**Cover Page:**

**Brief Title: 18F-DCFPyL PET/CT Impact on Treatment Strategies for Patients With Prostate Cancer**

**NCT Number: NCT04390880**

**Unique Protocol Id: 2019-099757**

**Date: 08/22/2023**

Preliminary Results:

## PSMA-based $^{18}$F-DCFPyL PET/CT scan for Detection and Staging of Prostate Cancer in Comparison with Multiparametric MRI

**Introduction and Objective:** F-[18]-labelled DCFPyL is a 2nd generation prostate-specific membrane antigen (PSMA)-based PET tracer. This study aimed to assess the efficacy of $^{18}$F-DCFPyL PET/CT scan for detection of intra-prostatic and extra-prostatic lesions in individuals with clinically significant prostate cancer (PCa), compared to multiparametric MRI (mpMRI) of prostate.

**Methods:** This IRB-approved, HIPAA-compliant, single-center, prospective study was nested in a clinical trial which assesses clinical applications of $^{18}$F-DCFPyL PET/CT in individuals with PCa. Data of 150 patients who had undergone $^{18}$F-DCFPyL PET/CT scan were reviewed and 41 patients (mean age 69, ranged 55-92 years, mean serum PSA 18.6 ng/mL at the time of performing scan) who had completed a diagnostic mpMRI no more than three months before acquisition of $^{18}$F-DCFPyL PET/CT were included. PET/CT scans and mpMRIs were interpreted independently and findings were compared later. Positive mpMRI was defined as having PIRADS category 3-5 lesion(s). The pre- and post- scan questionnaires were completed by the referring physician within two weeks before and four weeks after $^{18}$F-DCFPyL PET/CT study, respectively.

**Results:** For localization of intraprostatic lesions, $^{18}$F-DCFPyL PET/CT scan and mpMRI were concordant in 78% (32/41) of the study cohort. The scans were discordant in 9 patients for this purpose, of whom two had negative, and one had non-diagnostic mpMRI. Positive regional and non-regional lymph nodes were found in 31.7% (13/41) and 7.3% (3/41) of individuals on $^{18}$F-DCFPyL PET/CT, respectively, vs. regional pelvic lymph nodes in 2.4% (1/41) on mpMRI. Skeletal metastasis was detected in 17.1% (7/41) by $^{18}$F-DCFPyL PET/CT compared to 2.4% (1/41) by mpMRI. Overall, based on the results of $^{18}$F-DCFPyL PET/CT scan, staging was altered in 43.9% (18/41) of patients.

**Conclusion:** $^{18}$F-DCFPyL PET/CT scan and mpMRI were concordant for localization of intraprostatic lesions in 78% of the study cohort. $^{18}$F-DCFPyL PET/CT is more sensitive to detect regional and non-regional lymph nodes and skeletal metastasis. Concurrent acquisition of $^{18}$F-DCFPyL PET/CT and mpMRI can be beneficial for patient care in the diagnostic path of PCa.

# 1 Clinical Protocol

## 1.1 IMPACT OF $^{18}$F-DCFPyL PET/CT ON INITIAL AND SUBSEQUENT TREATMENT STRATEGIES OF PATIENTS WITH PROSTATE CANCER (PROSPYL).

### 1.1.1 BACKGROUND AND RATIONALE

Prostate cancer is the most commonly diagnosed cancer and second leading cause of cancer death in American men (Edwards et al., 2014). Imaging and staging of prostate cancer is critical for treatment planning. Existing conventional imaging (CT, MRI and bone scans) has a low sensitivity in detecting local recurrence or metastatic disease. Choline based PET tracers are commonly used because of their affinity to prostate cancer but their diagnostic capability is limited, and they cannot reliably identify local recurrence, lymph node involvement, or soft-tissue deposits (Evangelista et al., 2013; Perera et al., 2016). Gallium-68 labeled HBED-CC PSMA (more commonly called $^{68}$Ga-PSMA-11) has been shown to be superior to choline based PET agents for the staging of prostate cancer, both Carbon11 and Fluorine-18 compounds (Afshar-Oromieh et al., 2014; Morigi et al., 2015; Schwenck et al., 2017). PSMA is expressed on the majority of prostate cancer cells, and is an ideal cell membrane protein to image. The detection rate of PSMA-11 for metastatic lesions in patients with recurrent prostate cancer is high: 50% for patients with a PSA less than 1 ng/ml, and above 85% for patients with a PSA greater than 2 ng/ml (Eiber et al., 2015; Perera et al., 2016). Several studies have reported a high impact on management of patients with biochemical recurrence after curative primary treatment with a rate of management change of 61%, 53%, 62%, 76% (Albisinni et al., 2017; Hope et al., 2017; Roach et al., 2017; Sterzing et al., 2016). In two studies, the impact on management was lower for initial staging indication: 26% and 21% (Roach et al., 2017; Sterzing et al., 2016). Limitations of $^{68}$Ga-PSMA-11 PET imaging include: a) rapid urinary excretion resulting in intense bladder accumulation obscuring the prostate region, 2) the requirement of local radionuclide generators for labeling 3) shorter half-life and reduced spatial resolution as compared to $^{18}$F agents. Recently developed second-generation PSMA PET probes using an $^{18}$F label, for example $^{18}$F-DCFPyL, overcome these limitations of $^{68}$Ga-based tracers. Preliminary studies have shown that $^{18}$F-DCFPyL to be promising for evaluation of metastatic prostate cancer. Therefore, we intend to perform a separate analysis of initial versus subsequent management as management options are considerably different (curative versus salvage/palliative).

### 1.1.2 OBJECTIVE

To determine the impact of $^{18}$F-DCFPyL PET/CT on initial and subsequent treatment strategies of patients with prostate cancer.

### 1.1.3 STUDY SYNOPSIS

This is a prospective, Phase II, open-label study in patients with prostate cancer. Study participants will receive intravenous administration of $^{18}$F-DCFPyL and undergo a PET/CT imaging study. Patients may be reenrolled in the study, if $^{18}$F-DCFPyL PET/CT is performed for subsequent management decision.

#### 1.1.3.1 Trial Size

400 total patients

### 1.1.3.2 Study Schedule and Flow Chart

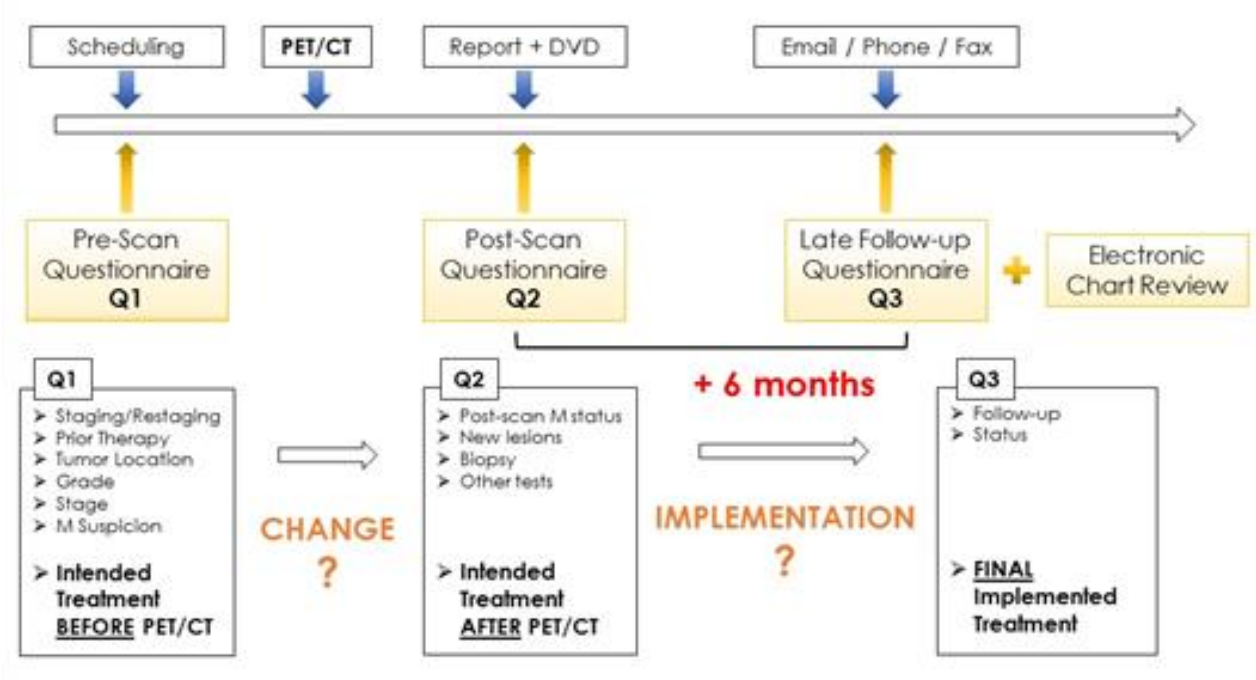


**Figure 1: Questionnaires timeline**

### 1.1.3.3 Endpoints Primary

**Endpoint:**

Intended and implemented management changes after $^{18}$F-DCFPyL PET/CT assessed separately for initial and subsequent treatment decisions.

**Secondary Endpoints:**

1. Prognostic value of the $^{18}$F-DCFPyL PET/CT miTNM classification (described below) for biochemical PFS, radiographic PFS and overall survival.
2. Positive predictive value (PPV) on a per-patient and per-region basis (Table 1) of $^{18}$F-DCFPyL PET for detection of tumor location confirmed by histopathology/biopsy or follow-up assessed separately for initial staging and restaging.

| Region | Description |
|---|---|
| 1 | Prostate Bed |
| 2 | Pelvic lymph nodes |
| 3 | Extrapelvic soft tissue, lymph nodes and visceral metastases |
| 4 | Bone metastases |

**Table 1: Region Definition**

### 1.1.3.4 Study Timeline Primary

**Completion:**

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

**Study Completion:**

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

### 1.1.4 INCLUSION EXCLUSION CRITERIA

**Inclusion criteria**

1. Patients who fulfill criteria for initial staging or restaging as outlined below:

*1) Initial treatment strategy decisions (initial staging)*

All patients with histologically proven prostate cancer or strong suspicion of prostate adenocarcinoma based on very high PSA levels (>50 ng/mL) who require an initial treatment/management decision who may be candidate for any of the following strategies:

A) Surgery
B) External radiation therapy (RT) C) Other focal therapies
D) Systemic medical treatment E)
Watchful waiting

*2) Assessment for Subsequent treatment strategy (restaging), any of the following:*

A) Patients with biochemical recurrence who are potential candidates for any salvage treatment. Biochemical recurrence is defined by rising PSA after definitive therapy with prostatectomy or radiation therapy, as any of the following:
   a. Post radical prostatectomy (RP): PSA equals to or greater than 0.2 ng/mL measured more than 6 weeks after RP
   b. Post-radiation therapy : Nadir + greater than or equal to 2 ng/mL rise in PSA
B) Patients with known prostate cancer who undergo restaging because of new symptoms
C) Patients with known metastatic prostate cancer who undergo restaging because of rising PSA with negative or inconclusive conventional imaging
D) Patients with known prostate cancer who are treated medically or with RLT in whom response to treatment is assessed

2. Capability to provide written informed consent
3. Able to remain still for duration of each imaging procedure (about 30 minutes)

* Patients may be reenrolled in the study, if $^{18}$F-DCFPyL PET/CT is performed for subsequent management decision.

**Exclusion criteria**

1. Less than 18 years-old at the time of radiotracer administration
2. Inability to complete the needed investigational and standard-of-care imaging examinations due to other reasons (severe claustrophobia, radiation phobia, etc.)
3. Any additional medical condition, serious concurrent illness, or other extenuating circumstance that, in the opinion of the Investigator, may significantly interfere with study compliance.
4. Inability to provide written informed consent

## 1.1.5 ENROLLMENT PROCEDURES

### 1.1.5.1 Patient screening:

Laboratory values: all patients must have a recent serum PSA measurement (within 30 days prior to the $^{18}$F-DCFPyL)

### 1.1.5.2 Informed Consent Process:

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

## 1.1.6 IMAGING AGENT INFORMATION

### 1.1.6.1 Study Agent:

- 18F-DCFPyL Injection is a sterile, clear particle-free solution supplied at a specific activity of at least 1000 mCi/μmol at the Time of Administration (TOA), and a radioactivity concentration (RAC) of 1-90 mCi/mL at the Time of Calibration (TOC). The TOC is at the end of synthesis (EOS). A dose of 9 ± 1 mCi (333 ±37 MBq) 18F-DCFPyL Injection will be administered via an in-dwelling catheter placed in an antecubital vein or an equivalent venous access under the direct supervision of study personnel. The bolus will be injected at a rate of approximately 1ml/3-5 seconds. The maximum amount of injected active drug will be less than 4.02mcg. The injection will be followed by a 10-ml saline flush (sodium chloride IV infusion 0.9%) over approximately 10 seconds. The pre-injection and post-injection syringe assay will be measured for total administered dose measurement. 18F-DCFPyL will be provided by Progenics pharmaceutical Inc. and sent directly to the VA GLA Healthcare System Imaging Service – Department of Nuclear Medicine. Drug will be stored per manufacturers' recommendations in the Radio-isotope Lab until it is injected into the subject. A single dose will be ordered the day before study intervention and will be delivered by the afternoon of the day of study intervention by air and ground transportation.

### 1.1.6.2 Characteristics of 18F-DCFPyL Injection:

- *Dosage Form:* Sterile solution for intravenous injection
- *Appearance:* Clear and free of visible particulate matter
- *pH:* 4.5 – 7.5
- *Total Radioactivity ($^{18}$F) per dose at TOA:* 4.5 – 7.5
- *Radiochemical Purity:* ≥95%
- *Specific Activity at TOA:* ≥1000 mCi/μmol

### 1.1.6.3 Storage and Handling:

Following releasing the drug product by the cGMP-compliant PET production facility, each unit dose of $^{18}$F-DCFPyL Injection for intravenous injection should be stored at room temperature and administered by the labeled expiration time (10 hours from EOS). $^{18}$F-DCFPyL Injection must not be diluted. The drug product contains radioactive material and should only be handled by

personnel trained and experienced in the use of radioactive isotopes with proper shielding and monitoring. Receipt and use are limited to a facility licensed by the Federal or State office for Radioactive Substances. Unused or residual waste should be disposed of as radioactive waste following the institution's standard operating procedures (SOPs) and/or applicable regulations or guidance.

The study drug will be delivered by Progenics contract manufacturer, at ~9mCi dose syringe. It will be able to deliver the final drug product to the VA Greater Los Angeles, department of Nuclear Medicine.

Toxicity will be attributed to specific study drugs based on judgment of the treating physician, or study PI or co-investigators. Toxicity will be judged as likely related, possibly related, or unlikely related to the study drug. If likely or possibly related, the next $^{18}$F-DCFPyL PET-CT imaging will be canceled. In the situation where an unexpected toxicity is observed but not clearly attributable to a study drug or procedure, then attempts will be made to identify the source of toxicity along with treatment and/or palliation of the toxicity.

### 1.1.7 STUDY PROCEDURE AND IMAGING SPECIFICS

#### 1.1.7.1 Modality:

PET/CT

#### 1.1.7.2 Study Procedures:

**Patient preparation**

1. No fasting is required.
2. All patients will be screened by a VA Nuclear Medicine physician and then accepted for scanning if clinically appropriate.
3. Informed consent will be obtained.

**Investigational drug administration:**

1. A dose of ~9mCi $^{18F}$-DCFPyL i.v. will be administered.
2. Oral hydration and voiding is recommended immediately before start of the scan.

**Safety Monitoring**

1. Vital signs will be assessed before and after injection of $^{18}$F-DCFPyL (HR and supine BP).
2. Patients will be monitored for adverse events during injection and for two hours after radiotracer administration.

**Imaging Specifics**

1. Whole-body (skull base to mid-thighs) PET/CT images will be obtained using the Siemens Biograph mCT or Vision scanners.
2. PET/CT images will be acquired in 3D mode at 50-100 minutes after injection of ~9mCi of $^{18}$F-DCFPyL.

3. Scan coverage will extend from mid-thigh to the base of the skull, starting from the mid-thighs to prevent urinary bladder radiotracer accumulation at the start of PET imaging. In certain circumstances, coverage may be extended to the toes.
4. A minimum of 3 minutes per bed position or equivalent will be used.
5. Contrast may be administered if requested by the referring clinician and is decided site dependent.
6. The PET emission scan is corrected using segmented attenuation data of the CT scan. PET images are reconstructed using ordered subset expectation maximization (OSEM) with 2 iterations and 8 subsets.

**1.1.7.3 Analysis:**

1. PET/CT Images will be reviewed and analyzed using Siemens Syngo/TrueD workstation and Oasis workstation by a board-certified nuclear medicine physician experienced in reading PET/CT.
2. A molecular imaging TNM (miTNM) framework for $^{18}$F-DCFPyL PET/CT prostate cancer staging will be used (described in 2.3.8 Analysis Specifics).

## 1.1.8 ANALYSIS SPECIFICS

### 1.1.8.1 Impact on Management Questionnaires to Referring Physicians

A pre-scan questionnaire (Q1), a post-scan questionnaire (Q2) and a follow-up questionnaire (Q3) will be used to determine whether $^{18}$F-DCFPyL PET/CT affected intended patient management and whether these intended treatment strategies were finally implemented. Patients can only be enrolled in the study if the pre-PET questionnaire (Q1) is completed.

The post-test questionnaire (Q2), has to be completed by the referring physician within 4 weeks after each $^{18}$F-DCFPyL PET/CT. The final third late follow-up questionnaire (Q3), has to be completed by the referring physician within 3 to 6 months after each $^{18}$F-DCFPyL PET/CT. Verification of management changes will also be done via chart review and telephone interview.

Treatment Modalities and sub-modalities will be categorized as following for modality based analysis:

*A) Surgery*

a. Prostatectomy or Prostate Bed Surgery
b. Pelvic Lymph Node dissection
c. Solitary LN dissection
d. Other

*B) External radiation therapy (RT)*

a. Prostate or Prostate Bed RT
b. Pelvic lymph node RT
c. Solitary LN Stereotactic body radiation therapy (SBRT)
d. Lumbo-aortic RT (standard or SBRT)
e. Oligo-metastasis SBRT *C) Other focal therapies*

a. HIFU
b. Brachytherapy

c. Cryotherapy
d. Other

*D) Systemic medical treatment*

a. ADT
b. Chemotherapy
c. Immunotherapy *E) Radionuclide therapy*

a. bone targeted radionuclide therapy
b. PSMA targeted radionuclide therapy *F) Watchful waiting*

Treatment management will also be categorized as follow for disease stage management based analysis:

*A) Local Prostate Fossa therapy B) Regional Pelvic therapy*
*C) Lombo-aortic LN focused therapy*
*D) Solitary LN or oligometastatic disease focused therapy*
*E) Metastatic disease systemic therapy*

### 1.1.8.2 Molecular Imaging TNM (miTNM) Framework

$^{18}$F-DCFPyL PET/CT provides unprecedented accuracy for whole body staging of prostate cancer. As $^{18}$F-DCFPyL PET/CT is increasingly adopted in clinical trials and routine practice worldwide, a unified language for image reporting is urgently needed. We anticipate worldwide adoption of PSMA PET/CT fueled by upcoming evidence and inclusion into guidelines. Thus, reporting standards must now be created to aid reproducible staging and restaging, enhance communication and ultimately support acceptance of this technology to the benefit of prostate cancer patients.

Our group (UCLA) has made a proposal of a molecular imaging tumor, node and metastasis system (miTNM Version 1.0) as a standardized reporting framework for $^{18}$F-DCFPyL PET/CT or PET/MRI.

miTNM organizes staging of whole-body prostate cancer by including information on exact location, pattern of disease distribution, PSMA expression and level of confidence. miTNM aims to aid information exchange by unifying clinical and research reporting of $^{18}$F-DCFPyL PET/CT. miTNM has to be prospectively evaluated to assess its impact on patient prognosis and management.

The details of miTNM are provided below:

***A) PSMA expression score:***

PSMA expression categories are defined in relation to mean uptake in blood pool, liver and parotid gland. Results are reported 0, +, ++, +++ for no, low, intermediate or high level of PSMA expression, respectively, as outlined below (Table 2, Figure 2). Scores ++ and +++ are considered typical for prostate cancer lesions and favorable for PSMA-directed radioligand therapy.

| Score | PSMA expression | Uptake |
|---|---|---|
| 0 | no | Below bloodpool |
| + | low | Equal to or above bloodpool and lower than liver |
| ++ | intermediate | Equal to or above liver and lower than parotid gland |
| +++ | high | Equal to or above parotid gland |

**Table 2: miPSMA expression score.**

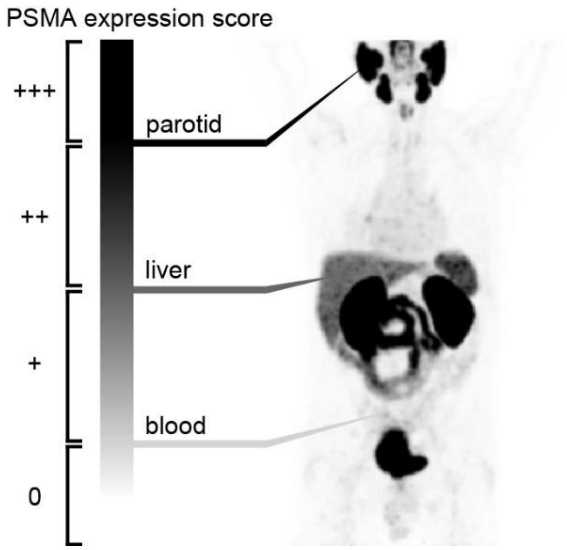


**Figure 2: PSMA expression score.** Thresholds are demonstrated on a $^{18}$F-DCFPyL PET maximumintensity projection image. Note that bloodpool uptake is determined in the center of the aortic arch.

***B) Local tumor (T) (Table 3, Figure 3)***

miT2 to T4 categorize tumor extent with prostate in place, both treated or untreated. Local organ confined tumor is defined as miT2u for unifocal and miT2m for multifocal involvement. Extraprostatic extension is classified by three categories, in accordance with clinicopathologic TNM: Limited extraprostatic extension (miT3a); involvement of seminal vesicles (miT3b); infiltration of external sphincter, rectum, bladder, levator muscles, and/or pelvic wall (miT4).
The presence of local recurrence in men after radical prostatectomy is categorized by miTr. Infiltration of pelvic structures should be detailed in the report.

| Local tumor (T) | |
|---|---|
| miT0 | No local tumor |
| miT2 | Organ confined tumor, report intraprostatic tumor location(s) on sextant base |
| u | Unifocality |
| m | Multifocality |
| miT3 | Non-organ confined tumor, report intraprostatic tumor location(s) on sextant base |
| a | Extracapsular extension |

| | | |
|---|---|---|
| miT4 | b | Tumor invades seminal vesicle(s) |
| | | Tumor invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall. |
| miTr | | Presence of local recurrence after radical prostatectomy |

**Table 3: Molecular imaging T classification for PSMA PET/CT.**

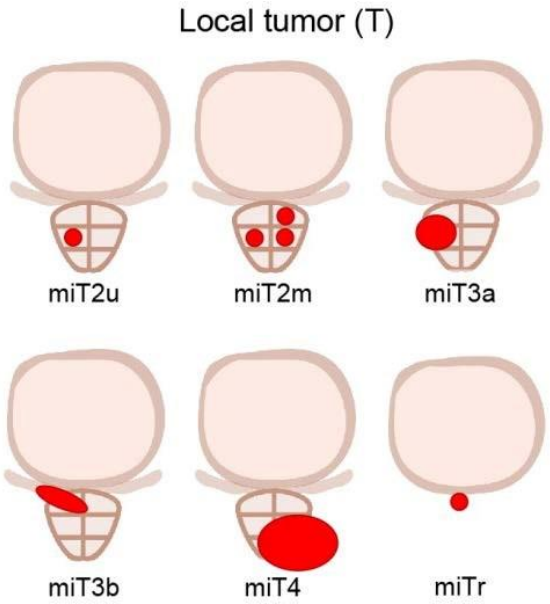


**Figure 3: miTNM categories and pattern of local tumor extent**

Anatomical distribution of intraprostatic tumor extension information of prostate involvement is described on sextant base. For sextant segmentation the craniocaudal extent of the prostate is divided into three volumes of equal thickness. Volumes will be separated into left and right of the urethra, so as to obtain left basal (LB), right basal (RB), left mid (LM), right mid (RM), left apical (LA), right apical (RA) segments (Table 4).

| Segment | miT2-4 template |
|---|---|
| LB | Left base |
| RB | Right base |
| LM | Left mid |
| RM | Right mid |
| LA | Left apex |
| RA | Right apex |

**Table 4: Sextant segmentation of prostate gland**

Probability of local tumor increases with focal uptake, higher PSMA expression score in the prostate other than the bladder neck/urethra area, higher PIRADS score, circumscribed CT contrast enhancement and/or signs of extra prostatic extension.

PSMA-positive pitfalls such as acute prostatitis and MRI-positive pitfalls such as post-biopsy changes and benign nodules have to be ruled out.

***C) Pelvic nodes (N)***

Pelvic nodal metastases will be categorized into single (miN1) and multiple (miN2) diseased lymph node regions (Table 5).

| Regional nodes (N) | |
|---|---|
| miN0 | No positive regional lymph nodes |
| miN1 | Single lymph node region harbors lymph node metastases, report location by a standardized template. |
| miN2 | Multiple (≥2) lymph node regions harbor lymph node metastases, report location(s) by a standardized template. |

**Table 5: Molecular imaging N classification for $^{18}$F-DCFPyL PET/CT.**

A standardized template for pelvic lymph node regions will be used (Table 6, Figure 4). This template covers the different regions usually approached when extended lymph node dissection is performed. Each region is encoded by a latin number; bilateral regions by a side (left/right, L/R).

| Region | miN1/2 template | Report left/right |
|---|---|---|
| I | Internal iliac | Yes |
| II | External iliac | Yes |
| III | Common iliac | Yes |
| IV | Obturator | Yes |
| V | Presacral | No |
| VI | Other pelvic (specify) | No |

**Table 6: Pelvic Lymph node regions.**

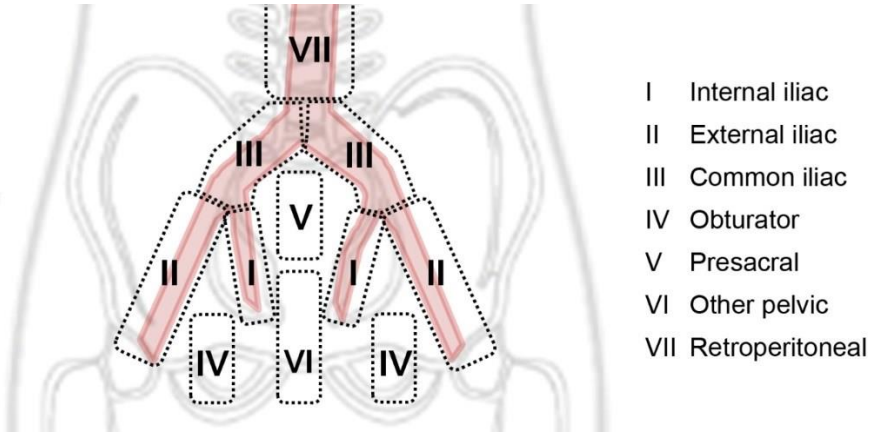


**Figure 4: miTNM standard template for pelvic lymph node regions. Transition to the extrapelvic region VII is indicated.**

Probability of nodal involvement increases with focal uptake, higher PSMA expression score and/or CT/MRI abnormalities such as increased short axis diameter, regional grouping, loss of fatty hilum, focal necrosis or increased contrast enhancement.
PSMA-positive pitfalls such as focal uptake in an adjacent ureter, inflammation or lymphedema have to be ruled out.

***D) Extra pelvic nodes and distant metastases (M)***

In accordance with clinicopathologic TNM, distant metastases will be separated into three categories: Any extra pelvic lymph nodes (miM1a); bone metastases (miM1b); organ metastases (miM1c) (Table 7).

| Distant metastases (M) | |
|---|---|
| miM0 | No distant metastasis |
| miM1 | Distant metastasis a Extrapelvic lymph node(s), additionally report location by a standardized miM1a template |
| b | Bone(s), additionally report pattern and involved bone(s) in case of unifocal or oligo metastatic |
| c | Other site(s), additionally report involved organ. |

**Table 7: Molecular imaging N classification for $^{18}$F-DCFPyL PET/CT.**

*miM1a nodes*

Location of miM1a nodes will be categorized based on a standard template into retroperitoneal, supradiaphragmatic or other regions (Table 8). Other regions need to be further specified in the final report.

| | miM1a template | |
|---|---|---|
| VII | Retroperitoneal | No |
| VIII | Supradiaphragmatic | Yes or No |
| IX | Other extra pelvic (specify) | Yes or No |

**Table 8: Extra-Pelvic Lymph node regions.**

*miM1b bone metastasis*

Bone disease will be sub-categorized by pattern of involvement in unifocal, oligometastastic, disseminated disease and diffuse marrow involvement (Table 9).

| Abbreviation | Pattern of bone involvement |
|---|---|
| uni | Unifocal |
| oligo | Oligometastatic (n≤3) |
| diss | Disseminated |
| dmi | Diffuse marrow involvement |

**Table 9: Pattern of bone involvement.**

Oligometastatic bone involvement is diagnosed in case of three or less bone lesions (Schweizer et al., 2013). In case of unifocal or oligometastatic disease, involved bones will be specified. Pattern of bone involvement can have important implications for prognosis (Ost et al., 2014; Schweizer et al., 2013) and management (Tosoian et al., 2016). For instance unifocal disease may be targetable with curative intent by external-beam radiation therapy and diffuse marrow involvement indicates elevated risk for hematotoxicity after radionuclide therapy (Jong et al., 2015; Parker et al., 2013; Rahbar et al., 2016).

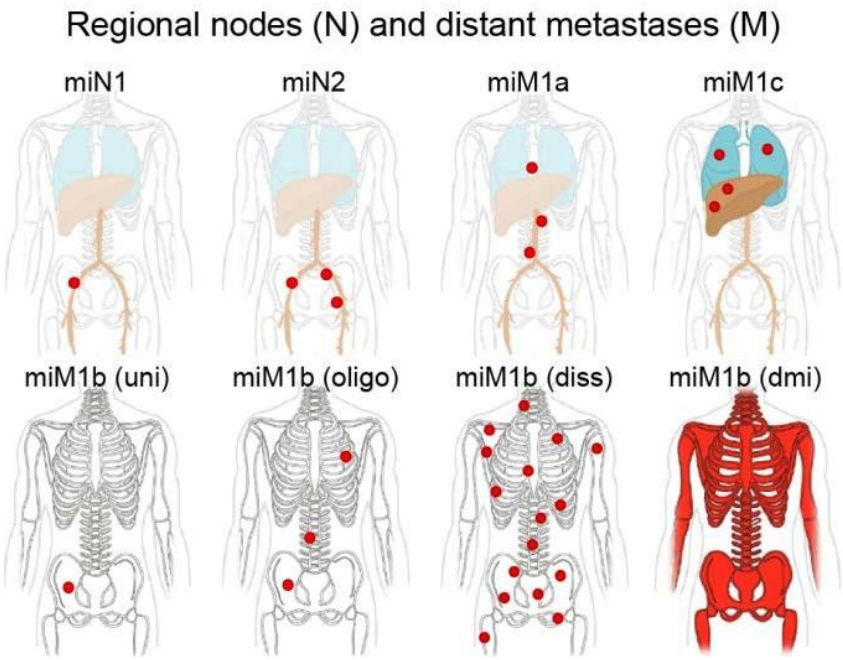


**Figure 5: miTNM categories and pattern of pelvic nodal, distant metastases and bone involvement for reporting prostate cancer stage by $^{18}$F-DCFPyL PET/CT**. Tumor involvement is delineated in red. Abbreviations: uni, unifocal; oligo, oligometastatic; diss, disseminated; dmi, diffuse marrow involvement.

In patients with organ involvement (miM1c) all involved organs need to be specified in the final report.

Probability of bone or organ involvement increases with focal uptake, higher PSMA expression score and/or CT/MRI abnormalities. For bone metastases common CT findings include sclerotic, rarely lytic lesions with or without extraosseous extension; common MRI findings include low signal on unenhanced T1 images.

PSMA-positive pitfalls such post-traumatic rib uptake, or non-prostate cancer related primary malignancies have to be ruled out (Rauscher et al., 2016).

***E) Level of Certainty***

Reporting level of certainty will be performed as previously proposed by Panicek et al (Panicek and Hricak, 2016) (Table 10).

| Term | Numeric estimate |
|---|---|
| Consistent with | >90% |
| Suspicious for/Probable/Probably | ~75% |
| Possible/Possibly | ~50% |
| Less likely ~25% Unlikely | <10% |

**Table 10: Level of certainty.**

Certainty will substantially vary depending on uptake, location and CT or MRI findings. For instance at biochemical recurrence certainty of tumor localization will be substantially higher in case of focal uptake at a common location (e.g. internal iliac lymph node) as compared to an uncommon location (e.g. rib).

Standardized wording for level of certainty will improve communication between the reader and the treating physician.

### 1.1.8.3 Treatment Response Assessment

***1. miTNM***

*a.* Any decrease in miTNM class (ex: miT0N2M1b(uni) to miT0N1M1b(uni)) is considered partial response,
*b.* Any increase in miTNM class (ex: miTr N1 (IVL) M0 to miT0 N2 M0) is considered progressive disease.
*c.* Complete resolution on $^{18}$F-DCFPyL PET is complete response,
*d.* No change in miTNM class is stable disease.

***2. total PSMA tumor volume***

Delineation of total PSMA tumor volume on PET by a yet to be determined algorithm.

a. Decrease by 30% = PR,
b. increase by 30% = PD,
c. Volume = 0 = complete response,
d. Otherwise stable disease.

### 1.1.8.4 Measurements

***1) Primary Outcome Measurement:***

A separate analysis of initial versus subsequent management will be performed.

The principal goal of this study is to evaluate the impact of $^{18}$F-DCFPyL PET/CT on patient management in patients with prostate cancer. The study includes a total of 3 questionnaires; Questionnaires 1 and 2 will be collected from referring physicians prior to and just after completion of the imaging study; these are designed to determine the intended patient management before and intended management changes after PET/CT.

Patients can only be enrolled in the study if the pre-PET questionnaire (Q1) is completed.

*Treatment Modality Analysis*: 3 categories of management changes will be evaluated:

- no change
- Inter-modality management changes (Major), i.e. change in modality or addition/removal of one or more modalities in the overall management

- Intra-modality management changes (Minor), i.e. same modality before and after PSMA PET/CT, however for instance:
  - Changes in Medical treatment
  - Changes in radiation approach
  - Changes in surgical approach
  - Addition/removal of concomitant ADT

*Disease stage based management Analysis*:
Treatment management will also be categorized as follow: A/ Local Prostate Fossa therapy, B/ Regional Pelvic therapy, C/ Lombo-aortic LN focused therapy, D/ Solitary LN or oligometastatic disease focused therapy and E/ Metastatic disease systemic therapy.

Management change will be classified as: 1/ no change or 2/ change (addition/removal of one or more of these disease stage based treatment strategies)

Questionnaire 3 will be mailed to referring physicians 3-6 months after completion of the imaging study to determine whether intended management changes were implemented.

To assess the implemented treatment management, following methods will be used, in descending priority:

1. Systematic electronic chart review when available
2. Questionnaire
3. Referring physician contact (email, phone or fax)
4. Patient contact (email, phone or fax)

***2) Secondary Outcome Measurement:***

**A) FOLLOW-UP IMAGING:**

All patients will be followed up 3-12 months with conventional imaging (dedicated CT, MRI and/or bone scan). Interpretation of follow-up imaging will be performed by local read. For lesions that are reported in the blinded reads but not reported in the local evaluation of follow-up imaging, the local readers will be informed of the location of the lesions and follow-up will be performed for these additional lesions. Preferably, the follow-up conventional imaging should be the same modality/modalities as the initial staging work-up to allow for reproducible and accurate comparisons.

***Lymph Nodes lesions:***
$^{18}$F-DCFPyL positive lymph nodes will be considered. Lymph nodes will be assessed by change in size.

*True positive*:

1) For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lymph nodes seen

on CT or MRI decrease by more than 30% in short axis diameter and PSA declines by more than 50%.
   - If PSA increases by more than 50% on systemic therapy, then a increase in the size of lesion by more than 20% will be considered a true positive lesion.
2) In subjects with localized suspected lymph node(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet true positive disease:
   - If the subject shows a decrease of PSA by greater than 50% after targeted treatment and the lymph node does not enlarge (change in size less than 20% or less than 3 mm increase in short axis diameter) [OR]
   - If on post-treatment follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI decrease by more than 30% in short axis diameter (with a minimum of 3 mm in change in size)
3) For untreated patients: If on follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI increase by more than 20% in short axis diameter (with a minimum of 3 mm in change in size).

*False positive:*

1) For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI increase by more than 20% in short axis diameter and PSA decreases by more than 50%.
2) In subjects with localized suspected lymph node(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet false positive disease:
   - If the subject does not demonstrate a decrease of PSA by greater than 50% after targeted treatment [OR]
   - If on post-treatment follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI increase by more than 20% in short axis diameter (with a minimum of 3 mm in change in size)
3) For untreated patients: If on follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI decrease by more than 30% in short axis diameter (with a minimum of 3 mm in change in size).

If all regions in a patient/region do not meet criteria for either True positive or False positive disease, then the patient/region will be considered unevaluable for primary endpoint.

***Visceral lesions:***

$^{18}$F-DCFPyL positive visceral lesions will be considered. Visceral lesions (non-lymph node soft tissue or organ) will be assessed by change in size.

*True positive:*

1) For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter and PSA declines by more than 50%.

- If PSA increases by more than 50% on systemic therapy, then a increase in the size of lesion by more than 20% will be considered a true positive lesion.

2) In subjects with localized suspected lesions(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet true positive disease:
   - If the subject demonstrates a decrease of PSA by greater than 50% after targeted treatment [OR]
   - If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter (with a minimum of 3 mm in change in size)
3) For untreated patients: If on follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter (with a minimum of 3 mm in change in size).

*False positive*

1) For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter and PSA decreases by more than 50%.
2) In subjects with localized suspected lesions(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet false positive disease:
   - If the subject does not demonstrate a decrease of PSA by greater than 50% after targeted treatment [OR]
   - If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter (with a minimum of 3 mm in change in size).
3) For untreated patients: If on follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter (with a minimum of 3 mm in change in size).

If all regions in a patient/region do not meet criteria for either True positive or False positive disease, then the patient/region will be considered unevaluable for primary endpoint.

***Bone lesions***

$^{18}$F-DCFPyL positive bone lesions will be considered.

*True positive:*

1) If there was a corresponding positive sclerotic lesion on the CT portion of the $^{68}$Ga-$^{18}$F-DCFPyL PET or on a separate CT obtained $\leq$ 30 days before or after the PET/CT in the same location as the PSMA uptake.
2) If there is focal uptake seen in the same location as the PSMA uptake on the baseline bone scan performed within one month of $^{18}$F-DCFPyL PET.
3) If there is a lesion noted in the same location as the PSMA uptake on the initial MRI performed within one month of $^{18}$F-DCFPyL.

4) If within 12 months follow-up CT demonstrates development of sclerosis in the same location as the PSMA uptake.
5) If within 12 months follow-up MRI demonstrates a new bone lesion in the same location as the PSMA uptake.
6) If within 12 months follow-up bone scan demonstrates new focal uptake in the same location as the PSMA uptake.
7) In subjects with localized suspected bone lesion(s) receiving targeted treatment without concomitant systemic treatment:
   - If the subject demonstrates a decrease of PSA by greater than 50% after targeted treatment.

*False positive:*

1) In subjects with localized suspected bone lesion(s) receiving targeted treatment without concomitant systemic treatment:
   - If the subject does not demonstrate a decrease of PSA by greater than 50% after targeted treatment with curative intent (ie non-palliative radiation).
2) If $^{18}$F-DCFPyL positive bone lesions do not meet the criteria for true positive findings, and appropriate correlative and follow-up imaging was acquired.

If bone lesions do not meet criteria for either true positive or false positive disease listed above, then the patient/region will be considered unevaluable for primary endpoint.

***Prostate lesions:***

$^{18}$F-DCFPyL positive prostate bed and prostate lesions will be considered:

*True positive:*

1) For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter
2) In subjects with localized suspected lesions(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet true positive disease:
   - If the subject demonstrates a decrease of PSA by greater than 50% after targeted treatment [OR]
   - If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter (with a minimum of 3 mm in change in size)
3) For untreated patients: If on follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter (with a minimum of 3 mm in change in size).

*False positive:*

1) For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT

or MRI increase by more than 20% in long axis diameter and PSA decreases by more than 50%.

2) In subjects with localized suspected lesions(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet false positive disease:
   - If the subject does not demonstrate a decrease of PSA by greater than 50% after targeted treatment [OR]
   - If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter (with a minimum of 3 mm in change in size)
3) For untreated patients: If on follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter (with a minimum of 3 mm in change in size).

If the lesion does not meet criteria for either True positive or False positive disease, then the lesion will be considered inevaluable for primary endpoint.

**B) HISTOPATHOLOGY/BIOPSY:**

Localization of lesions for histopathology/biopsy will be a classified by regions as specified in the miTNM framework. $^{18}$F-DCFPyL positive findings are aimed to be confirmed by histopathology (HP)/biopsy if clinically feasible. Pathology performed 60 days before the $^{18}$F-DCFPyL PET will be available for correlation. Histopathological procedures, biopsies and follow-up imaging will be performed as clinically indicated and as per institutional protocol.

The following elective procedures may guide the investigator:

Positive HP/Biopsy: Confirmed sites of metastatic or tumor involvement by histopathology/biopsy will be discussed with the responsible physician/surgeon.

a) *True Positive*: lesion is positive on targeted biopsy/surgical sampling and is read as positive on $^{18}$F-DCFPyL PET.
b) *False Negative*: lesion is positive on targeted biopsy/surgical sampling and is read as negative on $^{18}$F-DCFPyL PET.

Negative HP/Biopsy: Patients with suspected tumor recurrence on $^{18}$F-DCFPyL PET with negative histopathology/biopsy will be handled as outlined below:

1) *Lymph nodes:*
   i) For patients undergoing nodal dissection: Patients will be rescanned with dedicated CT, MRI or a repeat $^{18}$F-DCFPyL PET to determine if the suspicious $^{18}$F-DCFPyL positive node was removed.
      (1) If $^{18}$F-DCFPyL positive lymph node is still present, a repeat biopsy can be pursued if clinically feasible and applicable, or follow-up using imaging as described above will be performed.
      (2) If the corresponding node was removed, then this will be considered a False Positive.

ii) For patients undergoing needle biopsy: Images of the procedure will be reviewed to determine if the correct node was biopsied.
   (1) If the correct node was biopsied, then a negative biopsy will be considered a False Positive.
   (2) If the incorrect node was biopsied, then follow-up imaging as described above will be performed.

2) *Bone lesions:* Given the high rate of false negative biopsies for osseous metastases in patients with prostate cancer, patients with negative bone biopsies of PSMA PET positive lesions will be further evaluated:
   a) If pathology demonstrates an alternative diagnoses that is known to be PSMA positive (eg Renal Cell Carcinoma metastases, Paget's disease), then this will be considered a False Positive.
   b) If pathology is indeterminate, then follow-up imaging as described above will be performed to determine if the lesion is a True Positive or False Positive.

3) Although not routinely performed during standard practice, immunohistochemical staining for PSMA of tumor specimens (primary and lymph node metastases) may be performed, although not required.

**C) DEFINITIONS OF TRUE POSITIVE, FALSE POSITIVE, TRUE NEGATIVE, AND FALSE NEGATIVE PATIENTS AND REGIONS**

Pathology will be considered superior to imaging and clinical follow-up when available as described below. Patient and region level classification will be performed for each blinded reader, and be reported separately. The following criteria serve as a guide for interpretation. However not all findings on a lesions, region and patient level can be detailed here and investigators may deviate from these criteria in individual patients. These will be recorded for each interpretation that is not described in this protocol for the definition of a region or patient.

1) Patient level evaluation:

   a) *True positive patient*: A single region in a patient contains a true positive node either by pathology or imaging/clinical follow-up.
      i) For a patient to be considered a True Positive, only one region is required to have a true positive lesion as described above, unless one region is categorized as a false positive based on pathology. This means that a single pathology false positive region outweighs regions with imaging/clinical follow-up true positive disease.
      ii) A patient will be considered a True Positive if one region contains a lesion that is True Positive, even if other regions are categorized as inevaluable or false positive based on imaging or clinical follow-up.

b) *True negative patient*: in the absence of True Positive or False Positive lesions, a patient will be considered a True Negative if there is pathology that is negative for disease and corresponding lesion is negative by $^{18}$F-DCFPyL PET.

c) *False positive patient:*
   i) Pathology confirms a false positive lesion that is read as positive on $^{18}$F-DCFPyL PET.
   ii) In the absence of pathology: there are no true positive regions, and there is a region that is categorized as false positive based on imaging or clinical follow-up.

d) *False negative patient*: in the absence of True Positive or False Positive lesions, a patient will be considered a False Negative if there is pathology that is positive for disease and corresponding lesion is negative by $^{18}$F-DCFPyL PET.

2) Region level evaluation: Each patient will have four evaluable regions (Table 1: prostate bed, pelvis, extrapelvic soft tissue, and bone metastases). Each region will be categorized as true positive or false positive as described above. Regions without evidence of $^{18}$F-DCFPyL positive disease or deemed unevaluable will not be included in the analysis.

a) *True positive region*:
   i) Pathology confirms a $^{18}$F-DCFPyL avid lesion as a true positive in the region. ii) In the absence of pathology, clinical or imaging follow-up demonstrates a true positive lesion within the region independent of the presence of an inevaluable lesion or a false positive lesion (ie true positive disease will supersede a false positive lesion in the region based analysis if based on imaging/clinical follow-up).

b) *True negative region*: in the absence of True Positive or False Positive lesions within a region, the region will be considered a True Negative if there is pathology that is negative for disease in the region and corresponding lesion is negative by $^{18}$F-DCFPyL PET.

c) *False positive region*:
   i) Pathology confirms a $^{18}$F-DCFPyL avid lesion as a false positive in the region
   ii) In the absence of pathology, there are no true positive lesions in the region, and there is a false positive lesion by clinical or imaging follow-up.

d) *False negative region*: in the absence of True Positive or False Positive lesions in a region, the region will be considered a False Negative if there is pathology that is positive for disease in the region and corresponding lesion is negative by $^{18}$F-DCFPyL PET.

## 1.1.9 STATISTICAL CONSIDERATIONS

### 1.1.9.1 Randomization

No randomization will be done.

### 1.1.9.2 Analysis Population

Endpoints will be analyzed for the entire patient cohort and for treatment groups separately (Initial and subsequent).

**1.1.9.3 Impact on Management Analysis Plan:**

The impact of $^{18}$F-DCFPyL PET on clinical management patients will be evaluated using descriptive statistics for both the treatment modality analysis and the disease stage based management analysis.

**1.1.9.4 Prognostic Value Analysis:**

Clinical outcome is defined by:

- Radiographic PFS: time from inclusion to date until first site of disease is found to progress or death (whichever occurs first)

a) Nodal and visceral disease is evaluated on cross-sectional imaging using RECIST 1.1/PCWG3 criteria

b) Bone metastases are evaluated using bone scintigraphy and new lesions have to be confirmed on a second scan (2+2 rule) using PCWG3 criteria

- Biochemical PFS: time from inclusion to date until PSA progression or death (whichever occurs first) (Scher et al., 2016)

a) *for patients with PSA decline*: Time from baseline to time the PSA increase to 25% and 2 ng/ml above nadir which is confirmed by a second value ≥3 weeks later

b) *for patients without PSA decline*: Time from baseline to time the PSA increase to 25% and 2 ng/ml above baseline

- Overall survival: Time from inclusion to date of death.

**1.1.9.5 Positive predictive value (PPV) on a per-patient and per-region basis Analysis:**

PPVs on a per-patient and per-region-basis of $^{18}$F-DCFPyL PET for detection of tumor location confirmed by histopathology/biopsy, clinical and conventional imaging follow-up will be calculated and reported along with the corresponding two-sided 95% confidence intervals. The confidence intervals will be constructed using the Wilson score method. PPV will be reported for each of the three blinded readers independently.

Detection rates on a per-patient basis of $^{18}$F-DCFPyL PET stratified by PSA value (0.2 - <0.5, 0.5 - <1.0, 1.0 - <2.0, 2.0 - <5.0, ≥5.0) will be summarized in tabular format and compared between PSA strata using chi-square analysis.

Detection rate is defined as number of patients with $^{18}$F-DCFPyL positive disease, independent of pathology, imaging or clinical follow-up. A detection rate will be reported for each reader independently stratified by PSA.

**1.1.9.6Sample Size**

Based on a previous study (Calais et al, 2017), we anticipate that 53% of patients will undergo an implemented change in management after $^{18}$F-DCFPyL PET/CT. Based on our previous experience and interim analysis, due to incomplete patient data, especially low turn-in rate from referring treating physician for post PET/CT intended treatment (Questionnaire 2), a sample size of 400 patients would provide >90% power to determine whether the proportion of patients implementing change in management exceeds 40%, assuming an exact binomial test, and a one-sided alpha of 0.025. A sample size of 400 patients is expected to produce a margin of error for the proportion of patients implementing change in management ranging from 6.9%, assuming a two-sided 95% confidence level. Sample size calculation was conducted in collaboration with the UCLA Department of Biostatistics (D. Elashoff, S. Vangala).

#### 1.1.9.7Accrual Estimates

We plan to enroll 100 participants/year and this is achievable given our experience with other protocols and the expected support from the referring physicians within the Los Angeles region and beyond.

## 1.1.10 CRITERIA FOR REMOVAL FROM STUDY

The Principal Investigator may withdraw subjects from the study for one or more of the following reasons:

- failure to follow the instructions of the Principal Investigator and/or study staff;
- determination that continuing the participation could be harmful to the subject; ▪ the study is cancelled
- other administrative reasons.

## 1.1.11 ADVERSE EVENTS AND REPORTING PROCEDURES

### 1.1.11.1 Potential Adverse Events:

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

This research study involves exposure to radiation from one $^{18}$F-DCFPyL PET/CT. The effective dose from one typical 140 MBq administration of $^{18}$F-DCFPyL is 3.54 mSv. The effective dose from one CT attenuation scan is 4 mSv. Therefore, the effective dose from one $^{18}$F-DCFPyL PET/CT is 7.54 mSv, approximately equal to 15% of the limit that radiation workers (for example, a hospital x-ray technician) are allowed to receive in one year.

### 1.1.11.2 Adverse Event Reporting

We do not anticipate hazardous situations for the subjects as a result of this protocol. However, procedures will be in place for verification of correct radiopharmaceutical dose and route of administration (i.e., each dose will be double checked for dosimetry and quality by a researcher and technologist). The study Principal Investigator (PI) or his designee will report unanticipated

AEs to the VA IRB within 10 working days of becoming aware of the event (5 days if the event is life-threatening or resulted in death). If the principal investigator determines the unanticipated adverse device effect presents an unreasonable risk to subjects, the study will be terminated as soon as possible. Adverse events will be reported to the FDA.

## 1.1.12 REGULATORY CONSIDERATIONS

### 1.1.12.1 ClinicalTrials.gov

The protocol will be registered on clinicaltrials.gov.

### 1.1.12.2 Institutional Review of Protocol

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

### 1.1.12.3 Data Management Plan

The CRFs will be stored in a locked office in the Nuclear Medicine Department. During the clinical investigation, the Principal Investigator will evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome.

## References:

Afshar-Oromieh, A., Zechmann, C.M., Malcher, A., Eder, M., Eisenhut, M., Linhart, H.G., Holland-Letz, T., Hadaschik, B.A., Giesel, F.L., Debus, J.*, et al.* (2014). Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging *41*, 11-20.

Albisinni, S., Artigas, C., Aoun, F., Biaou, I., Grosman, J., Gil, T., Hawaux, E., Limani, K., Otte, F.X., Peltier, A.*, et al.* (2017). Clinical impact of 68 Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) in patients with prostate cancer with rising prostate-specific antigen after treatment with curative intent: preliminary analysis of a multidisciplinary approach. BJU international *120*, 197-203.

Calais J, Fendler WP, Eiber M, Gartmann J, Chu FI, Nickols NG, Reiter RE, Rettig MB, Marks LS, Ahlering TE, Huynh LM, Slavik R, Gupta P, Quon A, Allen-Auerbach MS, Czernin J, Herrmann K. (2018) Impact of $^{68}$Ga-PSMA-11 PET/CT on the Management of Prostate Cancer Patients with Biochemical Recurrence. J Mucl Med *59(3)*:434-441

Edwards, B.K., Noone, A.M., Mariotto, A.B., Simard, E.P., Boscoe, F.P., Henley, S.J., Jemal, A., Cho, H., Anderson, R.N., Kohler, B.A.*, et al.* (2014). Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer *120*, 1290-1314.

Eiber, M., Maurer, T., Souvatzoglou, M., Beer, A.J., Ruffani, A., Haller, B., Graner, F.P., Kubler, H., Haberhorn, U., Eisenhut, M.*, et al.* (2015). Evaluation of Hybrid (6)(8)Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. Journal of nuclear medicine : official publication, Society of Nuclear Medicine *56*, 668-674.

Evangelista, L., Guttilla, A., Zattoni, F., Muzzio, P.C., and Zattoni, F. (2013). Utility of choline positron emission tomography/computed tomography for lymph node involvement identification in intermediate- to high-risk prostate cancer: a systematic literature review and meta-analysis. European urology *63*, 10401048.

Hartmann, H., ZÃƒphel, K., Freudenberg, R., Oehme, L., Andreeff, M., Wunderlich, G., Eisenhofer, G., and Kotzerke, J. (2009). [Radiation exposure of patients during 68Ga-DOTATOC PET/CT examinations]. Nuclear-Medizin *48*, 201-207.

Hope, T.A., Aggarwal, R., Chee, B., Tao, D., Greene, K.L., Cooperberg, M., Feng, F., Chang, A., Ryan, C.J., Small, E.J.*, et al.* (2017). Impact of Ga-68 PSMA-11 PET on Management in Patients with Biochemically Recurrent Prostate Cancer. Journal of nuclear medicine : official publication, Society of Nuclear Medicine.

Jong, J.M., Oprea-Lager, D.E., Hooft, L., de Klerk, J.M., Bloemendal, H.J., Verheul, H.M., Hoekstra, O.S., and van den Eertwegh, A.J. (2015). Radiopharmaceuticals for Palliation of Bone Pain in Patients with Castration-resistant Prostate Cancer Metastatic to Bone: A Systematic Review. European urology *70*, 416426.

Kim, J., Lee, J., Kang, K., Lee, H.-Y., Han, S.-W., Kim, T.-Y., Lee, Y.-S., Jeong, J., and Lee, D. (2012). Whole-body distribution and radiation dosimetry of (68)Ga-NOTA-RGD, a positron emission tomography agent for angiogenesis imaging. Cancer biotherapy and radiopharmaceuticals *27*, 65-71.

Morigi, J.J., Stricker, P.D., van Leeuwen, P.J., Tang, R., Ho, B., Nguyen, Q., Hruby, G., Fogarty, G., Jagavkar, R., Kneebone, A.*, et al.* (2015). Prospective Comparison of 18F-Fluoromethylcholine Versus 68Ga-PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy. Journal of nuclear medicine : official publication, Society of Nuclear Medicine *56*, 1185-1190.

Ost, P., Decaestecker, K., Lambert, B., Fonteyne, V., Delrue, L., Lumen, N., Ameye, F., and De Meerleer, G. (2014). Prognostic factors influencing prostate cancer-specific survival in non-castrate patients with metastatic prostate cancer. The Prostate *74*, 297-305.

Panicek, D.M., and Hricak, H. (2016). How Sure Are You, Doctor? A Standardized Lexicon to Describe the Radiologist's Level of Certainty. AJR American journal of roentgenology *207*, 2-3.

Parker, C., Nilsson, S., Heinrich, D., Helle, S.I., O'Sullivan, J.M., Fossa, S.D., Chodacki, A., Wiechno, P., Logue, J., Seke, M.*, et al.* (2013). Alpha emitter radium-223 and survival in metastatic prostate cancer. The New England journal of medicine *369*, 213-223.

Perera, M., Papa, N., Christidis, D., Wetherell, D., Hofman, M.S., Murphy, D.G., Bolton, D., and Lawrentschuk, N. (2016). Sensitivity, Specificity, and Predictors of Positive 68Ga-Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer: A Systematic Review and Meta-analysis. European urology *70*, 926-937.

Pettinato, C., Sarnelli, A., Di Donna, M., Civollani, S., Nanni, C., Montini, G., Di Pierro, D., Ferrari, M., Marengo, M., and Bergamini, C. (2008). 68Ga-DOTANOC: biodistribution and dosimetry in patients affected by neuroendocrine tumors. European journal of nuclear medicine and molecular imaging *35*, 72-79.

Rahbar, K., Ahmadzadehfar, H., Kratochwil, C., Haberkorn, U., Schafers, M., Essler, M., Baum, R.P., Kulkarani, H.R., Schmidt, M., Bartenstein, P., *et al.* (2016). German multicenter study investigating 177LuPSMA-617 radioligand therapy in advanced prostate cancer patients. Journal of nuclear medicine : official publication, Society of Nuclear Medicine.

Rauscher, I., Maurer, T., Fendler, W.P., Sommer, W.H., Schwaiger, M., and Eiber, M. (2016). (68)Ga-PSMA ligand PET/CT in patients with prostate cancer: How we review and report. Cancer imaging : the official publication of the International Cancer Imaging Society *16*, 14.

Roach, P.J., Francis, R., Emmett, L., Hsiao, E., Kneebone, A., Hruby, G., Eade, T., Nguyen, Q., Thompson, B., Cusick, T., *et al.* (2017). The impact of 68Ga-PSMA PET/CT on management intent in prostate cancer: results of an Australian prospective multicenter study. Journal of nuclear medicine : official publication, Society of Nuclear Medicine.

SandstrÃƒm, M., Velikyan, I., Garske-RomÃƒn, U., SÃƒrensen, J., Eriksson, B., Granberg, D., Lundqvist, H., Sundin, A., and Lubberink, M. (2013). Comparative Biodistribution and Radiation Dosimetry of 68GaDOTATOC and 68Ga-DOTATATE in Patients with Neuroendocrine Tumors. The Journal of nuclear medicine *54*, 1755-1759.

Scher, H.I., Morris, M.J., Stadler, W.M., Higano, C., Basch, E., Fizazi, K., Antonarakis, E.S., Beer, T.M., Carducci, M.A., Chi, K.N., *et al.* (2016). Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. Journal of clinical oncology : official journal of the American Society of Clinical Oncology *34*, 1402-1418.

Schweizer, M.T., Zhou, X.C., Wang, H., Yang, T., Shaukat, F., Partin, A.W., Eisenberger, M.A., and Antonarakis, E.S. (2013). Metastasis-free survival is associated with overall survival in men with PSArecurrent prostate cancer treated with deferred androgen deprivation therapy. Annals of oncology : official journal of the European Society for Medical Oncology *24*, 2881-2886.

Schwenck, J., Rempp, H., Reischl, G., Kruck, S., Stenzl, A., Nikolaou, K., Pfannenberg, C., and la Fougere, C. (2017). Comparison of 68Ga-labelled PSMA-11 and 11C-choline in the detection of prostate cancer metastases by PET/CT. Eur J Nucl Med Mol Imaging *44*, 92-101.

Sterzing, F., Kratochwil, C., Fiedler, H., Katayama, S., Habl, G., Kopka, K., Afshar-Oromieh, A., Debus, J., Haberkorn, U., and Giesel, F.L. (2016). (68)Ga-PSMA-11 PET/CT: a new technique with high potential for the radiotherapeutic management of prostate cancer patients. Eur J Nucl Med Mol Imaging *43*, 34-41.

Tosoian, J.J., Gorin, M.A., Ross, A.E., Pienta, K.J., Tran, P.T., and Schaeffer, E.M. (2016). Oligometastatic prostate cancer: definitions, clinical outcomes, and treatment considerations. Nature reviews Urology *14*, 15-25.