Pilot Study of ^{18}F-DCFPyL PET/CT in the Evaluation of Men with an Elevated PSA Following Radical Prostatectomy

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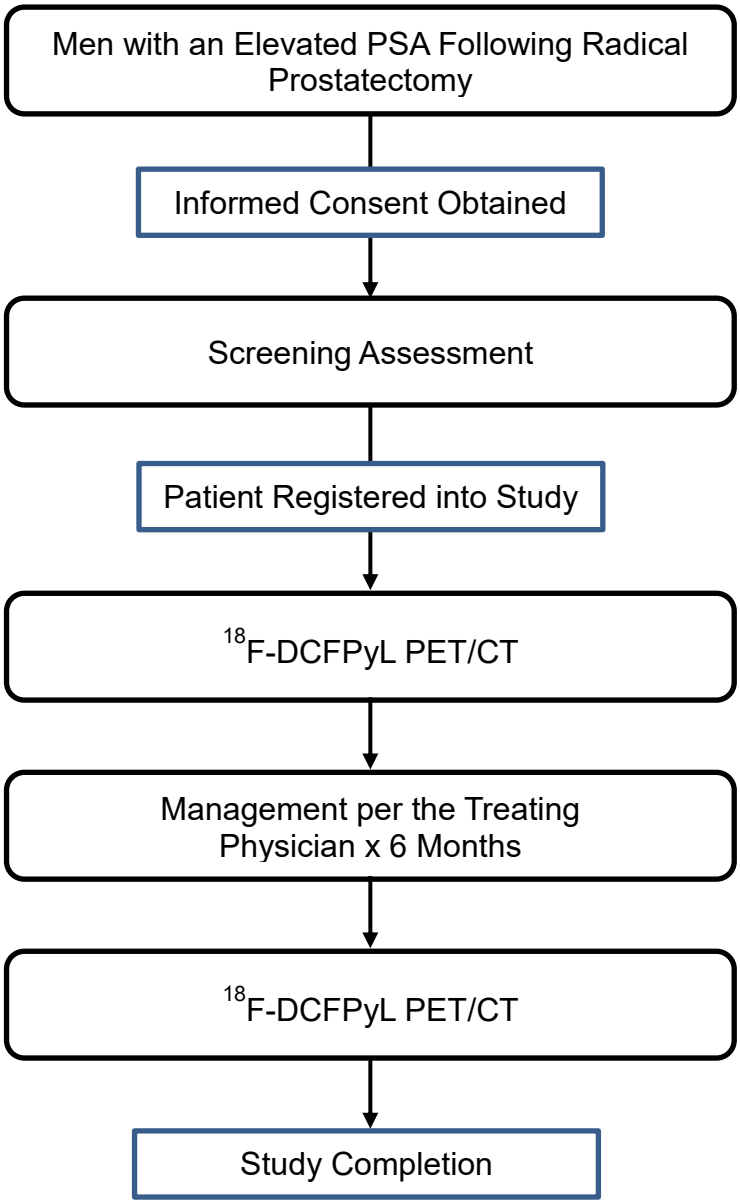
1. STUDY SUMMARY

PROTOCOL TITLE	Pilot Study of ^{18}F-DCFPyL PET/CT in the Evaluation of Men with an Elevated PSA Following Radical Prostatectomy
IRB NUMBER	IRB00062296
IND NUMBER	121064
INVESTIGATIONAL AGENT	^{18}F-DCFPyL
PATIENT POPULATION	Men with an elevated PSA level following radical prostatectomy for adenocarcinoma of the prostate
SAMPLE SIZE	N = 50
ENDPOINTS	• Description of the number and location of putative sites of metastatic disease as determined by ^{18}F-DCFPyL PET/CT • Correlation of findings on ^{18}F-DCFPyL PET/CT with those found on conventional imaging • Correlation of findings on ^{18}F-DCFPyL PET/CT with tissue histology and PSMA expression of biopsied/resected pathology specimens • Assessment of treatment response by ^{18}F-DCFPyL PET/CT following 6 months of management per the treating physician • Correlation of ^{18}F-DCFPyL PET/CT findings with PSA levels and time to disease progression

2. STUDY SCHEMA



3. BACKGROUND & RATIONALE

Prostate cancer represents the most common non-dermatologic malignancy in men, with an estimated 235,000 new cases diagnosed annually in the United States.[1] At initial presentation, the majority of cases are organ-confined[2,3] and will be adequately treated with radiation therapy or radical prostatectomy[4]. Following local treatment, nearly 20% of men will experience a biochemical recurrence and up to half of these men will go on to develop overt metastatic disease.[5-7] Additionally, a subset of patients treated with definitive therapy will continue to have an elevated prostate specific antigen (PSA), suggestive of clinically occult metastatic disease at the time of diagnosis. Alternatively, a subset of these men will have local disease which was inadequately treated. Thus, in men presenting with an elevated PSA following initial local therapy, it is of critical importance to define the location and extent of disease in order to deliver salvage therapy to active sites of malignancy (i.e. local versus systemic therapy). Unfortunately, at the present time conventional imaging with bone scan, computed tomography (CT) and magnetic resonance imaging (MRI) are woefully inadequate to detect small volume sites of disease.[8-10] This has left clinicians to base decisions regarding the timing and mode of salvage treatment on imperfect clinical parameters such as PSA kinetics, surgical margin status and other pathologic data.[11,12]

An alternative to conventional imaging is positron emission tomography (PET) combined with CT (PET/CT). PET/CT is a highly sensitive imaging modality that allows for the visualization of small volume sites of disease following accumulation of various radiotracers. In the field of oncology, PET/CT is most commonly performed using ^{18}F-labeled fluorodeoxyglucose (FDG). Unfortunately, studies employing FDG have demonstrated mixed results in the imaging prostate cancer.[13] Based on these data, many in the field have abandoned FDG PET/CT for the study of novel radiotracers against prostate cancer specific targets. One such target which has received considerable attention is prostate specific membrane antigen (PSMA). PSMA is a type II transmembrane glycoprotein found in approximately 95% of prostate cancer specimens.[14] An FDA approved ^{111}In-labeled antibody agent, ProstaScint[15,16] has been previously used for single-photon emission computed tomography (SPECT) imaging of PSMA. Unfortunately, ProstaScint has fallen short in clinical testing owning issues of to low tissue permeability and slow clearance from the blood pool. To improve upon ProstaScint imaging, a handful of small molecule PET radiotracers have been developed and shown great promise in preclinical and early human testing.[15,16]

In this study, we aim to preliminarily investigate the diagnostic utility of ^{18}F-DCFPyL, a novel low-molecular weight PSMA PET/CT imaging agent[17], in men with an elevated PSA following local treatment with radical prostatectomy. At the time of writing this protocol, ^{18}F-DCFPyL has been studied in 9 men with metastatic prostate cancer and has proven safe without any serious adverse events (Appendix A). Moreover, ^{18}F-DCFPyL has proven to be a highly sensitive imaging agent, detecting >400% more putative sites of disease as compared to conventional imaging techniques (Appendix B). Thus, given the outstanding safety and diagnostic sensitivity of this imaging agent, we hypothesize that ^{18}F-DCFPyL PET/CT will aid in the evaluation of men with otherwise clinically unapparent sites of disease and perhaps one day help direct salvage therapy in the setting of an elevated PSA following failed local therapy.

4. ENDPOINTS

- Description of the number and location of putative sites of metastatic disease as determined by ^{18}F-DCFPyL PET/CT

- Correlation of findings on ^{18}F-DCFPyL PET/CT with those found on conventional imaging (bone scan and cross-sectional imaging)

- Correlation of findings on ^{18}F-DCFPyL PET/CT with tissue histology and PSMA expression of biopsied/resected pathology specimens

- Assessment of treatment response by ^{18}F-DCFPyL PET/CT following 6 months of management per the treating physician

- Correlation of ^{18}F-DCFPyL PET/CT findings with PSA levels and time to disease progression

5. PATIENT SELECTION & ELIGIBILITY

5.1. NUMBER OF PATIENTS

This study aims to enroll 50 participants.

5.2. INCLUSION CRITERIA

1. Age ≥18 years

2. History of adenocarcinoma of the prostate treated with radical prostatectomy

3. Serum PSA level ≥0.2 ng/mL at least 45 days prior to study enrollment

4. Completed staging evaluation with bone scan as well as CT or MRI of the abdomen and pelvis at least 45 days prior to study enrollment

5.3. EXCLUSION CRITERIA

1. History of other malignancy (with the exception of squamous cell or basal cell carcinoma of the skin) diagnosed within the last 3 years

2. Intention to enroll in a blinded therapeutic clinical trial

5.4. INCLUSION OF WOMEN AND MINORITIES

Males of all races and ethnic groups are eligible for this study and encouraged to participate. Women are excluded by virtue of the pathology being studied.

6. SUBJECT RECRUITMENT AND INFORMED CONSENT

Urologists at Johns Hopkins will be educated about the study including patient eligibility criteria. At the treating physician's discretion, patients will in turn be educated about the study and their interest in participation assessed. Any patient who expresses interest in participating in the study will then either be directly introduced to the study team staff, who will be present on select days in the urology clinic, or provided with the contact information of the study coordinator. Alternatively, patients learning about the protocol on ClinicalTrials.gov may contact the study coordinator directly. In all cases, as much time as is needed to consider study participation will be allowed to possible participants; resulting in multiple phone calls, visits, emails, or other communication, as necessary.

The principal investigator or designated individual will discuss the study with interested patients. Patients will be provided with the Institutional Review Board (IRB) approved consent form for review and given sufficient time to consider participation in the study. Once a decision has been made to enter into the study, a signature will be obtained from the patient to confirm consent.

Patients may voluntarily withdraw consent at any point following enrollment in the study. At the time of informed consent patients will be instructed that they may withdraw consent by contacting the principal investigator or study coordinator.

7. RISKS & BENEFITS

7.1. RISKS

^{18}F-DCPyL is a novel imaging agent, which to date, has been studied in only 9 men with advanced prostate cancer under IRB protocol NA_00092956. Despite this small number, the compound appears to be very well tolerated with no reported serious adverse related events.

During the course of this study patients will be exposed to 3.18 rem (1.59 rem per PET/CT) of radiation.

The risks related to both DCFPyL and radiation exposure will be explained to the patient during the informed consent process.

7.2. BENEFITS

By participating in this research study, patients and their physicians will have access to the results of the PET/CT scans which may be used to personalize an individual patient's cancer treatment plan.

8. STUDY PROCEDURES

1. Eligability screening and informed consent

2. ^{18}F-DCFPyL PET/CT scan performed within 45 days of latest PSA, bone scan and cross-sectional imaging

3. Assessment of adverse events via phone call at 1-3 days following PET/CT

4. Management per the treating physician including periodic PSA measurements and re-staging imaging as clinically indicated

5. ^{18}F-DCFPyL PET/CT scan performed 6 months following the first PET/CT (window -1 to +2 months)

6. Assessment of adverse events via phone call at 1-3 days following PET/CT

7. Collection of PSA, imaging and treatment data generated as part of routine clinical care for up to three years following the second ^{18}F-DCFPyL PET/CT

9. PROTOCOL FOR ^{18}F-DCFPYL PET/CT

1. Patient will fast for 4 to 6 hours prior to injection of ^{18}F-DCFPyL

2. An intravenous peripheral intravenous catheter will be placed (or an upper-extremity existing central line accessed) in order to inject the radiotracer

3. Intravenous fluid (5% dextrose + 0.45% normal saline) will be delivered at a low flow rate during the duration of the study (maximum 2 litters)

4. A bolus of less than or equal to 9 mCi (333 MBq) of ^{18}F-DCPyL will be injected into the IV line by slow push

5. At approximately 60 minutes after the administration of ^{18}F-DCFPyL, IV fluids will be discontinued and the patient will be asked to void. A whole-body CT and PET scan will then be acquired from the mid-thigh to the vertex of the skull. The PET/CT will be performed on a Discovery DRX PET/CT scanner (GE Healthcare) operating in 3-dimensional emission acquisition mode. Scans will include approximately 8 to 9 fields-of-view, depending on patient height.

6. Temporary IV access will be removed

10. STUDY STATISTICS

Descriptive statistics (i.e. proportions/percentages for categorical variables and medians with interquartile ranges for continuous variables) will be used to detail the study cohort and findings on^{18}F-DCFPyL PET/CT. More specifically, we plan to report data individually and in aggregate for patient age, race/ethnicity, TNM stage, pathologic Gleason score, surgical margin status, prior cancer treatment and interval treatment following the first PET/CT scan. Additionally we will report the number and location of putative sites of disease detected on PET/CT for both time points. These putative sites will be correlated to findings on available bone scan and cross-sectional imaging obtained during the course of routine clinical care and their rate of concordance reported with 95% confidence intervals. Similarly, we plan to correlate findings on PET/CT scan with the tissue histology and PSMA expression (as determined by immunohistochemistry) of pathology specimens collected in follow-up as part of routine clinical care. Finally, we plan to evaluate change in the number, size and SUV_{max}/SUV_{mean} values of putative sites of disease following 6 months of therapy as prescribed by the treating physician. For this analysis, paired scans will analyzed with the McNemar's test for categorical variables and the Wilcoxon signed-rank test for continuous variables. As an additional secondary endpoint, PET/CT findings will be correlated with serial PSA values as well as time to disease progression.

11. SAFETY MONITORING

Patients will be contacted 1 to 3 days following each ^{18}F-DCFPyL PET/CT via phone call by a designated study team member to assess for study related adverse events. Any patient experiencing an adverse event will be instructed to go to the nearest emergency room for evaluation by a physician. The outcome of this call with appropriate follow-up will be documented in the medical record as a phone note. All adverse events will be recorded using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 and will be submitted to the IRB per policy 103.6b.

12. DATA HANDLING AND RECORD KEEPING

Paper consent forms, enrollment check sheets and W9 forms will be kept in a study binder. This binder will be stored in a locked office available only to the study team.

Electronic data will be housed in a secure password protected REDCap database maintained by the Data Informatics Services Core within the Johns Hopkins Biostatistics Center. Only the study coordinator and investigators will have access to this secure database. Of note, to maintain the protected healthy information of patients enrolled in this study, only the study Principal Investigator and coordinator will have the ability to export data containing identifying information from this master database. For the purposes of analysis, only de-identified data will be exported.

13. DISCLOSURE OF DATA

The results of each ^{18}F-DCFPyL PET/CT will be made available to both patients and treating physicians. Because this is a novel diagnostic test, all will parties requesting scan data will be explicitly reminded as to the experimental nature of the results. Additionally, at the time of informed consent, it will be explained to patients that the results of these scans may prompt additional confirmatory imaging and/or invasive procedures that would not have otherwise been contemplated had the patient not participated in this study.

14. PATIENT REMUNERATION

Following successful completion of each ^{18}F-DCFPyL PET/CT, patients will be compensated with $100 and a voucher for free parking.

15. FUNDING

The study will be supported by private philanthropic funds raised by the Johns Hopkins Department of Urology.

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Appendix A. Safety of ^{18}F-DCFPyL PET/CT in 9 Patients with Metastatic Prostate Cacncer[1]

Type of Event	Number Encountered
All Adverse Events	3 (33.3%)[2]
Life-Threatening Adverse Event or Life-Threatening Suspected Adverse Reaction	0
Serious Adverse Event or Serious Suspected Adverse Reaction	0
Suspected Adverse Reaction	0
Unexpected Adverse Event or Unexpected Suspected Adverse Reaction	0

[1]Data current as of February 29, 2015

[2]Adverse events included headache and epistaxis in the same patient and thrombocytopenia in a separate patient. All adverse events were grade 1 and categorized as unlikely to be related to radiotracer administration.

Appendix B. ^{18}F-DCFPyL PET/CT Imaging Data from 9 Patients with Metastatic Prostate Cancer[1]

Modality	All lesions		Bone lesions		Lymph node lesions		Prostate, Prostate bed, Peri-prostatic tissue, and Other soft tissue lesions	
	Definite	Equivocal	Definite	Equivocal	Definite	Equivocal	Definite	Equivocal
^{18}F-DCFPyL PET/CT	138	1	73	1	56	0	9	0
CECT	20	11	8	9	7	0	5	2
BS	13	5	13	5	N/A	N/A	N/A	N/A
Combined CIM	30	15	18	13	7	0	5	2

CECT = contrast-enhanced CT, BS = bone scan, CIM = conventional imaging modalities (CECT + BS)

[1]Data current as of February 29, 2015