluciclovine PET-MRI with lower window of PET window set to 1.3 times blood pool. The suspicious LN is segmented in red. Right image is the treatment planning CT for the same patient with $CTV_{LN\ BOOST}$ delineated in green and the associated PTV in blue.

registration in the biochemical recurrence setting indicates that rigid co-registration results in good anatomic agreement in the majority of cases[8]. Using the registered PSMA-PET/MRI we will delineate an additional CTV:

$CTV_{LN\ BOOST}$ will contain LNs with maximum SUV greater than 1.3 times the blood pool reference. The LNs will be segmented on the MRI portion of the PSMA-PET/MRI and superimposed on the co-registered CT simulation scan. The resulting structure will be edited to create $CTV_{LN\ BOOST}$ by excluding bowel structures and barriers to tumor spread (e.g. muscle or bone). We note that suspicious LNs are likely to be smaller on the CT simulation scan due to the initiation of androgen suppression, but $CTV_{LN\ BOOST}$ will not be further reduced so as to account for potential microscopic tumor extension. This concept is analogous to involved node radiotherapy utilized for post-chemotherapy consolidation of lymphoma[9].

Planning target volume (PTV) expansions for CTV_{P+SV} will be 4mm posteriorly and 7mm in all other directions. PTV expansions for CTV_{eLN} and $CTV_{LN\ BOOST}$ will be 8mm in all directions.

6.5.3 **RADIOTHERAPY TREATMENT PLANNING AND DELIVERY**

We will utilize a moderately hypofractionated dose regimen which is standard-of-care at our institution. Our institutional technique for elective pelvic irradiation with a simultaneous integrated boost to the prostate and proximal seminal vesicles has been described in multiple peer-reviewed publications[10-13] and moderate hypofractionation is recognized by the National Comprehensive Cancer Network as an appropriate dose regimen for men with high-risk and node positive prostate cancer[14]. We will prescribe 70 Gy to PTV_{P+SV}, 60.2 Gy to $PTV_{LN\ BOOST}$, and 50.4 Gy to PTV_{eLN}

simultaneously in 28 fractions of 2.5 Gy, 2.15 Gy, and 1.8 Gy, respectively. Treatment plans will be generated to meet the criteria specified in **Table 2.** The prescription to $PTV_{LN\ BOOST}$ may be escalated beyond 60.2 Gy at the discretion of the treating radiation oncologist if all organ-at-risk constraints are met, but will not be allowed to exceed 70 Gy. Treatment plans will utilize either intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). Daily image guidance will be performed utilizing cone beam CT performed prior to the delivery of each fraction and emphasis of patient alignment will be at the prostate-rectum interface.

Table 2: Pre-specified dosimetric criteria for plan acceptability.

Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
PTV_{P+SV}	V70 Gy[%]	≥95%	≥90%
	Maximum dose	<75 Gy	<77 Gy
$PTV_{LN\ BOOST}$	V60.2 Gy[%]	≥90%	-[1]
	Maximum dose	<66 Gy	<68 Gy
PTV_{eLN}	V50.4 Gy[%]	≥95%	≥90%
	Maximum dose	<55 Gy	<58 Gy
Rectum	V70 Gy[cc]	<3cc	<5cc
	V60 Gy[%]	<10%	<15%
	V50 Gy[%]	<25%	<40%
Small bowel	Maximum dose	<54 Gy	<58 Gy
	V54 Gy[cc]	0cc	<20cc
	V45 Gy[cc]	<120cc	Not specified
Bladder	V60 Gy[%]	<20%	<25%
	V40 Gy[%]	<50%	<60%
Femoral heads	V50 Gy[%]	<5%	<10%

[1]No minimum acceptable coverage of $PTV_{LN\ BOOST}$ is specified due to potential overlap between the target volume and bowel structures is may occur. In such instances effort should be made to ensure $CTV_{LN\ BOOST}$ V60.2 Gy[%] ≥ 90%.

6.5.4 **RADIOTHERAPY ASSESSMENTS**

Clinical toxicity during and after radiation therapy will be scored using the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). Response to therapy will be assessed with interval PSA measurement. All of these measures will be assessed per standard-of-care intervals for all patients undergoing radiation therapy for prostate cancer. We will utilize a battery of validated measures:

Table 3: Study Calendar.			
	Pre-Study	**Imaging Visit - 1-2 weeks before radio-therapy**	**As part of clinical care**
H&P	X		X
PSMA-11 PET-MRI		X	
PSA†			X
CTCAE Toxicity Assessment†			X

†Performed as part of clinical care

6.5.5 **Study Variables and Key Endpoints**

For specific aim 1, we will assess the concordance between prostate MRI and PSMA-PET/MRI for the detection of seminal vesicle invasion and pelvic metastatic disease. The total number of pelvic nodal metastases detected on MRI and PSMA-PET/MRI will be compared. The confidence in detection of seminal vesicle invasion on a 0-3 Likert scale will also be compared between MRI and PSMA-PET/MRI. The primary endpoint for specific aim 1 number of patients who demonstrate pelvic LN metastases on PSMA-PET/MRI that were not detected on conventional anatomic imaging. We expect at least 25% of patients to demonstrate pelvic LN metastases that were not detected on conventional anatomic imaging.

For specific aim 2, study participants who remain eligible for pelvic radiation therapy (e.g. no distant metastases) will be subdivided into two cohorts: those without suspicious extraprostatic activity on PSMA-PET/MRI and those whose PSMA-PET/MRI demonstrates suspected seminal vesicle invasion and/or pelvic nodal metastatic disease. Those without suspicious extraprostatic uptake will undergo standard-of-care radiation therapy. Patients with positive PSMA-PET/MRI scans will undergo radiation treatment planning with a boost given to the suspicious lesions. The primary endpoint of specific aim 2 is to assess the number of patients with positive PSMA-PET/MRI scans where the radiation boost is feasible. We expect that the radiation treatment planning will be feasible in at least 90% of patients with positive PSMA-PET/MRI scans. A secondary endpoint is to compare the frequency of acute radiation toxicities between the cohorts. We expect that less than 15% of patients who undergo PSMA-PET/MRI directed LN radiotherapy boost will experience CTCAE v5.0 grade 3+ genitourinary or gastrointestinal toxicities and that no patient will experience a grade 5 genitourinary or gastrointestinal toxicity. All grade 3 toxicities will be reviewed by the radiation oncology sub-investigator. If any grade 4 or 5 events occur, the cases will be reviewed among members of the study team and the study will potentially be paused/terminated if there is concern that deviation from standard of care radiation therapy has caused undue harm to the patient.

6.5.6 **Study Termination**

The study will stop enrolling patients once the target number has been reached.

6.6 Statistical Considerations

6.6.1 **Study Design and Sample Size Calculation**

Given the pilot nature of this study and small sample size, no formal power or sample size calculations were performed.

6.6.2 Definition of Analyzed Study Population

Study population is adult males with treatment-naïve prostate adenocarcinoma who meet the inclusion criteria listed above.

6.6.3 Analysis

Demographic and clinical characteristics of all the enrolled patients will be summarized using descriptive and graphical statistics. Mean and standard deviation will be provided for continuous variable and counts and percentage will be for categorical variables. To ensure the quality of imaging data, imaging data from three readers will be assessed first using Kappa statistics (K) for inter-rater agreement.

For the primary analysis in Aim 1, the number of patients who are identified with lymph node metastases (positive nodal) will be counted, and percentage and 95% exact confidence interval will be calculated using the Clopper-Pearson method for PSMA-PET/MRI and MRI respectively. Concordance and agreement between two methods will be evaluated using Cohen's kappa statistic, κ. For the primary analysis in Aim 2, SUV thresholding, CTV, and other imaging parameters between PSMA-PET/MRI and MRI will be determined using the Bland-Altman plot analysis in addition to descriptive analysis. Safety analysis of acute radiation toxicities related AE/SAE in Aim 2 will be descriptive, such as frequency and percentage will be reported. We will also report the frequency of patients with any grade 3 GI or GU toxicity, and any grade 4-5 toxicity. All statistical analysis will be carried out using the Statistical Analysis Software SAS v 9.4.

6.7 Pre-Study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.
Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

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

6.7.1 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UAB IRB. Prior to obtaining IRB approval, the protocol must be approved by the by the UAB Comprehensive Cancer Center Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

6.7.2 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The

participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

6.7.3 **Changes in the Protocol**

Once the protocol has been approved by the UAB IRB and FDA, any changes to the protocol must be documented in the form of an amendment, submitted to and approved by both IRB and FDA.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation.

6.8 Adverse Event Reporting

As with many IV administered agents, [^{68}Ga]PSMA-11 could cause an allergic reaction that could potentially pose a threat to life (anaphylaxis). This has not been observed in limited human exposure to date. Reasonable precautions should be taken, consistent with normal radiologic and clinical facility practice. The patient should be monitored until the PET procedure is completed, and trained personnel and emergency equipment should be available per facility standards.

Qualifying Adverse Events (AEs), including Serious Adverse Events (SAEs), as defined herein, will be reported via the FDA Adverse Event Expedited Reporting System (AERS). For the [^{68}Ga]PSMA IND we will report adverse events based on the FDA final rule for IND safety reporting requirements under 21 CFR part 312 published on September 29, 2010 and implemented on March 28, 2011. This investigational study is not a BA or BE study so 21 CFR part 320 is not applicable. Adverse events will also be reported to the UAB IRB according to their requirements.

6.8.1 **General Definitions (from 21 CFR 312.32 (a))**

Adverse Event (AE): An Adverse Event is an untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related. For this study, the drug is [^{68}Ga]PSMA and adverse events would include any events experienced by a study participant during the Adverse Event reporting period defined in Table 1 whether or not it was considered to be related to the [^{68}Ga]PSMA. At the conclusion of the imaging study, the imaging technologist will observe the patient and also inquire if they are back to their usual state of health. If a negative answer is received, then the physician will be called to investigate this report as a possible adverse reaction.

Adverse Reaction: An Adverse Reaction is any adverse event caused by a drug. In this study, the drug is [^{68}Ga]PSMA.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the IND drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

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

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include: allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

Investigational Agent: An investigational agent is any agent held under an Investigational New Drug (IND) application. For purposes of this study, [^{68}Ga]PSMA is the investigational agent.

6.8.2 **AE Reporting Requirements**

The investigators on this protocol will report any suspected adverse events that occur after [^{68}Ga]PSMA administration and within the specified follow-up period to Dr. Galgano and they will work together to determine whether there was an adverse event or adverse reaction and the severity of the adverse event or reaction.

All AEs will be followed by the investigators until resolution, stabilization, scientifically and clinically satisfactory explanation as to attribution and etiology is achieved, or until subject is lost to follow up.

6.8.2.1 **CAEPR/ASAE for [^{68}Ga]PSMA**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. The Agent Specific Adverse Event List (ASAEL) would include the expected adverse events associated with the use of [^{68}Ga]PSMA. At this time, there have rare reported AEs associated with the use of a [^{68}Ga]PSMA in clinical studies (≤1% of patients). The most common adverse reactions were injection site pain and injection site erythema. We will continue to update our CAEPR and ASAE lists as this study progresses, including by reviewing the literature and our in-house data safety monitoring. If any are found, we will begin an ASAE list. Any information on reported AEs for [^{68}Ga]PSMA will be provided by the sponsor to all of the investigators on this protocol.

6.8.2.2 **Potential but Unexpected AE for [^{68}Ga]PSMA**

There have rare reported AEs associated with the use of a [^{68}Ga]PSMA in clinical studies (≤1% of patients). The most common adverse reactions were injection site pain and injection site erythema.

Other general risks for PET/MRI imaging include:

- The injection site may become infected.
- The dose might be extravasated into tissues surrounding the vein catheter leading to localized pain/discomfort.

Radiation risks: [^{68}Ga]PSMA injection contributes to lifetime radiation accumulation. The smallest dosage for imaging and safe handling are used for these protocols. The organ and total body doses associated with [^{68}Ga]PSMA imaging are comparable to those associated with other widely used clinical nuclear medicine procedures.

6.8.2.3 **Review of Safety Information**

As required by 21 CFR 312.32(b), the physician investigators will promptly review all information relevant to the safety of the drug. The physician investigators will also be providing much of this information to the local IRB as well for data safety and review monitoring. The review will include determining whether there is a safety event over time and the causality. Reporting will be as described in Table 4.

Characterization of the severity of an Adverse Event: Adverse events will be graded as below.

Grade: Grade denotes the severity of the AE. An AE is graded using the following categories:

- Mild
- Moderate
- Severe
- Life-threatening or disabling
- Fatal

NOTE: Severity is graded on the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE) based scale for each adverse event. For example, an abnormal hemoglobin value is graded for severity from 1 to 5 [death] based upon where that value falls on the CTCAE scale of abnormal hemoglobin values. "Severity" is NOT the same as "Seriousness." All appropriate clinical areas should have access to a copy of the most current CTCAE and a copy of the CTCAE can be downloaded from (http://ctep.cancer.gov).

Attribution of cause: The physician investigators will determine whether an adverse event was related to a medical treatment or procedure. Definitions taken from our work with CTEP and NIH give the following definitions for "Attribution" that we will adopt for this IND study: Attribution is a clinical determination, by the investigator, as to whether an AE is related to a medical treatment or procedure. Attribution categories are:

- **Definite:** The AE is **clearly related** to a treatment or procedure
- **Probable:** The AE is **likely related** to a treatment or procedure
- **Possible:** The AE **may be related** to a treatment or procedure
- **Unlikely:** The AE is **likely unrelated** to a treatment or procedure
- **Unrelated:** The AE is **clearly not related** to a treatment or procedure
- **NOTE:** Attribution is part of the assessment of an adverse event. Determining that an event is 'unlikely related' or 'unrelated' to a study agent or procedure does NOT make the event unreportable, or disqualify the event as an AE. As defined above, an AE is reportable as specified herein if it occurred: **"during the Adverse Event reporting period defined in the protocol**, or by applicable guidance, regulation, or policy."

6.8.2.4 **Adverse Event Reporting**

Expedited AE reporting for this study will be done through the Cancer Consortium, IRB and FDA and as required by FDA MedWatch. These requirements are briefly outlined in the table below.

Table 4. Reporting Requirements.

	Unexpected			**Expected**
	Adverse Reaction (known or suspected attributable to the use of [^{68}Ga]PSMA		**AE not attributable to [^{68}Ga]PSMA**	**AE, AR**
	Serious including life-threatening (or death)	Nonserious	Life-Threatening or serious or not serious	None are expected for [^{68}Ga]PSMA
Reporting Time Requirement to the FDA	**Report to FDA ASAP and within 7 days of discovery of event**	Annual Continuation Review submission	Annual Continuation Review submission	Not applicable to [^{68}Ga]PSMA
Reporting Form for the FDA	IND Safety report of potentially serious risk	Annual Reports / Case reports	Annual Reports / Case reports	Not applicable to [^{68}Ga]PSMA
Reporting Time Requirement to the local IRB	**Report to IRB ASAP within 10 days of discovery of event** (suspected is defined as 50% probability attributable to [^{68}Ga]PSMA study) this also includes any increased risks with the study even without an AE	At continuation review time	At continuation review time	Not applicable to [^{68}Ga]PSMA
Reporting form for the IRB	Expedited Reporting Form for Unanticipated Problems or Noncompliance and Adverse Event Reporting Form	Form for Unanticipated Problems or Noncompliance, Case reports on continuation form, Data Safety Monitoring Reports	Form for Unanticipated Problems or Noncompliance, Case reports on continuation form, Data Safety Monitoring Reports	Not applicable to [^{68}Ga]PSMA

6.8.2.5 **Expedited Adverse Reaction Reporting Guidelines**

Life-threatening (or fatal) adverse reactions must be reported within 7 days to the FDA. The FDA should be notified as soon as the adverse reaction is discovered by telephone or fax or email. The instructions and forms are available at http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm The report should be sent

ASAP by mail and followed with a follow-up report. Individual IND safety reports to FDA are submitted on the Medwatch FDA Form 3500A as an "IND Safety Report". The form should be sent to The Director, Office of Generic Drugs in the Center for Drug Evaluation and Research at FDA. The address and phone numbers are available at: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm119100.htm.

All life threatening adverse reactions reports are submitted to the FDA, THE UAB IRB and to all investigators. A copy of the report is kept on file.

6.8.3 Protection of Privacy

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

6.9 Data Management

All patient data will be anonymized and stored on encrypted password-protected computers with access only given to members of the research team. Standard precautions regarding HIPAA will be taken to avoid any breach in patient privacy.

6.10 References

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