Abbreviated Title: SBRT for Recurrent Prostate Ca
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Title: Phase I Trial of Image Guided Focally Dose Escalated Prostate SBRT for Locally Recurrent Prostate Cancer after Prior Radiotherapy

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Drug Name:	18F-DCFPyL
IND Number:	133631
Sponsor:	NCI CCR
Manufacturer:	NIH PET department
Supplier	NIH PET department

Commercial Agents: Radiation

PRÉCIS

Background:

- Prostate cancer that recurs after prior radiation treatment can be challenging to cure due to the side effects of available treatments such as surgery and cryoablation.
- Re-irradiation with brachytherapy or stereotactic approaches has shown excellent rates of prostate cancer disease control with tolerable side effects.
- Using image guidance to allow highly conformal focal re-irradiation may potentially increase the efficacy of re-irradiation.

Objectives:

- Define the maximum tolerated dose (MTD) of image guided, focally dose escalated prostate radiation with stereotactic body radiation therapy (SBRT) in patients with a local recurrence of prostate cancer after prior radiotherapy.

Eligibility:

- Histological confirmation of recurrent prostate cancer after prior irradiation (external beam or brachytherapy)
- No evidence of distant metastases of prostate cancer
- No prior prostatectomy
- Subject is ≥18 years old
- ECOG performance status ≤2 (Karnofsky ≥60%)

Design:

- This is a Phase I trial of focal dose escalation with SBRT using image and pathologic guidance.
- Areas in the prostate shown to have tumor on biopsy or with advanced imaging studies will be treated with highly conformal SBRT over a period of two to three weeks. Treatment will be guided and gated by fiducials implanted in the prostate.
- Patients will be treated to escalating doses based on tolerability of the treatment.
- Quality of life and functional outcomes such as urine, bowel, and erectile function will be assessed with questionnaires.
- Up to 46 patients will be enrolled.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- Define the MTD of image-guided, focally dose escalated prostate SBRT in patients with a local recurrence of prostate cancer after prior radiotherapy.

1.1.2 Secondary Objectives

- Define the dose-limiting toxicities and toxicity profile of image-guided, focally dose escalated prostate SBRT in patients previously treated with radiotherapy.
- Describe the rate of PSA control (biochemical progression free survival, bPFS) at 1 and 2 years after treatment with focally dose escalated SBRT for locally recurrent prostate cancer after irradiation.
- Describe the effects of focally dose escalated prostate SBRT on patient reported outcomes (SHIM, AUA Symptom Index, EPIC-26) in patients previously treated with radiotherapy
- Evaluate 18F-DCFPyL imaging as a method to detect locally recurrent prostate cancer after radiation

1.1.3 Exploratory Objectives

- Evaluate the feasibility of a patient specific circulating DNA mutation panel for predicting biochemical recurrence
- Evaluate decision regret at the time of enrollment and at the end of follow up relating to the primary treatment for prostate cancer to determine if successful salvage mitigates decision regret.
- Evaluate for the presence of neuroendocrine markers and markers of resistance in recurrent prostate cancer after prior irradiation.
- Describe cellular, molecular, genetic and genomic biology through whole exome or genome sequencing and targeted analysis in blood and tumor tissue.

1.2 BACKGROUND AND RATIONALE

Radiation is an effective therapy for localized prostate cancer. Although most patients are cured of their prostate cancer by external beam radiation therapy (EBRT) and/or brachytherapy, a subset of patients will develop biochemical failure, defined as a rise in the PSA of more than 2 ng/dL above the post radiation nadir. The risk of biochemical recurrence after irradiation using more modern approaches varies greatly depending on pretreatment risk grouping. Biochemical recurrence rates may be as high as 50% for patients categorized as high risk (1). The natural history of local recurrence is largely unknown, as most patients that develop a biochemical recurrence after radiotherapy have been treated with androgen suppression without further investigation of the site of failure. Indeed, although biochemical failure rates are well known after irradiation, patterns of failure are only now being determined with the development of improved staging modalities, such as multiparametric MRI.

Patients with biochemical failure may harbor local recurrence or metastatic disease. Immediate or delayed androgen deprivation therapy, a non-curative therapy, is most often used for treatment of these patients (2). Data from prospective studies including prostate biopsies after EBRT have suggested that local persistence of disease serves as a source of metastases and contributes to a reduction in disease free survival (3).

In the absence of metastatic disease, local salvage therapies offer a potentially curative treatment option for patients with a local recurrence after prostate radiotherapy; however, many of these therapeutic approaches are associated with substantial treatment morbidity and remain underutilized (4). The most commonly used options for salvage after radiation include cryoablation (5-10), prostatectomy (11-13), and re-irradiation (14-22). Developing less toxic local salvage therapies may provide a more acceptable curative treatment option for these patients.

Although salvage prostatectomy can be toxic, it can also be effective as a salvage therapy for recurrent prostate cancer after irradiation. Most published studies have included standard imaging studies (bone scan, CT, and in some cases MRI) for restaging prior to treatment of the recurrent cancer. In addition, patients undergoing salvage prostatectomy are often highly selected based on initial T stage, Gleason score, young age, and lack of comorbidities. Biochemical recurrence free survival after salvage prostatectomy in this carefully selected patient subset is approximately 80-85% (23, 24).

Because many patients who undergo curative radiotherapy for prostate cancer are not surgical candidates due to age, comorbidities, or disease extent, many of these patients do not have salvage prostatectomy as an option if their first course of radiotherapy is not effective. In these patients, salvage reirradiation is a potentially attractive option.

1.2.1 Salvage reirradiation

Most studies of re-irradiation for locally recurrent prostate cancer after prior irradiation have used prostate brachytherapy to deliver a high radiation dose to the prostate gland (14-21). Brachytherapy is highly conformal and allows for lower exposures to normal tissues than conventionally fractionated radiotherapy. In the context of brachytherapy, a sufficient number of catheters must be inserted to obtain an optimal dose distribution, making focal dosing challenging. Some small series have used fusion of MRI to guide focal brachytherapy (25, 26). These methods were feasible, however there was a substantial rate of genitourinary toxicity with this approach, likely due to the use of normal tissue constraints similar to the definitive setting. Of note, with brachytherapy approaches, the dose to structures such as the urethra may be quite large compared to those delivered with EBRT approaches. Several published series of salvage brachytherapy have reported encouraging rates of biochemical control at 5 years of 65-85%, with cause specific survivals of 80-95% (14-21). Thus, these results compare favorably with the salvage prostatectomy approaches in a cohort of patients with a higher incidence of substantial co-morbidities.

Because brachytherapy approaches are technically demanding and can have an increased rate of toxicity after prior irradiation, few practitioners offer them in the setting of recurrence. Brachytherapy also requires some form of anesthesia, and in some cases an overnight hospitalization and temporary indwelling urine catheter until acute urinary symptoms resolve. The development of SBRT approaches that can be provided as an outpatient procedure without anesthesia, would enhance patient and practitioner acceptance.

SBRT has been investigated as a method to salvage patients with biochemical recurrence and documented local recurrence after radiotherapy for prostate cancer, but has only been reported in a single series (22). This approach takes advantage of the capacity for highly conformal therapy to minimize dose to surrounding structures while delivering a relatively homogenous dose compared to brachytherapy. Thus, areas of high dose to urethra and other structures are limited at the cost of increased low to moderate dose to surrounding rectum and bladder. In this series of 29 patients, SBRT was delivered to the prostate gland to a dose of 34 Gy in 5 fractions. In this series, dose was escalated to the peripheral zone, presumably to cover areas at "high risk" of recurrence, although the actual area of recurrence was not evaluated or escalated. The goal of this escalation as a prescribed dose of 42 Gy. Fourteen of these patients had residual toxicity from prior radiation treatments prior to receiving SBRT, and received a prior median radiation dose of 73.8Gy (range 68.4 Gy-81 Gy). Following SBRT treatment, these patients had a 2-year biochemical progression free survival (bPFS) of 82% using the Phoenix criteria. In regard to toxicity, 3 of the 29 patients developed late grade 2 genitourinary (GU) toxicity and one patient developed acute and late grade 3 GU toxicity (urethral obstruction with a suprapubic catheter and hemorrhagic cystitis). In addition, one patient required cystoprostatectomy for grade 4 hemorrhagic cystitis. Thus, the rates of GU toxicity for the 29 patients were 18% ≥Grade 2 GU toxicity and 7%≥ Grade 3 toxicity.

1.2.2 Molecular imaging of prostate cancer

The ability to detect prostate cancer with imaging is a critical component of successful focal therapy. There are few FDA approved molecular imaging radiotracers to detect soft tissue prostate cancer metastases. ^{111}In Prostascint, based on a prostate specific membrane antigen (PSMA) antibody, has proven to be suboptimal because of its low uptake in target tissues, high non-specific background and it use of single photon emission. As a result, it is not used in most clinical settings. ^{11}C Choline, was recently approved by the FDA, but because of the short half-life of the agent, its use is limited to facilities with on-site cyclotrons.

There is tremendous interest in prostate-specific membrane antigen (PSMA) as a target for molecular imaging (27). PSMA is a type II cell surface membrane glycoprotein receptor found in almost all prostate cancers, especially in advanced, hormone-independent and metastatic disease. It can also be found in endothelial cells of the neovasculature of nearly all solid tumors (28, 29). It is also seen in normal prostate, small bowel, proximal renal tubules, salivary glands and brain but at 100 to 1000 fold lower expression (30). Monoclonal antibodies have been developed against PSMA, but the first agent, ^{111}In Prostascint, targeted an intracellular epitope that is inaccessible in viable tumor cells which is one factor contributing to its lack of clinical utility (31). ^{111}In is a single photon emitter and as such results in a less sensitive and lower resolution image than PET emitters.

Mease and Pomper et al developed fluorine-18, N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-[^{18}F]fluorobenzyl-L-cysteine (^{18}F-DCFBC) at Johns Hopkins University as the first ^{18}F agent designed specifically for clinical PET imaging of prostate cancer.(32) ^{18}F DCFBC is a small molecule targeting an external binding domain of PSMA. Cho et al reported initial clinical experience with ^{18}F DCFBC in five metastatic prostate cancer patients.(33) Focal abnormal PET uptake was seen in 32 metastatic lymph nodes and bone lesions with median SUV_{max} of 5.6 for lymph nodes, and 3.6 for bone. Conventional imaging was concordant with PET findings in 21 sites, 5 of them bone. Discordant positive PET findings were attributed to possible early bone metastases or subcentimeter lymph nodes. All 10 positive sites on conventional imaging that

were negative on PET, were in bone and considered indeterminate for malignancy or due to trauma. One true metastatic bone lesion that was PET negative may have been suppressed by antiandrogen therapy. Surprisingly, blood pool activity remained moderately persistent throughout the imaging. Possible explanations include binding to a free form of PSMA circulating in the blood or non-specific protein binding.

The relationship between androgen receptor (AR) and PSMA expression is complex. Evans et al demonstrated that a functional androgen receptor (AR) is required for PSMA expression and AR suppression results in lower expression which can be quantitatively imaged with PET. (34) However, Androgen deprivation therapies, such as MDV3100 can increase ^{64}Cu –antiPSMA J591 uptake. The NIH Molecular Imaging Clinic's (MIC) experience with ^{18}F-DCFBC in metastatic prostate cancer suggests that patients fully suppressed on androgen deprivation therapy (ADT) have low PSMA expression and patients who are manifestly castrate resistant have high PSMA expression. Interestingly, ^{18}F DCFBC scans show a mix of lesions, some suppressed and others expressing PSMA among the various metastases. The NCI Molecular Imaging Clinic/Molecular Imaging Branch (MIB) has imaged 45 patients with localized, recurrent or metastatic disease with ^{18}F-DCFBC. Encouraging observations of localized disease show focal uptake in tumor and not in benign hyperplasia (**Figure 1**).

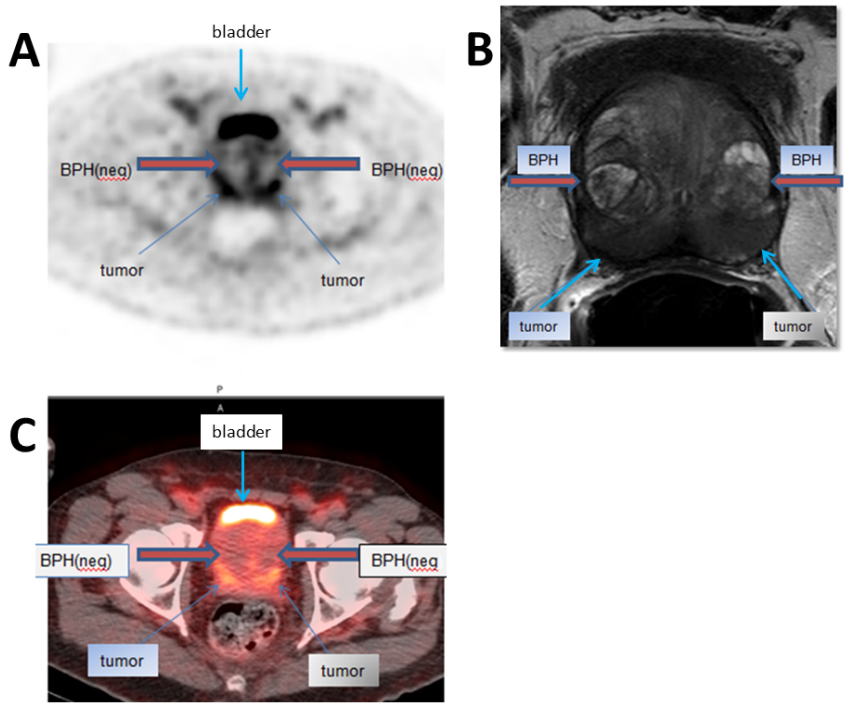

Figure 1**.** Localized prostate cancer images in patient with high risk cancer (A) Axial ^{18}F-DCFBC PET demonstrating focal uptake in tumor but not in benign prostatic hyperplasia. (B) Corresponding MR image showing malignant and benign lesions. (C) Axial ^{18}F-DCFBC PET and CT fusion image.

Dr. Pomper's group at Johns Hopkins University developed a second-generation low molecular weight, PSMA targeted radiotracer, 2-(3-(1-carboxy-5-[(6-[^{18}F] fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid (18F-DCFPyL). This compound is similar to the first-

generation molecule but with enhanced features. They found tissue binding affinity to be more than 5 times greater than ^{18}F DCFBC and with significantly less blood pool activity. Their preclinical studies in prostate cancer mice models revealed a maximum target to muscle background ratio of 400:1 at 120 minutes compared to ^{18}F DCFBC's ratio of 20:1. (35) They noted comparably favorable pharmacokinetics and dosimetry profile.

In their recent publication(36), nine prostate cancer patients were studied with this tracer to evaluate, safety, biodistribution and radiation dosimetry with favorable results. Physiologic radiotracer activity is seen in the salivary glands, lacrimal glands, liver, spleen and intestines with excretion through the kidneys and bladder. Blood pool activity rapidly cleared. The effective dose for a 370 MBq (10 mCi) dose of 18F-DCFPyL was 6.1 mGy (0.61 rem) or 0.0165 mSv/MBq. The highest radiation dose is the kidneys (0.0945 mGy/MBq) then the bladder wall (0.0864 mGy/MBq) which can be ameliorated by continuous bladder irrigation, submandibular glands (0.0387 mGy/MBq) and liver (0.0380 mGy/MBq). Radiation dose estimates for the other organs are in **Table 1**.

Table 1. Radiation dose estimates for 18F-DCFPyL

Organ	Absorbed dose (mGy/MBq)
Adrenals	3.11E-02
Brain	2.19E-03
Breasts	4.57E-03
Gallbladder wall	1.44E-02
Heart wall	1.29E-02
Kidneys	9.45E-02
Lacrimal glands	3.50E-02
Lens	1.25E-03
Liver	3.80E-02
LLI wall	1.05E-02
Lungs	1.08E-02
Muscle	6.32E-03
Osteogenic cells	9.58E-03
Ovaries	8.89E-03
Pancreas	2.44E-02
Parotid glands	2.68E-02
Red marrow	1.04E-02
Skin	4.05E-03
Small intestine	9.13E-03
Spleen	1.85E-02
Stomach wall	1.16E-02
Submandibular glands	3.87E-02
Testes	1.01E-02
Thymus	5.56E-03
Thyroid	8.56E-03
ULI wall	1.67E-02
Urinary bladder wall	8.64E-02
Uterus	1.15E-02

Tumor uptake was much higher with 18F-DCFPyL than ^{18}F-DCFBC and increased with time. Focal radiotracer activity could be seen in some lesions at the earliest imaging point at 5 minutes and all known lesions were visualized with highest uptake after 2-hours post-injection. 18F-DCFPyL uptake identified cancer lesions in the bone, prostate, lymph nodes and soft tissue. They did note that most lesions were visualized by 1h post-injection; however, there were a few

small lesions only visible at 2 hours. They suggested that patients with biochemical recurrence might be best imaged at the 2nd hour point.

Szabo et al (36) studied five patients with metastatic prostate cancer and none experienced any severe adverse events. Three grade I NCI CTCAE adverse events were reported. One patient reported a mild headache and nosebleed (two adverse events) that resolved without treatment and were deemed unlikely to be attributed to the radiotracer. The third event was a decreased platelet count found on routine post-imaging follow-up labs that was attributed to the patient starting treatment for prostate cancer. No heart rate or blood pressure events occurred that were related to the radiotracer. The effective radiation dose to patients with 18F-DCFPyL was reported as 0.0165 mSv/MBq by Szabo et al (36). Doses to most radiosensitive organs were much lower than with the first-generation, ^{18}F-DCFBC.

In summary, 18F-DCFPyL is a low molecular weight, second generation radiofluorinated PSMA targeted PET radiotracer that has been demonstrated to have efficacy in detecting local and metastatic prostate cancer in patients (37). In a study conducted in the Molecular Imaging Branch, NCI, a related PSMA PET radiotracer detected all clinically significant prostate cancers. PSMA expression is correlated with tumor aggressiveness, and similar PSMA targeted radionuclides have been shown to accurately detect the location of biochemical failure after radiotherapy, including local failures (38, 39).

The natural history disease in patients with 18F-DCFPyL detected local recurrence is not known, however given that patients will also undergo the current best staging (NaF PET/CT and multiparametric MRI), it is anticipated that patients with local only disease detected with this imaging will have improved outcomes as they may be less likely to harbor occult metastatic disease after an additional imaging modality. The use of an additional imaging modality may improve oncologic outcomes by avoiding ineffective local treatment of patients with occult metastatic disease and by enhancing certainty of sites requiring treatment, thus allowing escalation of portions of the prostate to doses that may not be possible if the entire gland required treatment.

1.2.3 Neuroendocrine Differentiation and Radiation Outcomes

Neuroendocrine cells can be found in healthy prostate tissue typically situated in the basal cell layer and urothelium and typically account for less than 1% of cells (40) and generally stain positive for Chromogranin A. In contrast, neuroendocrine differentiation of prostate cancer has been suggested to portend poor prognosis. Neuroendocrine cells in prostate cancer often do not express androgen receptor (AR) or PSA (41). Neuroendocrine differentiation can occur in different patterns in prostate cancer: focal neuroendocrine differentiation, carcinoid tumor, or small cell of the prostate (42). Several markers can be used to define neuroendocrine differentiation of prostate cancer, including Chromogranin A, Neuron specific enolase, somatostatin, and 5-HT.

Several studies have suggested that patients with prostate cancer with neuroendocrine features or a certain percentage of cells staining positive for neuroendocrine markers correlates with worse outcome following treatment, including definitive radiation treatment. Krauss et al. performed Chromogranin A staining on prostate biopsy tissue in 289 patients with a Gleason's core of 7-10 who received definitive radiation treatment (43). In this subset, 30% of patients had positive staining of their biopsy tissue for Chromogranin A. Patients in this study with

more than 1% of cells staining positive for Chromogranin A had inferior biochemical control and cause specific survival and a higher rate of clinical failure and distant metastases.

Interestingly, some preclinical work has suggested that radiation can induce neuroendocrine differentiation in surviving clones via enhanced nuclear phosphoCREB (44, 45). These clones demonstrate enhanced expression of Chromogranin A and neuron specific enolase. Indeed, serum Chromogranin A has been demonstrated to increase in patients receiving radiotherapy for prostate cancer (45, 46). It is not known if neuroendocrine differentiation or neuroendocrine features are common in patients with recurrent prostate cancer after irradiation as this has not been studied previously.

1.2.4 Purpose of this study

The goal of this study is to develop an effective and tolerable strategy for salvage of locally recurrent prostate cancer following radiation. This study is distinct from prior efforts as it seeks to de-escalate therapy to uninvolved areas of the prostate gland and to limit escalation to imaging defined tumor. This study will evaluate focal re-irradiation with SBRT for locally recurrent prostate cancer. The highest dose of escalation, 45 Gy, is moderately higher than was previously tested. The dose to the remainder of the gland is reduced and will only be delivered in patients suspected of having disease in other locations in the prostate gland, namely those who have biopsy findings consistent with disease outside of the imaging identified lesion and patients who have undergone prior brachytherapy for whom MR imaging may be suboptimal. The area of focal escalation in this study will be guided by MRI findings in addition to findings from 18F-DCFPyL/CT and biopsy confirmation. We will include tissue staining for neuroendocrine markers in biopsy specimens harboring recurrent prostate cancer.

1.2.5 Study MTD Determination/Dose Expansion

Arm 1 (Amendment Version Date 4/13/2021)

At dose level 1, only mild radiation related AEs have occurred with no PSA recurrence of the as of yet. At dose level 2, 2 participants in arm 1 have had some significant urine toxicity (Grade 3 hematuria, transient and Grade 3 urinary incontinence) that do not meet the protocol endpoint for maximum tolerated dose (MTD).

Since no one has failed at dose level 1 and the toxicity was less significant, the protocol has been amended to change the criteria for late DLT to Grade 3 urinary toxicity (instead of Grade 4), which would allow us to consider dose level 1 as MTD in Arm 1, trigger expansion at that cohort, and halt dose escalation. These changes would reduce the risk to participants.

Arm 2 (Amendment Version Date 10/12/2021)

Determination has been made to expand dose level 2 for arm 2. Three patients have been treated at dose level 1 and three patients have been treated at dose level 2 (one is currently undergoing treatment). Toxicity has not exceeded grade 2 urinary or grade 3 bowel. Of all 5 patients in this arm who have completed treatment, there is no evidence of recurrence.

Based on recent accumulating literature from the definitive treatment setting (no prior radiation), it is clear that further escalation of dose may have long term toxicity. Thus, in the face of excellent disease control, we feel it would be inappropriate to increase dose further as it will expose patients to risk without additional benefit.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histologically confirmed locally recurrent adenocarcinoma of the prostate after prior radiation (EBRT or brachytherapy)

2.1.1.2 PSA failure after definitive radiation as defined by the Phoenix criteria (PSA elevation at least 2 ng/dL above post-radiotherapy nadir)

2.1.1.3 Age ≥18 years

2.1.1.4 ECOG performance status ≤ 2 (Karnofsky ≥60%, see **Appendix A**)

2.1.1.5 Ability of subject to understand and the willingness to sign a written informed consent document

2.1.2 Exclusion Criteria

2.1.2.1 Patients who are receiving any other investigational agents

2.1.2.2 PSA ≥ 20 ng/dL if no prior DCFPyL scan obtained (If PSA ≥ 20 and DCFPyL obtained within 3 months prior to enrollment shows no evidence of metastatic disease, subjects may be included in the study)

2.1.2.3 Biochemical recurrence within one year of completion of radiotherapy

2.1.2.4 Need for chronic anticoagulation therapy (chronic low dose aspirin is not an exclusion)

2.1.2.5 Pre-existing and ongoing radiation-related grade 3 bowel or bladder toxicity

2.1.2.6 Inflammatory bowel disease

2.1.2.7 Active Lupus or Active scleroderma

2.1.2.8 Patients with distant metastatic disease (prostate adjacent adenopathy is not an exclusion)

2.1.2.9 Prior prostatectomy

2.1.2.10 Subjects with any coexisting medical or psychiatric condition that is likely to interfere with study procedures and/or results

2.1.2.11 Subjects with severe claustrophobia that is unresponsive to oral anxiolytics

2.1.2.12 Other medical conditions deemed by the Principal Investigator (or associates) to make the subject unsafe or ineligible for protocol procedures

2.1.2.13 Subjects weighing > 350 lbs. (weight limit for scanner table), or unable to fit within the imaging gantry

2.1.2.14 Serum creatinine > 2 times the upper limit of normal

2.1.2.15 Total bilirubin > 2 times the upper limit of normal OR in patients with Gilbert's syndrome, a total bilirubin > 3.0

2.1.2.16 Liver transaminases (ALT, AST) greater than 3 times the upper limit of normal

2.1.2.17 Patients with positive Human Immunodeficiency Virus (HIV) status and currently

requiring treatment with agents known to sensitize to irradiation, such as protease inhibitors

2.1.3 Recruitment Strategies

Participants will be identified from Dr. Citrin's referral base, largely via screening for 13-C-0119, which includes an arm for locally recurrent prostate cancer after radiotherapy. Dr. Citrin has developed an excellent professional relationship with numerous referring physicians in the surrounding area who send patients with PSA recurrence after radiotherapy. Dr. Citrin will expand these efforts. Dr. Citrin also participates in the RecurRx network, a multi-institutional group evaluation recurrence after radiotherapy. She expects referrals from this source given that she has a therapeutic intervention or these patients. In addition, patients will be recruited from the prostate multidisciplinary clinic.

This protocol may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms.

2.2 SCREENING EVALUATION

Note: Screening evaluation testing/procedures are conducted under the separate screening protocol, 01-C-0129 (Eligibility Screening and Tissue Procurement for the NIH Intramural Research Program Clinical Protocols). Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

- Clinical Evaluation: Complete history and physical examination, including weight and performance status within 4 weeks of study entry.
- Laboratory Evaluation: CBC with differential, chemistries (to include creatinine BUN, PSA, testosterone, Alk Phos, ALT, AST, Bilirubin), PT, PTT within 4 weeks of study entry.
- Viral serologies: HIV screening within 4 weeks of study entry
- Radiographic Evaluation: Whole body bone scan, F18 NaF PET, and multiparametric MRI of the prostate. In selected patients, a CT of the abdomen and pelvis (with oral and IV contrast) may also be obtained for staging, particularly if MRI is not felt to adequately have staged the pelvic and abdominal lymph nodes. All imaging studies should be completed within 3 months of study entry. MRI of the prostate obtained more than 3 months (no greater than 5 months prior to entry) may be used if a biopsy has recently been performed, as post-biopsy MRI may not be easily interpretable due to hemorrhage.

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g. when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at:
https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.3.1 Treatment Assignment Procedures

Cohorts

Number	Name	Description
Cohort 1	EBRT	Patients with locally recurrent prostate cancer after treatment with EBRT. These patients cannot have had permanent brachytherapy as part of their treatment.
Cohort 2	Brachytherapy	Patients with locally recurrent prostate cancer after treatment with brachytherapy +/- EBRT. These patients must have had brachytherapy as part of their treatment.

Arms

Number	Name	Description
1	Tumor Irradiation	SBRT will be delivered to areas of recurrent prostate cancer identified on imaging and biopsy
2	Prostate and Tumor Irradiation	SBRT will be delivered to areas of recurrent prostate cancer identified on imaging and biopsy; and a reduced dose will be delivered to the entire prostate

Treatment Assignment

There is no randomization or stratification on this study.

Subjects in Cohort 1 will be directly assigned to Arm 1.

Subjects in Cohort 2 will be directly assigned to Arm 2.

2.4 BASELINE EVALUATION

- Clinical evaluation: clinical assessment with attention to any new medications or interventions since screening history and physical examination (to be completed within 2 weeks of study entry, screening history and physical examination is acceptable if obtained within the 2-week interval)
- Laboratory evaluation: CBC with differential, BUN, Creatinine, Alk Phos, ALT, AST, Total Bilirubin, PSA, Testosterone, PT, PTT, Hepatitis B, and Hepatitis C (within 4 weeks of study entry)
- 18F-DCFPyL imaging (will not be repeated if performed on a different protocol within 4 months prior to study enrollment).
- Post-Imaging research and diagnostic biopsies of areas in the prostate identified as suspicious and systematic biopsy. If recent systematic biopsies were obtained (within 5 months) systematic biopsies will not be repeated. Fiducial markers to guide radiation

treatment will be implanted simultaneously if not previously placed or visible

- Questionnaires (to be completed prior to treatment and within 2 weeks prior to SBRT). See Section **3.4** for further details. Expanded Prostate Cancer Index Composite (EPIC-26), SHIM, AUA-SI, PROMIS Depression SF4a, PROMIS Anxiety SF4a, PROMIS Psychological Impact Positive SF 4a, Decision Regret Scale
- Correlative assays (to be completed prior to treatment and within 2 weeks prior to SBRT). See Section **5.1** for further details. Collection of Plasma – three 8 cc EDTA), urine (15cc in a sterile cup), and research biopsies. In patients with active Hepatitis B or C, some research blood work may not be drawn.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

Patients with locally recurrent prostate cancer following radiotherapy will be enrolled in this study if they have no evidence of distant metastatic disease on staging studies. If abnormalities are noted on bone scan and/or NaF PET/CT, the results of these studies will be reviewed by the PI and radiology/nuclear medicine colleagues. On a case by case basis, the likelihood of metastasis will be determined if evidence of abnormalities is visible. In general, NaF PET will be considered more sensitive. Multiparametric MRI of the prostate and 18F-DCFPyL imaging will be obtained to assess for areas of local recurrence. Patients found to have regional adenopathy that is distant to the prostate or metastatic disease at other sites on staging studies such as 18F-DCFPyL will undergo biopsy confirmation if clinically appropriate to confirm metastatic disease and will be removed from the study and replaced if metastases are confirmed. Patients deemed to have a non-metastatic local recurrence will undergo targeted (research and diagnostic) and systematic biopsies of the prostate (diagnostic) to confirm areas of recurrence and correlate imaging with pathology. Areas noted to have uptake on 18F-DCFPyL imaging will also be biopsied if they represent areas not seen on MRI. During the same procedure, fiducials to guide radiotherapy will be placed if not previously placed or visible. Approximately one week after fiducial placement or biopsy (if fiducial placement not required), patients will undergo treatment planning for SBRT.

There will be two Cohorts in this trial. Cohort 1 includes patients with prior EBRT for the treatment of prostate cancer. These patients may have received ADT with EBRT but have not received brachytherapy. Patients enrolled in Cohort 2 will have received brachytherapy of the prostate as a component of the initial radiation treatment (either alone or in combination with EBRT and/or ADT). See section **2.3.1**.

SBRT will be delivered to areas of recurrent prostate cancer identified on imaging and biopsy (all patients, Arms 1 and 2) and a reduced dose will be delivered to the entire prostate (Arm 2). The low dose total prostate exposure is used in Arm 2 as MR imaging may be moderately compromised in after prior brachytherapy.

Table 2: Dose Levels

	Arm 1: Tumor Irradiation		Arm 2: Prostate and Tumor Irradiation	
Dose level	**Dose to prostate**	**Dose to tumor**	**Dose to prostate**	**Dose to tumor**
Level 1	-	**40 Gy**	**30 Gy**	**40 Gy**
Level 2	-	**42.5 Gy**	**30 Gy**	**42.5 Gy**
Level 3*		**45 Gy**	**30 Gy**	**45 Gy**

* As of amendment version dates 4/13/2021 and 10/12/2021, determination has been made not to escalate to dose level 3 for both arms. Refer to section **1.2.5**.

3.1.1 Dose Limiting Toxicity

Dose-limiting toxicities will be defined as follows (during treatment and within the first three weeks after treatment):

- Grade 3 rectal, small bowel, or urinary toxicity that does not resolve to Grade 2 or less within 4 days with appropriate medical management
- Other grade 3 in-field toxicities attributable to SBRT that do not resolve to Grade 2 or less within 4 days with appropriate medical management
- Delays of more than one week in completing radiation treatment due to toxicity (cumulative duration of delay over the course of the entire treatment).

Additionally, late toxicities (those that occur after 90 days following completion of treatment) will be followed and scored but will not be used for escalation with the following exception.

If Grade ≥4 late bowel or Grade ≥3 bladder injury is observed in 2 patients in any cohort, dose escalation will be terminated in that arm and the dose below that dose level in which the toxicity was observed will be considered the MTD. The criteria for late DLT for bladder were changed to Grade 3 to Grade 4 via amendment version date 04/13/2021, and should apply retroactively to all prior participants. MTD will be determined for each arm separately. Early and late toxicities used for assessment of DLTs should be attributable (possible, probable or definite) to SBRT. Changes in sexual and erectile function will not be considered a DLT.

3.1.2 Dose Escalation

Dose escalation will proceed in parallel in Arm 1 (Tumor Irradiation) and Arm 2 (Prostate and Tumor Irradiation) in groups of 3–6 patients. The MTD is the dose level at which no more than 1 of up to 6 patients experience DLT during treatment and up to 3 weeks following completion of treatment, and the dose below that at which at least 2 (of ≤6) patients have DLT as a result of treatment. If a patient did not experience DLT and did not finish treatment, he will not be evaluable for toxicity and will be replaced in the dose level (See **Table 2**).

Dose escalation will follow the rules outlined in **Table 3** below for each Arm (1 or 2) independently as MTD and toxicities are expected to be different as a result of prior treatment.

Table 3: Escalation Decision Rule

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter up to 3 patients at the next dose level
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter up to 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. UP to three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is the MTD and is generally the recommended phase 2 dose. 6 additional patients may be entered at the recommended phase 2 dose.

3.2 DRUG ADMINISTRATION

Radiation delivery is described in Section **3.8**.

Patients will be instructed to maintain good hydration for the 24 hours prior to the 18F-DCFPyL PET/CT (recommended 1-2 liters of fluid, unless medically contraindicated). Patients will report to the NCI Molecular Imaging Clinic on the day of their 18F-DCFPyL PET/CT imaging sessions and peripheral venous access will be obtained. Patency of the venous access will be demonstrated with a saline flush and the patient will then receive 6-6.5 mCi of 18F-DCFPyL as an IV bolus (dosing may be modified per Molecular Imaging Branch procedures). A static whole body PET/CT will be performed as part of the 18F-DCFPyL study approximately 2-hours post - injection. In the event that the MIC is unable to accommodate the scan due to machine down time or other unexpected emergency, the scan may be performed in the PET department if the available MIC AI is in agreement. Every attempt will be made to have all scans completed in the same facility for each patient.

3.3 DOSE MODIFICATIONS

There will be no radiation dose modifications.

Due to potential unpredictable delays and the short half-life of 18F, the total dose of 18F-DCFPyL administered may be reasonably reduced at the discretion of the principal investigator or her designee. The lowest acceptable limit for dosing will be 5mCi with increased scan time of 4 minutes per bed, anything lower than this activity will not be injected.

3.4 QUESTIONNAIRES

The following measures/questionnaires will be collected on this trial via paper or electronically. The timing of collection is noted on the study calendar in Section **3.6.** The total time anticipated to complete all questionnaires below is 20 minutes.

- The Expanded Prostate Cancer Index Composite (EPIC-26) is a prostate cancer health-related quality of life (HRQOL) patient self-administered instrument that measures urinary, bowel, sexual, and hormonal symptoms related to radiotherapy and hormonal therapy. The EPIC-26 was developed from the 50-item EPIC questionnaire and was validated using question responses from 252 subjects who had undergone brachytherapy, external beam radiotherapy, or prostatectomy for prostate cancer. A high correlation was observed between the EPIC-50 and EPIC-26 versions for the urinary incontinence, urinary irritation/obstruction, bowel, sexual, and vitality/hormonal domain scores (all r >/=0.96). The correlations between the different domains were low, confirming that EPIC-26 retained the ability to discern the distinct HRQOL domains. The internal consistency and test-retest reliability for EPIC-26 (Cronbach's alpha >/=0.70 and r >/=0.69, respectively for all HRQOL domains) supported its validity. EPIC-26 has been used in multiple RTOG protocols and phase II publications for hypofractionated radiotherapy to the prostate.
- Sexual Health Inventory for Men (SHIM) is a prostate specific questionnaire for assessment of erectile dysfunction. Initially derived from the IIEF, a shortened version to six questions the IIEF-6 or SHIM was created for increased usability in the clinic.
- American Urologic Association Symptom Index Score (AUA-SI) has been established as a measure of radiation morbidity in patients treated for prostate cancer with respect to urinary function and is used routinely as the basis for treatment decisions. Moderate agreement was observed between EPIC domains and the American Urological Association Symptom Index (AUA-SI), providing criterion validity without excessive overlap.
- PROMIS – Depression SF4a: The PROMIS Depression item bank assesses self-reported negative mood (sadness, guilt), views of self (self-criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose). The depression short forms are universal rather than disease-specific. All assess depression over the past seven days. PROMIS instruments are scored using item-level calibrations.
- PROMIS – Anxiety SF4a: The PROMIS Anxiety item banks assess self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness). Anxiety is best differentiated by symptoms that reflect autonomic arousal and experience of threat. Only one behavioral avoidance item is included in the adult item bank; therefore, behavioral fear avoidance is not fully evaluated. The anxiety measures are universal rather than disease-specific. All assess anxiety over the past seven days.

- PROMIS – Psychosocial Impact Positive SF 4a assess positive psychosocial (emotional and social) outcomes of illness, previously conceptualized in various ways including post-traumatic growth, benefit-finding, and meaning making. Positive Illness Impact refers to positive psychosocial outcomes of illness that can occur as a result of confrontation with one's mortality, such as greater life appreciation, interpersonal relationships and personal resources.
- Decision Regret Scale (DRS) is a 5-item scale measuring distress or remorse after a health case decision. It has been psychometrically validated in the prostate cancer population. The score correlated with satisfaction with the decision (r=-0.40 to -0.60), decisional conflict (r=0.31 to 0.52), and overall rated quality of life (r=-0.25 to -0.27).

Once data is abstracted, questionnaires will be maintained in the research chart (print or electronic). If stored, electronically, these files will have restricted access and be accessible only to members of the study team. In the event that questionnaires are stored electronically, paper copies will be shredded.

3.5 MONITORING DURING STUDY

Six months following treatment, patients in both arms will undergo repeat 18F-DCFPyL imaging only if pretreatment imaging was informative. Serial PSA and serial correlative studies will be collected for two years post-treatment.

3.6 STUDY CALENDAR

Procedure	Screening/ Baseline	Active SBRT treatment	Post Therapy Follow-up (1, 3 mos) 15	Post Therapy Follow-up 6 months post-SBRT	Post Therapy Follow-up (9 mos and q 3 mos until 24 mos) 8
History and PE	X				
Vital signs 10	X		X	X	X
Performance Score	X				
Weight	X				
Labs CBC, Acute care panel, LFTs, Testosterone, PT/PTT, Viral serologies 2	X				
PSA 4	X		X11	X11	X11
Biopsies (ultrasound guided)/fiducials 5	X				
mpMRI 3	X3			X12	
18F-DCFPyL PET/CT imaging	X7			X6, 12	
18F-NaF PET/CT imaging 3	X				
Whole body bone scan 3	X				
Clinical evaluation		X	X9	X9	X9
Adverse Events	X	Monitored continuously			
Concomitant Medications	X	Monitored continuously			
Correlatives					
Research Biopsy 5	X				
Blood 12	X	X1	X	X	X
Urine 12	X		X	X	X
Questionnaires EPIC-26, SHIM, AUA-SI, DRS, PROMIS 13, 14	X		X	X	X

1. Correlative blood sampling should be performed within 24 hours after the last dose of irradiation.
2. CBC with differential, chemistries (to include creatinine BUN, PSA, testosterone, Alk Phos, ALT, AST, Bilirubin), PT, PTT within 4 weeks of study entry. Viral serologies: HIV, Hepatitis B, and Hepatitis C screening within 4 weeks of study entry. Acute Care Panel: (Sodium (NA), Potassium (K), Chloride (CL) Total CO2 (Bicarbonate), Creatinine, Glucose, Urea nitrogen, eGFR).
3. Whole body bone scan, F18 NaF PET, and multiparametric MRI of the prostate. In selected patients, a CT of the abdomen and pelvis (with oral and IV contrast) may also be obtained for staging, particularly if MRI is not felt to adequately have staged the pelvic and abdominal lymph nodes. All imaging studies should be completed within 3 months prior to study entry. MRI of the prostate obtained more than 3 months (no greater than 5 months prior to entry) may be used if a biopsy has recently been performed, as post-biopsy MRI may not be easily interpretable due to hemorrhage.
4. PSA failure after definitive radiation as defined by the Phoenix criteria (PSA elevation at least 2 ng/dL above post-radiotherapy nadir). Serial PSA and serial correlative studies will be collected for two years post-treatment.
5. Post-Imaging research and diagnostic biopsies of areas in the prostate identified as suspicious and systematic biopsy. If recent systematic biopsies were obtained (within 5 months) systematic biopsies may not be repeated. Fiducial markers to guide radiation treatment will be implanted simultaneously. If biopsy tissue was obtained within 5 months on another protocol and is available for transfer, biopsy will not be repeated unless clinically indicated. Fiducials will not be implanted again if previously placed and visible.
6. Six months following treatment, patients in both arms will undergo repeat 18F-DCFPyL imaging only if pretreatment imaging was informative.
7. If an 18F-DCFPyL study was performed within 4 months prior to enrollment on a different protocol, it will not be repeated at baseline. In patients treated with androgen deprivation therapy that was initiated within 4 months of a DCFPyL obtained on another protocol, this DCFPyL scan may be used as the baseline scan if the patient remains on ADT and the scan was obtained within 12 months of enrollment.
8. +/- 2 weeks at and after 6 month time point.
9. May be completed by remote visit with a member of the study team (e.g., if the patient is not able to return to the NIH CC). Remote visits will be conducted in compliance with NIH, FDA regulations and local policy A patient may be referred to their local provider or asked to come to the NIH CC for an in-person assessment, if clinically indicated, and at the discretion of the PI. In the case of any visits with participants' local providers, records will be obtained.
10. Vital signs may be omitted during follow up visits if a patient is unable to return at the NIH clinical center and if the clinical evaluation does not indicate a need for collection.
11. As PSA is a standardized test and the results are comparable across laboratories, if the patient is not able to return to the NIH Clinical center, PSA may be obtained locally. If biochemical failure (PSA elevation at least 2 ng/dL above post-radiotherapy nadir) is identified, the second measurement will be obtained for confirmation per **6.3.2**, ideally at the NIH Clinical Center.
12. In the event that the patient is unable to return to the NIH Clinical Center during a follow up visit, imaging may be delayed, but will be completed as soon as feasible. Collection of research blood or urine will be omitted or collected in a delayed fashion.
13. Questionnaires may be collected electronically or by paper.
14. Questionnaires will be available one week prior to each clinical visit.

15. +/- 1 week 1 and 3 month follow up visits.

3.7 SURGICAL GUIDELINES

Patients will undergo targeted biopsies of the prostate prior to treatment and after MRI and 18F-DCFPyL imaging. Biopsies and fiducial placement will be performed at the Clinical Center by an interventional radiologist or member of the urology service. Prior to undergoing the procedure, patients will be screened for any contraindications such as significant thrombocytopenia or elevated PT/PTT.

Patients undergo preparation identical to that of standard prostate biopsy in that antibiotics consistent with the current standard of care is taken prior to the procedure. On the morning of the procedure, patients self-administer an over-the-counter saline enema. Patients may have a light meal for breakfast on the day of the procedure. Patients undergo pre-procedural assessment including verification of prophylactic regimen described above and normal temperature and vitals. The patient is positioned on a routine hospital gurney in the right or left decubitus position with the legs flexed. A transrectal ultrasound probe is advanced into the rectal vault, a 3D prostate volume is obtained and 10 mL of 1% lidocaine is administered transcutaneously under ultrasound guidance along the posterolateral margins of the prostate to achieve local anesthesia.

Standard comprehensive prostate biopsies will be performed if not performed within the past 4 months and additional biopsies will be targeted to the region of the prostate corresponding to the area of greatest likely tumor involvement as determined by imaging (MRI). Research biopsy samples will only be obtained from areas of the prostate with greatest likelihood of tumor involvement as determined by imaging (MRI and 18F-DCFPyL) or from an area that was dominant on pre-treatment imaging and biopsy confirmed to be malignant. A maximum of 4 regions of abnormality on MRI and 18F-DCFPyL will be targeted for research biopsies. Diagnostic biopsies will be analysed by the Laboratory of Pathology as per standard clinical care.

If possible, radiotherapy fiducial markers (Calypso markers preferred) will be placed as per the current standard of care during the same procedure. In general, 3-5 fiducial markers are placed in the prostate at the same time as a biopsy procedure to assist with treatment alignment. If a patient has indwelling fiducials from a prior radiotherapy treatment, additional fiducials do not need to be placed unless required for proper positioning.

3.8 RADIATION THERAPY GUIDELINES

3.8.1 Treatment Planning

Target definition: tumor will be defined by MRI, and 18F-DCFPyL, which will be fused to the treatment planning CT. For 18F-DCFPyL, regions of tumor recurrence will be defined based on a standardized uptake value (SUV) above the SUV mean of the blood pool, with exceptions made for physiologic uptake.

3.8.2 Target volume definitions

Treatment planning definitions

GTV: gross tumor volume

CTV: clinical target volume

PTV: planning target volume

Arm 1: tumor only treatment

GTV lesion(s): image defined tumor (CT, MRI, 18F-DCFPyL (biopsy confirmed))

PTV lesion(s): GTV lesion + 3 mm posterior and superior margin and 3-5 mm margin in all other dimensions (inferior, lateral, anterior) on the GTV lesion(s).

Arm 2: Prostate + tumor

Brachytherapy or tumor (Gleason > or = to 6) identified in regions outside of areas defined by imaging.

GTV lesion(s): image defined tumor (CT, MRI, 18FDCFPyL (biopsy confirmed))

PTV lesion(s): GTV lesion + 3 mm posterior and superior margin and 3-5 mm margin in all other dimensions (inferior, lateral, anterior) on the GTV lesion(s).

CTV prostate: The entire prostate as visualized on MRI and CT. The entire or partial seminal vesicle may be included in the CTV prostate if there is concern for invasion on MRI, biopsy, or recurrent tumor is located adjacent to the root of the seminal vesicle.

PTV prostate: 3 mm posterior and superior margin and 3-5 mm margin in all other dimensions (inferior, lateral, anterior) on the CTV prostate. In some instances, an additional 1-2 mm margin may be added to the seminal vesicles if substantial motion is documented on serial imaging.

Dose to PTV prostate (cohort 2 only) will be prescribed to 30 Gy in 5 fractions to a minimum of 95% of the PTV prostate. In both arms (1 and 2), the escalated dose should cover a minimum of 95% of the PTV tumor. Dose will be escalated as defined in **3.1.2**.

Table 4: Planning Target Volume (PTV)

	Arm 1: Tumor Irradiation		**Arm 2: Prostate and Tumor Irradiation**	
Dose level	**PTV prostate**	**PTV tumor**	**PTV prostate**	**PTV tumor**
Level 1	**-**	**40 Gy**	**30 Gy**	**40 Gy**
Level 2	**-**	**42.5 Gy**	**30 Gy**	**42.5 Gy**
Level 3*	**-**	**45 Gy**	**30 Gy**	**45 Gy**

* As of amendment version dates 4/13/2021 and 10/12/2021, determination has been made not to escalate to dose level 3 for both arms. Refer to section **1.2.5**.

3.8.3 Dose constraints

A goal V110 (of escalated dose/PTV tumor) will be <5%. The urethral dose will be limited to 105% PTV tumor dose. Bladder wall will be limited to 105% of the prescribed dose. Rectal wall will be limited to 100% of the prescribed PTV tumor dose if the area is not included in the PTV tumor (Rectal wall for normal tissue dose limits will be defined as the rectal wall minus the PTV tumor volume).

3.8.4 Treatment Delivery

An SBRT set up will be used for all treatments. Treatment will be delivered in 5 fractions over a span of 7-14 days. Image guidance will include pre-treatment cone beam CT as per standard of care. An additional post-treatment cone beam CT after each fraction will be obtained to assess intrafraction motion. Calypso beacons will be utilized for real time tumor tracking as per the standard of care if implanted.

3.9 Cost and Compensation

3.9.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by an insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.9.2 Compensation

Participants will not be compensated on this study.

3.9.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.10 Criteria for Removal from Protocol Therapy and Off Study Criteria

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 90 days following the last dose of study therapy.

3.10.1 Criteria for removal from protocol therapy

- Completion of protocol therapy
- Progressive disease
- Participant requests to be withdrawn from active therapy
- Unacceptable Toxicity as defined in Section **3.1.1**
- Investigator discretion

3.10.2 Off-Study Criteria

- Completed study follow-up period
- Participant requests to be withdrawn from study
- Death
- Investigator discretion
- Non-compliance with follow-up visits or protocol mandated procedures

- Permanent loss of capacity to consent
- Lost to follow-up

3.10.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

Supportive care with blood components, antibiotics, analgesics, and general medical therapy will be provided if the need relates to the performance of protocol assessments (biopsy and imaging procedures) or to treat side effects of therapy. Every effort will be made to refer the patient to their collaborating physician in the community for care unrelated to the protocol therapy or procedures. There are no limitations on the type of non-investigational concurrent medications allowed, as in general, these patients do not receive additional therapy for prostate cancer after radiotherapy, with the exception of hormonal therapy, which will not be delivered on this trial. Concurrent use of androgen deprivation therapy will be allowed but discouraged.

Radiation related side effects will be managed as per the current standard of care without restrictions in medications or procedures that may be performed for management.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

Tubes/media may be adjusted at the time of collection based upon materials available or to ensure the best samples are collected for planned analyses.

Test/assay	Volume (approx.)	Type of tube	Collection point (+/- 48hrs)	Location of specimen analysis
Plasma	Up to 24 mL	EDTA	Baseline, 1 month post SBRT, q 3 months after SBRT	Dr. Citrin's Lab Dr. Jones Lab
	Up to 8 mL	Cell-Free DNA BCT	Baseline, q 3 months after SBRT	Dr. Sowalsky's Lab
Urine	15 mL	Sterile cup	Baseline, q 3 months after SBRT	Dr. Citrin's Lab
Tumor biopsies	N/A	N/A	baseline	Dr. Sowalsky's lab

5.1.1 Plasma

Plasma will be sampled at baseline and every three months after SBRT

Three 8 mL aliquots of blood will be obtained in EDTA containing tubes, and one 8 mL aliquot of blood will be obtained in a Cell-Free DNA blood collection tube (BCT), such as Streck BCT. Following collection, tubes will be immediately placed on ice and transferred to the laboratory of Dr. Citrin for processing and storage, Building 10, B3-B100, Tel. 301-496-5457. The Cell-Free DNA BCT aliquot will be transferred to the laboratory of Adam Sowalsky, Building 37, Room 1056, Tel. 240-760-7118.

Plasma will be stored and batched for analysis.

Plasma assays in Dr. Citrin's laboratory will include ELISA/Bioplex analysis of predictive biomarkers recently identified by the Citrin laboratory that correlate with tumor resistance to radiotherapy (70 analytes). Studies in Dr. Sowalsky's laboratory will include germline DNA studies (baseline only) and circulating tumor DNA levels. Plasma studies in Dr. Jones' laboratory will include surface receptor analysis by nanoFACS and RNAseq, for exosome and extracellular RNA analysis.

5.1.2 Urine

Urine will be sampled at baseline and every three months after SBRT.

At least 15 mL of urine will be obtained in a sterile collection cup. Following collection, urine will be transferred to the laboratory of Dr. Citrin for processing, measurement of creatinine concentration, and storage.

Urine will be stored and batched for analysis.

Urine assays will include ELISA analysis of predictive biomarkers recently identified by the Citrin laboratory that correlate with tumor resistance to radiotherapy (70 analytes identified in tissue, screening for detection will occur in urine and plasma).

5.1.3 Prostate biopsy tissue

Prostate tissue will be sampled at baseline

Prostate biopsy tissue found to contain tumor will be stained for PSMA and somatostatin receptor. Additional neuroendocrine markers may also be stained (chromogranin A, NSE). If this work cannot be completed by the pathology collaborator, it will be referred for staining through a contract.

Prostate biopsy tissue will be collected into PaxGene preservative or snap frozen and subsequently transferred to the laboratory of Adam Sowalsky's. Tumor tissue will be used for RNA analysis (RNAseq or microarray) and DNA analysis (targeted sequencing, exome sequencing, or whole genome sequencing). Research cores will be collected for additional analyses such as whole genome/exome sequencing and RNA seq. If adequate tumor tissue is not available for these analyses, targeted mutation testing may be performed.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed.

Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

All samples will be labelled and catalogued with Lab Matrix in the laboratory of Deborah Citrin. Samples transferred to Dr. Sowalsky will be similarly catalogued in Lab Matrix. Samples will be stored at -80º C until use.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described above. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

Blood and urine samples may be subjected to protein or RNA analysis in the future to describe novel prognostic or predictive biomarkers.

If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

5.3 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.3.1 Description of the scope of genetic/genomic analysis

The anticipated analysis on whole blood DNA and tumor DNA will include whole exome or genome sequencing and targeted analysis in blood as described in Section **5.1**.

5.3.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Samples will be bar coded for storage and personal identifiers will be removed. Names and demographic data will be linked to bar codes in the password protected LabMatrix database. This data will be accessible only by the PI and the research nurses within the ROB.

Samples provided to CCR collaborators will be barcoded. No personally identifiable information will be released to Dr. Sowalsky.

Data from genomic and genetic data will be deposited in dbGAP and released in accordance with NIH guidelines.

As part of study efforts to provide confidentiality of subject information, this study will obtain a Certificate of Confidentiality. Please refer to Section **12.4**.

5.3.3 Management of Results

We plan to contact participants if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of secondary findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists). Unless requested otherwise, participants will be contacted at this time with a request to provide a sample to be sent to a CLIA certified laboratory.

5.3.4 Genetic counseling

If the research findings are verified in the CLIA certified lab, the participant will be offered the opportunity schedule a visit, in person (at our expense) or via telemedicine on an NIH approved platform to have genetic education and counseling to explain this result. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at the participant's expense).

The expenses related to verification of results in a CLIA certified laboratory and genetic counseling performed at the NIH will be funded by the Center for Cancer Research.

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

Participants will be requested to maintain up to date contact information to enable future contact.

We also plan to obtain permission from the participants at the time of consent to release results regarding incidental findings in the event the patient dies before results are available. The participant may designate the appropriate blood relative to be contacted if the patient is dead or unavailable in in a signed written release of medical information request.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Document AEs from the through 90 days after the intervention was last administered. During the study follow up period (following collection of AEs for MTD), only adverse events which are serious and related to the study intervention (radiation and 18F-DCFPyL) need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.1.1 Clinical Data

Clinical data including summary and demographic data will be collected and entered into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR. Data capture will include baseline and follow up PSA values, testosterone values, use of ADT, presence or absence of biochemical relapse, and questionnaire scores.

Imaging data will include storage of the reconstructed images and image derived parameters on a secure, password protected lab imaging database. Images may also be stored in the clinical center PACS. The lab imaging database will be stored and maintained in the Molecular Imaging Branch facilities. Personal identifiers will not be used when storing imaging data.

NCI Molecular Imaging Branch may exchange anonymized clinical data with working groups, and qualified investigators. The anonymized image data will be stored in an existing secure off-

site imaging database (EXEC PACS) and these images may be shared with researchers at other institutions.

6.1.2 Pre-Administration Events

The presence of any pre-administration event (baseline signs and symptoms present just before 18F-DCFPyL and SBRT administration) will be recorded in a 21 CFR Part 11-compliant data capture system provided by the NCI CCR.

The following information will also be recorded:

- The date and time of evaluation
- The onset time
- The resolution time or duration
- Action taken
- Status of symptom
- Intensity

6.1.3 Imaging Data

Extracted imaging data include:

(1) PET imaging data will include SUV for each region of interest

(2) All image data will be stored on a secure server, with access limited to credentialed users. This will permit flexible numeric raw data extraction for quantitative analysis and creation of summary data reports.

(3) Anonymized image data from this study will be stored in a secure database that is administered by the Cancer Imaging Program, NCI.

(4) Anonymized image data from this study will be stored in a secure database that is administered by the Cancer Imaging Program, NCI. The data may be shared with research collaborators to improve upon current methods of image analysis. The database is password protected and access is only given to qualifying collaborators.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows (check all that apply):

- Coded and linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository: Clinicaltrials.gov, dbGAP.

- BTRIS (automatic for activities in the Clinical Center).
- Publication and/or public presentations.

When will the data be shared?

- Before publication
- At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGAP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 1-3 months after treatment with a serum PSA measurement as per the study calendar. Response will be assessed based on PSA.

6.3.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with SBRT.

Evaluable for response: Only those patients who complete SBRT and have PSA measured after SBRT will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

6.3.2 Response Criteria

Biochemical control: Biochemical control will be defined using the Phoenix criteria (47). The post-SBRT nadir is the lowest PSA measurement obtained after treatment on this protocol. Biochemical control is defined as a serum PSA less than or equal to 2 ng/dL above the post-SBRT nadir.

Biochemical progression/biochemical failure: Serum PSA more than 2 ng/dL above the post-SBRT nadir. At least 2 PSA measurements separated by 1 month are needed to confirm biochemical failure.

6.3.3 Progression-Free Survival

Biochemical progression free survival (bPFS) will be evaluated on this trial as a secondary endpoint. bPFS is defined as the duration of time from start of treatment to time of PSA progression or death, whichever occurs first. PSA progression (also known as biochemical failure) is defined based on elevation of PSA 2 ng/dL beyond the post-treatment nadir PSA, using the Phoenix criteria (47). A total of 2 PSA values separated by at least 1 month are required to document biochemical recurrence and to reduce the risk of mistakenly classifying a PSA “bounce” as a failure. If the PSA remains elevated, the date of failure will be backdated to the first PSA measurement that exceeded 2 ng/dL above the nadir. Only PSA values collected at the NIH Clinical Center will be used to evaluate disease status given the variability in ranges obtained in different laboratories. Patients who have been treated with androgen deprivation therapy within 3 months before or during this study will not be evaluable for the bPFS endpoint

until their testosterone is within the institutional limit of normal for at least two sequential measurements spaced by 1 month.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements..

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports are not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience 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.

8.1.3 Life-threatening

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. (21CFR312.32).

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor.

8.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form.

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at:

https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 Safety Reporting Criteria to the Pharmaceutical Collaborators

All SAEs, regardless of attribution, will be reported to the manufacturer within 24 hours of learning of the events. For initial SAE reports, Investigators should record all case details that can be gathered within 24 hours on a MedWatch Form 3500a and submit the report via email to:

Peter Herscovitch, MD
Chief, Nuclear Medicine Department's Positron Emission Tomography Section
Email address: pherscovitch@cc.nih.gov

And

Tara Norouzi via email address: norouzit@cc.nih.gov

Relevant follow-up information should be submitted to the manufacturer as soon as it becomes available and/or upon request.

8.5 Reporting Pregnancy

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here:

https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.5.1 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 6 months after the last treatment with SBRT and 2 months after the last 18F-DCFPyL PET/CT.

Pregnancy of the patient's partner is not considered to be an AE. The outcome of all pregnancies occurring from the date of the first dose until 6 months after the last treatment with SBRT and 2 months after the last 18F-DCFPyL PET/CT should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy

registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.6 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.7 SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and,
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Sponsor and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and

frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

This is a single-institution, two-arm, Phase I trial, where patients with locally recurrent prostate cancer after prior radiotherapy will receive image-guided, focally dose escalated SBRT to the sites of local recurrence. Patients will be treated with escalated doses of radiation with the escalation on each arm occurring in parallel, and inclusion on each arm based on prior radiation treatment received. The primary endpoints will be to define the MTD of this approach. The secondary endpoints include to define DLTs, to describe the rate of 1 and 2-year biochemical relapse free survival (Phoenix criteria), to evaluate DCFPyL imaging as a method to detect locally recurrent prostate cancer after irradiation, and to define the quality of life changes that occur during and after this treatment. Exploratory endpoints include description of decision regret in patients who failed treatment and are successfully or unsuccessfully salvaged, evaluation of a personalized mutation panel for detection of early recurrence, and evaluation for the presence of neuroendocrine markers and markers of resistance in radio-recurrent prostate cancer.

10.1 STATISTICAL HYPOTHESIS

- Primary Endpoint: Define the maximum tolerated dose (MTD) of image-guided, focally dose escalated prostate SBRT in patients with a local recurrence of prostate cancer after prior radiotherapy. Assessment of toxicities for dose escalation will occur through 3 weeks after SBRT.
- Secondary Endpoints:
    - Define the dose-limiting toxicities and toxicity profile of image-guided, focally dose escalated prostate SBRT in patients previously treated with radiotherapy. Assessment of toxicities for dose escalation will occur through 3 weeks after SBRT.

- Describe the rate of PSA control (biochemical progression free survival, bPFS) at 1 and 2 years after treatment with focally dose escalated SBRT for locally recurrent prostate cancer after irradiation. We hypothesize that the rate of PSA control (bPFS) will compare favorably to the 75% rate obtained with brachytherapy in several previously published series.
- Describe the effects of focally dose escalated prostate SBRT on patient reported outcomes (SHIM, AUA Symptom Index, EPIC-26) in patients previously treated with radiotherapy. We hypothesize a reduction in quality of life (urinary and gastrointestinal side effects) after re-irradiation that persists for several months but returns to baseline in most patients by 2 years after treatment. We hypothesize that erectile dysfunction will progress after reirradiation without improvement over time.
- Evaluate 18F-DCFPyL imaging as a method to detect locally recurrent prostate cancer after radiation. We hypothesize that 18F-DCFPyL will have a high positive predictive value and sensitivity for diagnosing recurrent prostate cancer.

10.2 SAMPLE SIZE DETERMINATION

Initially, the planned sample size is a minimum of 4 evaluable patients (2 per arm) and a maximum of 48 evaluable patients (24 evaluable patients maximum per arm). As of amendment version dates 04/13/2021 and 10/12/2021, determination has been made not to escalate either arm to dose level 3. Accordingly, a maximum of 42 evaluable patients may be enrolled (21 evaluable patients maximum per arm). Estimates for sample size are based on the assumption that all dose levels will accrue a maximum of patients, thus sample size is likely over-estimated. We do not anticipate drop out during treatment or follow-up, however that remains a possibility. We anticipate drop out would be minimal as we tend to accrue these patients from mainly the local area. To allow for a small number of patients who drop out or are not evaluable, we will set the accrual ceiling at 46.

10.3 POPULATIONS FOR ANALYSES

All enrolled patients that initiate treatment with SBRT will be considered evaluable for toxicity. Patients that complete at least one post-treatment PSA will be considered evaluable for biochemical control and biochemical relapse free survival. Patients that complete QoL measures at 3 months will be considered evaluable for these measures. Patients undergoing biopsy following DCFPyL studies will be considered evaluable for the sensitivity and positive predictive value of this study regardless of whether treatment is received.

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

This is a phase I study. There are two arms to this study for 1) patients with prior brachytherapy as a component of their treatment for prostate cancer, and 2) patients with prior EBRT without brachytherapy. Arms are enrolled and escalated separately. Groups of 3-6 patients are evaluated at each dose level. The dose level on which 2 patients experience unacceptable toxicity is considered to have exceeded the MTD. The next lower dose level on which no more than 1/6 patients experience unacceptable toxicity is considered the MTD for each arm of the study.

10.4.2 Analysis of the Primary Endpoint

The primary endpoint will be to define the MTD of this approach.

10.4.3 Analysis of the Secondary Endpoints

- Define the dose-limiting toxicities and toxicity profile of image-guided, focally dose escalated prostate SBRT in patients previously treated with radiotherapy: DLTs will be reported descriptively.
- Describe the rate of PSA control (bPFS, PSA < 2 ng/dL above post SBRT nadir) at 1 and 2 years after treatment with focally dose escalated SBRT for locally recurrent prostate cancer after irradiation: bPFS will be estimated by the Kaplan-Meier survival analysis and effects of clinical variables on bPFS will be assessed by the Cox proportional hazards model.
- Describe the effects of focally dose escalated prostate SBRT on patient reported outcomes (SHIM, AUA Symptom Index, EPIC-26) in patients previously treated with radiotherapy. The quality of life scores will be summarized at baseline and for each visit. Linear mixed effects model will be used to model quality of life scores at baseline and during and after treatment in which random intercept and random slope are used to account for patient-specific trajectory of quality of life scores. Changes of quality of life scores during and after treatment will be calculated from the estimated linear mixed effect model.
- Evaluate 18F-DCFPyL imaging as a method to detect locally recurrent prostate cancer after radiation. The sensitivity and specificity of DCFPyL for detecting locally recurrent prostate cancer (at baseline) will be reported using biopsy as the gold standard.

10.4.4 Safety Analyses

Adverse events will be coded as per the CTCAE v5.0. Each AE will be coded once for each patient based on the maximum severity during the assessment period. The relationship of AEs to study intervention will be recorded in addition to the onset date, end date, severity, expectedness, and outcome.

Dose-limiting toxicities will be defined as described in section **3.1.1**.

10.4.5 Sub-Group Analyses

The primary endpoint is based on toxicity at a dose level. Only 3-6 patients will be included per dose level expect for the expansion cohort. Thus, it is not feasible to include sub-group analyses.

10.4.6 Tabulation of individual Participant Data

Individual participant data may be tabulated for the exploratory endpoint of detecting mutational panel as a predictor of recurrence.

10.4.7 Exploratory Analyses

- Evaluate the feasibility of a patient specific circulating cell free DNA (cfDNA) mutation panel for predicting biochemical recurrence. We will first perform whole exome sequencing on the biopsy tissue acquired at baseline, and use that sequencing data to derive data on somatic mutations and somatic copy number alternations. We will also perform low-pass whole genome sequencing on total DNA extracted from plasma. Mutations detected in prostate biopsies harboring tumor that are not found in germline considered as potential contributors to each patient's individualized mutation panel. We will make direct comparisons whether a subset or all of the copy number alterations or mutations detected during baseline are represented in plasma prior to treatment. This will be reported as a binomial proportion (percent of patients with some or all of the panel detected and percent that have none of the panel detected). These same mutations defined from pretreatment

samples (evident in pretreatment plasma) will be evaluated in cfDNA (plasma) at each time point of follow up. Direct comparisons of whether a subset or all of the copy number alterations or mutations detected at baseline are represented in plasma will be performed and reported as a binomial proportion (percent of patients with some or all of the panel detected and percent that have none of the panel detected). We hypothesize that patients experiencing relapse will show mutations and copy number alterations present in cfDNA, versus responders where ctDNA would comprise a very small (if any) proportion of the total cfDNA. Because radiation may not kill cells immediately, but can result in late necrosis or mitotic catastrophe, it is not known what the optimal time point for analyzing a "nadir" in detectable mutations is or if one will be detected. Thus, this is an exploratory and descriptive project.

- Evaluate decision regret at the time of enrollment and at the end of follow up relating to the primary treatment for prostate cancer to determine if successful salvage mitigates decision regret. The percentage of patients scored as having decision regret will be compared to the percentage of patients not exhibiting decision regret (regarding the initial radiation treatment). It is hypothesized the effective salvage therapy will mitigate decision regret expressed at the time of enrollment.
- Evaluate for the presence of neuroendocrine markers in recurrent prostate cancer after prior irradiation. The number of cores and percentage of tumor on each core that stains positive for neuroendocrine markers (generally accepted measure is >1% of all cells) will be evaluated and reported in a descriptive fashion.
- Evaluate for the presence of markers of resistance in recurrent prostate cancer after prior irradiation. Additional markers of resistance may be queried in prostate tissue if tissue is available for analysis. These may include expression of immune markers, expression of brachyury, or expression of other proteins or transcripts implicated in radiation or therapeutic resistance.
- Describe cellular, molecular, genetic and genomic biology through whole exome or genome sequencing and targeted analysis in blood and tumor tissue.

11 HUMAN SUBJECTS PROTECTIONS

11.1 RATIONALE FOR SUBJECT SELECTION

Subjects from all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. To date, there is no information that suggests that differences in disease response would be expected in one group compared with another. Efforts will be made to extend accrual to a representative population. If differences in outcome that correlate with ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully.

11.2 INCLUSION OF WOMEN

Women are excluded from this trial as prostate cancer does not occur in females.

11.3 PARTICIPATION OF CHILDREN

Patients under the age of 18 will not be eligible for participation in this study based on the fact that patients under 18 are unlikely to have this disease and the patterns of recurrence and natural history of the disease in patients under the age of 18 are unknown.

11.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

11.4.1 Risks

11.4.1.1 SBRT risks

The risks of participation are primarily those of re-irradiation. Re-irradiation has been studied in many series using radioactive sources, and has been found to be tolerable. Few studies have tested highly conformal, ablative doses of irradiation; thus, the risks are largely unknown. Based on the only series published in this setting, we anticipate a small risk of bowel, bladder, or urethral injury that could be severe. There is a more moderate risk of low grade, chronic bowel or bladder toxicity.

11.4.1.2 Risks Related to 18F-DCFPyL

- Leaking of the dose of 18F-DCFPyL into the skin and tissue around the IV
- Allergic reaction
- Fatigue
- Change in your sense of taste
- Headache

11.4.1.3 Risks of Exposure to Ionizing Radiation

There is a small risk of radiation from 18F-DCFPyL PET/CTs. The amount of radiation from these scans adds minimal additional risk to the higher radiation doses received in the course of treatment.

11.4.1.4 Blood Draw Risks

Blood draws may cause pain, redness, bruising, fainting or infection at the draw site. Up to 63 mL of blood will be obtained at screening/baseline, and up to 35.5 mL at each subsequent visit.

11.4.1.5 MRI and MRI Contrast Risks

Participants are at risk for injury from the MRI magnet if they have metal in their body. There is a possibility that participants may experience claustrophobia. There are risks of back discomfort related to lying in the scanner.

The most common side effects from MRI contrast (gadolinium) include injection site pain, nausea, itching, rash, headaches and dizziness. Serious but rare side effects such as gadolinium toxicity and nephrogenic systemic fibrosis, or NSF, are most often seen in patients with severe kidney problems.

11.4.1.6 Biopsy Risks

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent.

11.4.1.7 Conscious Sedation Risks

Conscious sedation may be used for the biopsy procedure. The common side effects of conscious sedation include drowsiness, delayed reflexes, hypotension, headache, and nausea. These are generally mild and last no more than a few hours.

11.4.1.8 CT Contrast Risks

Itching, hives or headaches are possible risks associated with contrast agents that may be used during CT imaging. Symptoms of a more serious allergic reaction include shortness of breath and swelling of the throat or other parts of the body. Very rarely, the contrast agents used in CT can cause kidney problems for certain participants, such as those with impaired kidney function.

11.4.1.9 Urine Collection Risks

There are no known risks associated with urine collection.

11.4.1.10 Questionnaire Risks

Questionnaires may contain questions that are sensitive in nature. The participants are asked to only answer questions they are comfortable with.

11.4.2 Benefits

The potential benefits of trial participation relate to potential curative treatment of recurrent prostate cancer. Many patients do not have a curative option after local failure following radiation treatment. This protocol would provide a potentially curative option. Currently, therapy for biochemical failure typically consists of the temporizing use of hormonal therapy if a patient is not a suitable candidate for other ablative treatments.

11.5 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at:
https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

12 REGULATORY AND OPERATIONAL CONSIDERATIONS

12.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

12.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

12.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research

information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

13 PHARMACEUTICAL INFORMATION

13.1 18F-DCFPyL

13.1.1 Classification

Radiopharmaceutical for imaging

13.1.2 Chemical Name

2-(3-(1-carboxy-5-[(6-[18F] fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid

13.1.3 Formulation and preparation

The drug product components include the drug substance 102.5 +/-97.5 mCi @ end of synthesis calibration time (EOS), 3.5 +/- 1mL ethyl alcohol 200 proof, 0.5 +/- 0.1 mL sodium phosphates, and 10 +/- 0.5mL sterile water.

13.1.4 Source

18F-DCFPyL will be prepared and handled in the PET department CC/NIH, Radiopharmacy according to the chemistry and manufacturing described in the IND. A delivery sheet/protocol will be provided with each delivery of 18F-DCFPyL which will contain the batch number, time of preparation, radioactive concentration (mCi/ mL) at a stated time, and shelf life information. The delivery sheet/protocol will include the expiration date and time (hh:mm), based on the chemical stability of the synthesized compound.

Before administration, the suitability of each preparation will be assessed by a number of QC tests ran by the PET department, which may include radioactivity content by well-counting, radiochemical purity by thin-layer chromatography, chemical content, and pH measurement, according to approved methods provided by in the IND. A document attesting to the passing of these quality control (QC) processes will be provided to the Molecular Imaging Clinic.

This documentation will be reviewed by trained individuals in MIB to ensure that the product quality meets the criteria for clinical use defined within the IND, and to certify (verbally, in writing or via email) that 18F-DCFPyL is released for clinical use. The medically responsible person at the PET imaging site will ensure that the correct dose is present in the injection syringe and that the product is used within the stability period of time stated on the delivery sheet/protocol prior to injection. A lower amount of radioactivity (potentially due to an unpredictable delay in delivery or injection time) may be administered at the discretion of MIB staff, and will be documented.

13.1.5 Agent Inventory Records

The investigator or appropriate investigator-designee will order subject doses of the IND agent for this specific trial. The investigational radiopharmaceutical will be shipped to the site on the day the participant is to be injected, taking into account varying radioactive half-lives for different radioactive imaging agents.

13.1.6 Stability and Storage

The in-use shelf-life of 18F-DCFPyL will be specified on the label. Although from a chemical perspective, the product remains stable beyond 6 hours, due to the short 109.8-minute half-life of 18F, the low level of activity present after 6 hours renders it unsuitable for positron imaging tomography studies. 18F-DCFPyL is stored in the original container at 4 °C under inert atmosphere.

13.1.7 Administration procedures

Subjects will receive 18F-DCFPyL under the direct supervision of study personnel. Each subject will receive a single IV dose of 18F-DCFPyL by bolus injection at a rate of approximately 1 ml/3-5 sec. The maximum amount of injected active drug will be less than 4.02 micrograms. The injection will be followed by a 10-ml saline flush (sodium chloride IV infusion 0.9% w/v) over ~10sec.

The target administered activity will be 6-6.5 mCi; dose variations will be in accordance with the Nuclear Regulatory Commission (NRC) standard dose variation (i.e. 20%) permitted for diagnostic clinical studies and per MIB procedures. The administered activity has been based upon the results of dosimetry analysis on data from 18F DCFBC prior pre-clinical and human studies.

The administration site should be evaluated just before, during and after injection, to assess for extravasation and/or for the presence of signs of local irritation.

18F-DCFPyL will be performed in MIC with a member of the MIB clinical team in attendance during the injection. In the event of an emergency, such as an allergic reaction, immediate treatment will be initiated using emergency medication available in the Molecular Imaging Clinic. If the subject requires admission due to the severity of the reaction, the subject will be admitted to the appropriate service for observation as the clinical situation dictates.

Any administration complication of the drug (e.g., overdose, observable extravasation, medication error) is a protocol related event and will be reported.

Due to potential unpredictable delays and the short half-life of 18F, the total dose of 18F-DCFPyL administered may be reduced at the discretion of the principal investigator or her designee.

13.1.8 Supply and Packaging

18F-DCFPyL for each study patient will be received in individual patient doses from the PET department. Containers that are radioactive or contain radioactive products will be disposed of per NIH Radiation Safety Guidelines.

14 COMMERCIAL DEVICE INFORMATION

The radiation device is an FDA cleared commercial device. The device will be used/investigated in accordance with labeling and therefore will be IDE exempt under 812.2 (c) – category 1.

14.1 SOURCE

The radiation device is a commercial device that will be located in the NIH Clinical Center.

14.2 TOXICITY

Refer to section **11.4**.

14.3 ADMINISTRATION PROCEDURES

Refer to section **3.8**.

15 REFERENCES

1. Michalski J, Winter K, Roach M, Markoe A, Sandler HM, Ryu J, et al. Clinical outcome of patients treated with 3D conformal radiation therapy (3D-CRT) for prostate cancer on RTOG 9406. Int J Radiat Oncol Biol Phys.83(3):e363-70.

2. Agarwal PK, Sadetsky N, Konety BR, Resnick MI, Carroll PR, Cancer of the Prostate Strategic Urological Research E. Treatment failure after primary and salvage therapy for prostate cancer: likelihood, patterns of care, and outcomes. Cancer. 2008;112(2):307-14.

3. Crook JM, Malone S, Perry G, Eapen L, Owen J, Robertson S, et al. Twenty-four-month postradiation prostate biopsies are strongly predictive of 7-year disease-free survival: results from a Canadian randomized trial. Cancer. 2009;115(3):673-9.

4. Tran H, Kwok J, Pickles T, Tyldesley S, Black PC. Underutilization of local salvage therapy after radiation therapy for prostate cancer. Urol Oncol. 2014;32(5):701-6.

5. Cornelis F, Havez M, Le Bras Y, Descat E, Richaud P, Grenier N. Salvage CT-guided transgluteal cryoablation for locally recurrent prostate cancer: initial experiences. J Vasc Interv Radiol. 2013;24(5):685-9.

6. Katz AE. Is salvage cryoablation effective in patients with prostate cancer who have failed radiation therapy? Nat Clin Pract Urol. 2008;5(3):136-7.

7. Kovac E, ElShafei A, Tay KJ, Mendez M, Polascik TJ, Jones JS. Five-Year Biochemical Progression-Free Survival Following Salvage Whole-Gland Prostate Cryoablation: Defining Success with Nadir Prostate-Specific Antigen. J Endourol. 2016;30(6):624-31.

8. Li YH, Elshafei A, Agarwal G, Ruckle H, Powsang J, Jones JS. Salvage focal prostate cryoablation for locally recurrent prostate cancer after radiotherapy: initial results from the cryo on-line data registry. Prostate. 2015;75(1):1-7.

9. Mouraviev V, Evans B, Polascik TJ. Salvage prostate cryoablation after primary interstitial brachytherapy failure: a feasible approach. Prostate Cancer Prostatic Dis. 2006;9(1):99-101.

10. Ng CK, Touma NJ, Chalasani V, Moussa M, Downey DB, Chin JL. The pattern of prostate cancer local recurrence after radiation and salvage cryoablation. Can Urol Assoc J. 2011;5(6):E125-8.

11. Mandel P, Steuber T, Ahyai S, Kriegmair M, Schiffmann J, Boehm K, et al. Salvage radical prostatectomy for recurrent prostate cancer: verification of European Association of Urology guideline criteria. BJU Int. 2016;117(1):55-61.

12. Chade DC, Eastham J, Graefen M, Hu JC, Karnes RJ, Klotz L, et al. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. Eur Urol. 2012;61(5):961-71.

13. Chade DC, Shariat SF, Cronin AM, Savage CJ, Karnes RJ, Blute ML, et al. Salvage radical prostatectomy for radiation-recurrent prostate cancer: a multi-institutional collaboration. Eur Urol. 2011;60(2):205-10.

14. Aaronson DS, Yamasaki I, Gottschalk A, Speight J, Hsu IC, Pickett B, et al. Salvage permanent perineal radioactive-seed implantation for treating recurrence of localized prostate adenocarcinoma after external beam radiotherapy. Bju International. 2009;104(5):600-4.

15. Burri RJ, Stone NN, Unger P, Stock RG. Long-term outcome and toxicity of salvage brachytherapy for local failure after initial radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2010;77(5):1338-44.

16. Grado GL, Collins JM, Kriegshauser JS, Balch CS, Grado MM, Swanson GP, et al. Salvage brachytherapy for localized prostate cancer after radiotherapy failure. Urology. 1999;53(1):2-10.

17. Lee B, Shinohara K, Weinberg V, Gottschalk AR, Pouliot J, Roach M, 3rd, et al. Feasibility of high-dose-rate brachytherapy salvage for local prostate cancer recurrence after radiotherapy: the University of California-San Francisco experience. Int J Radiat Oncol Biol Phys. 2007;67(4):1106-12.

18. Lee CG, Heijn M, di Tomaso E, Griffon-Etienne G, Ancukiewicz M, Koike C, et al. Anti-Vascular endothelial growth factor treatment augments tumor radiation response under normoxic or hypoxic conditions. Cancer Res. 2000;60(19):5565-70.

19. Vargas C, Swartz D, Vashi A, Blasser M, Kasraeian A, Cesaretti J, et al. Salvage brachytherapy for recurrent prostate cancer. Brachytherapy. 2014;13(1):53-8.

20. Henriquez I, Sancho G, Hervas A, Guix B, Pera J, Gutierrez C, et al. Salvage brachytherapy in prostate local recurrence after radiation therapy: predicting factors for control and toxicity. Radiat Oncol. 2014;9:102.

21. Yamada Y, Kollmeier MA, Pei X, Kan CC, Cohen GN, Donat SM, et al. A Phase II study of salvage high-dose-rate brachytherapy for the treatment of locally recurrent prostate cancer after definitive external beam radiotherapy. Brachytherapy. 2014;13(2):111-6.

22. Fuller DB, Wurzer J, Shirazi R, Bridge SS, Law J, Mardirossian G. High-dose-rate stereotactic body radiation therapy for postradiation therapy locally recurrent prostatic carcinoma: Preliminary prostate-specific antigen response, disease-free survival, and toxicity assessment. Pract Radiat Oncol. 2015;5(6):e615-23.

23. Bates AS, Samavedi S, Kumar A, Mouraviev V, Rocco B, Coelho R, et al. Salvage robot assisted radical prostatectomy: A propensity matched study of perioperative, oncological and functional outcomes. Eur J Surg Oncol. 2015;41(11):1540-6.

24. Kaffenberger SD, Keegan KA, Bansal NK, Morgan TM, Tang DH, Barocas DA, et al. Salvage robotic assisted laparoscopic radical prostatectomy: a single institution, 5-year experience. J Urol. 2013;189(2):507-13.

25. Mahal BA, Ziehr DR, Hyatt AS, Neubauer-Sugar EH, O'Farrell DA, O'Leary MP, et al. Use of a rectal spacer with low-dose-rate brachytherapy for treatment of prostate cancer in previously irradiated patients: Initial experience and short-term results. Brachytherapy. 2014;13(5):442-9.

26. Hsu CC, Hsu H, Pickett B, Crehange G, Hsu IC, Dea R, et al. Feasibility of MR imaging/MR spectroscopy-planned focal partial salvage permanent prostate implant (PPI) for

localized recurrence after initial PPI for prostate cancer. Int J Radiat Oncol Biol Phys. 2013;85(2):370-7.

27. Maurer T, Eiber M, Schwaiger M, Gschwend JE. Current use of PSMA-PET in prostate cancer management. Nat Rev Urol. 2016;13(4):226-35.

28. Kinoshita Y, Kuratsukuri K, Landas S, Imaida K, Rovito P, Jr., Wang C, et al. Expression of Prostate-Specific Membrane Antigen in Normal and Malignant Human Tissues. World J Surg. 2006;30(4):628-36.

29. Milowsky MI, Nanus DM, Kostakoglu L, Sheehan CE, Vallabhajosula S, Goldsmith SJ, et al. Vascular targeted therapy with anti-prostate-specific membrane antigen monoclonal antibody J591 in advanced solid tumors. J Clin Oncol. 2007;25(5):540-7.

30. Sokoloff RL, Norton KC, Gasior CL, Marker KM, Grauer LS. A dual-monoclonal sandwich assay for prostate-specific membrane antigen: Levels in tissues, seminal fluid and urine. The Prostate. 2000;43(2):150-7.

31. Troyer JK, Beckett ML, Wright GL, Jr. Location of prostate-specific membrane antigen in the LNCaP prostate carcinoma cell line. Prostate. 1997;30(4):232-42.

32. Mease RC, Dusich CL, Foss CA, Ravert HT, Dannals RF, Seidel J, et al. N-[N-[(S)-1,3-Dicarboxypropyl]carbamoyl]-4-[18F]fluorobenzyl-L-cysteine, [18F]DCFBC: a new imaging probe for prostate cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2008;14(10):3036-43.

33. Cho SY, Gage KL, Mease RC, Senthamizhchelvan S, Holt DP, Jeffrey-Kwanisai A, et al. Biodistribution, Tumor Detection, and Radiation Dosimetry of 18F-DCFBC, a Low-Molecular-Weight Inhibitor of Prostate-Specific Membrane Antigen, in Patients with Metastatic Prostate Cancer. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2012;53(12):1883-91.

34. Evans MJ, Smith-Jones PM, Wongvipat J, Navarro V, Kim S, Bander NH, et al. Noninvasive measurement of androgen receptor signaling with a positron-emitting radiopharmaceutical that targets prostate-specific membrane antigen. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(23):9578-82.

35. Chen Y, Pullambhatla M, Foss CA, Byun Y, Nimmagadda S, Senthamizhchelvan S, et al. 2-(3-{1-Carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pen tanedioic acid, [18F]DCFPyL, a PSMA-based PET imaging agent for prostate cancer. Clin Cancer Res. 2011;17(24):7645-53.

36. Szabo Z, Mena E, Rowe SP, Plyku D, Nidal R, Eisenberger MA, et al. Initial Evaluation of [F]DCFPyL for Prostate-Specific Membrane Antigen (PSMA)-Targeted PET Imaging of Prostate Cancer. Molecular imaging and biology : MIB : the official publication of the Academy of Molecular Imaging. 2015.

37. Rowe SP, Macura KJ, Mena E, Blackford AL, Nadal R, Antonarakis ES, et al. PSMA-Based [(18)F]DCFPyL PET/CT Is Superior to Conventional Imaging for Lesion Detection in Patients with Metastatic Prostate Cancer. Molecular imaging and biology : MIB : the official publication of the Academy of Molecular Imaging. 2016;18(3):411-9.

38. Hruby G, Eade T, Kneebone A, Emmett L, Guo L, Ho B, et al. Delineating biochemical failure with 68Ga-PSMA-PET following definitive external beam radiation treatment for prostate cancer. Radiother Oncol. 2017;122(1):99-102.

39. Albisinni S, Artigas C, Aoun F, Biaou I, Grosman J, Gil T, et al. 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 Int. 2016.

40. Vashchenko N, Abrahamsson PA. Neuroendocrine differentiation in prostate cancer: implications for new treatment modalities. Eur Urol. 2005;47(2):147-55.

41. Huang J, Yao JL, di Sant'Agnese PA, Yang Q, Bourne PA, Na Y. Immunohistochemical characterization of neuroendocrine cells in prostate cancer. Prostate. 2006;66(13):1399-406.

42. Sant'Agnese PAd, Egevad D, Epstein JI, Helpap B, Humphrey P, Montironi R, et al. Neuroendocrine tumours. World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs. Lyon, France: IARC Press; 2004. p. 207-8.

43. Krauss DJ, Amin M, Stone B, Ye H, Hayek S, Cotant M, et al. Chromogranin A staining as a prognostic variable in newly diagnosed Gleason score 7-10 prostate cancer treated with definitive radiotherapy. Prostate. 2014;74(5):520-7.

44. Deng X, Liu H, Huang J, Cheng L, Keller ET, Parsons SJ, et al. Ionizing radiation induces prostate cancer neuroendocrine differentiation through interplay of CREB and ATF2: implications for disease progression. Cancer Res. 2008;68(23):9663-70.

45. Deng X, Elzey BD, Poulson JM, Morrison WB, Ko SC, Hahn NM, et al. Ionizing radiation induces neuroendocrine differentiation of prostate cancer cells in vitro, in vivo and in prostate cancer patients. Am J Cancer Res. 2011;1(7):834-44.

46. Lilleby W, Paus E, Skovlund E, Fossa SD. Prognostic value of neuroendocrine serum markers and PSA in irradiated patients with pN0 localized prostate cancer. Prostate. 2001;46(2):126-33.

47. Roach M, 3rd, Hanks G, Thames H, Jr., Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys. 2006;65(4):965-74.

16 APPENDICES

16.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

16.2 APPENDIX B: QOL QUESTIONNAIRES

QoL questionnaires will be maintained in a separate document/manual.