Advanced PET-CT Directed Post-Prostatectomy Radiotherapy to Enhance Prostate Cancer Outcomes

Winship Protocol RAD4516-18

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1.0 Abstract

Currently, 50% of patients who have undergone post-prostatectomy radiotherapy after PSA failure manifest subsequent systemic disease. Compared to PET-CT with molecular radiotracers, conventional imaging methods fall short in identifying sites of prostate cancer recurrence. **Our goal is to address an unmet public health need by improving long term biochemical control of patients with recurrent prostate carcinoma.**

We have verified a key scientific premise that **advanced molecular imaging with the synthetic amino acid PET radiotracer fluciclovine (^{18}F) (*anti*-3-[^{18}F]FACBC) results in significantly greater disease detection, with a 40.5% change in management and 83.6% change in planning volumes (without dose escalation) compared with conventional imaging** (1-3). During the course of our trial, and in large part because of our translational work, fluciclovine (^{18}F) was FDA approved in 2016 for recurrent prostate cancer, contributing to a new standard of care (4-8). As of Version 1.2018, fluciclovine (^{18}F) has now been included in the National Comprehensive Cancer Network (NCCN) Guidelines for restaging recurrent prostate cancer. Moreover, **salvage radiotherapy is being offered at increasingly lower PSA levels**, and evidence is accumulating that **boosting radiotherapy dose to foci of active disease may result in clinical benefit** (9). We have also demonstrated that molecular imaging is an attractive modality to identify targets for dose escalation, while avoiding increased toxicity, which is not practically possible with conventional imaging (1, 2).

Preliminary analysis of still accruing data from our ongoing clinical trial (**5R01CA129356: NCT01666808**) suggests that integrating fluciclovine may result in a small improvement in failure rate, but not have adequate sensitivity to definitively achieve durable PSA control with standard radiotherapy doses. Yet, there is early evidence that a new class of PET radiotracer targeting the prostate specific membrane antigen (PSMA) receptor may have greater sensitivity at lower PSA levels for disease detection. Gallium-68 (^{68}Ga) PSMA is one such PSMA PET ligand. As will be outlined in our Scientific Premise section, each class of PET radiotracer, amino acid metabolic (fluciclovine) vs receptor based (PSMA), exhibits advantages and disadvantages. **Our hypothesis is that by utilizing a higher affinity PET ligand, we can better select and manage patients who will benefit from salvage radiotherapy undertaken at lower PSA levels**. In addition, **we hypothesize that by dose escalating targets identified with either fluciclovine (^{18}F) or ^{68}Ga PSMA, we will determine if dose escalation in itself provides improved PSA control**.

To test these hypotheses with the highest scientific rigor, we will conduct a prospective clinical trial in which patients who are eligible for salvage radiotherapy are randomized to either fluciclovine (^{18}F) or ^{68}Ga PSMA PET-CT. To that end we will employ our proven multidisciplinary team of experts and leverage data from our ongoing Early Detection Research Network (EDRN) study (**2U01CA113913**) in an exploratory aim to determine if positive specific tissue biomarker signatures may be useful to help predicts post-prostatectomy radiotherapy outcomes in combination with the standard risk criteria. Our proposal is timely since recent editorials in the literature regarding salvage radiotherapy post-prostatectomy call for integration of molecular imaging in prospective, randomized, controlled trials with toxicity profiles of the type we will carry out (10, 11).

2.0 Schema –

We will undertake a clinical trial of patients post-prostatectomy with any detectable PSA levels, allowing patients who are and are not traditionally offered radiotherapy to be enrolled. Patients may or may not have biopsy proof of local recurrence, but will be under active consideration for salvage radiotherapy based on PSA, physical examination, and pathologic features (margin positivity, seminal-vesicle involvement, extra-capsular extension, and/or nodal involvement). All patients will undergo conventional imaging - bone scan and either abdominopelvic CT scan or abdominopelvic MRI.

Patients (n = 140) will be randomized to A) a group in which fluciclovine (^{18}F) PET/CT imaging will be additionally employed (n = 70), or B) a group in which ^{68}Ga PSMA PET/CT imaging will be additionally employed (n = 70). Patients will be stratified according to: (a) PSA level (≤ 1.0 ng/mL vs higher), (b) adverse pathologic features (described above), and (c) androgen deprivation intent, resulting in 8 total bins (note that while data will be collected for subgroup analyses, the statistical plan is based on the entire study arm). In addition, for Specific Aim 2 (see below), we will analyze patients treated in both arms to identify treatment decision changes regarding (a) the decision of whether to offer post-prostatectomy XRT, (b) the decision of whether to treat the pelvic lymph nodes in addition to the prostate bed, and (c) the decision to boost areas of PET/CT uptake in the prostate bed and/or nodes This will be accomplished via an **intent to treat Radiotherapy Decision Attestation Sheet** that will be filled out prospectively by each treating radiation oncologist before and after each PET/CT (note that there are only 3 primary enrolling radiation oncologists who will be seeing patients on both arms, so there will be minimal variation in decision strategy minimizing decision biases). Each patient (Arms A and B) will be followed for a minimum of two years with PSA levels measured every 6 months and other clinical parameters to measure presence and time to PSA failure, as well as manifestation of clinical failure as defined by macroscopic identifiable disease. Outcomes will be compared between groups in aggregate and stratified by treatment bin. The endpoint will be 2-year disease-free survival. **These prospective intent to treat conditions and objective criteria for followup will enable the highest degree of scientific rigor.**

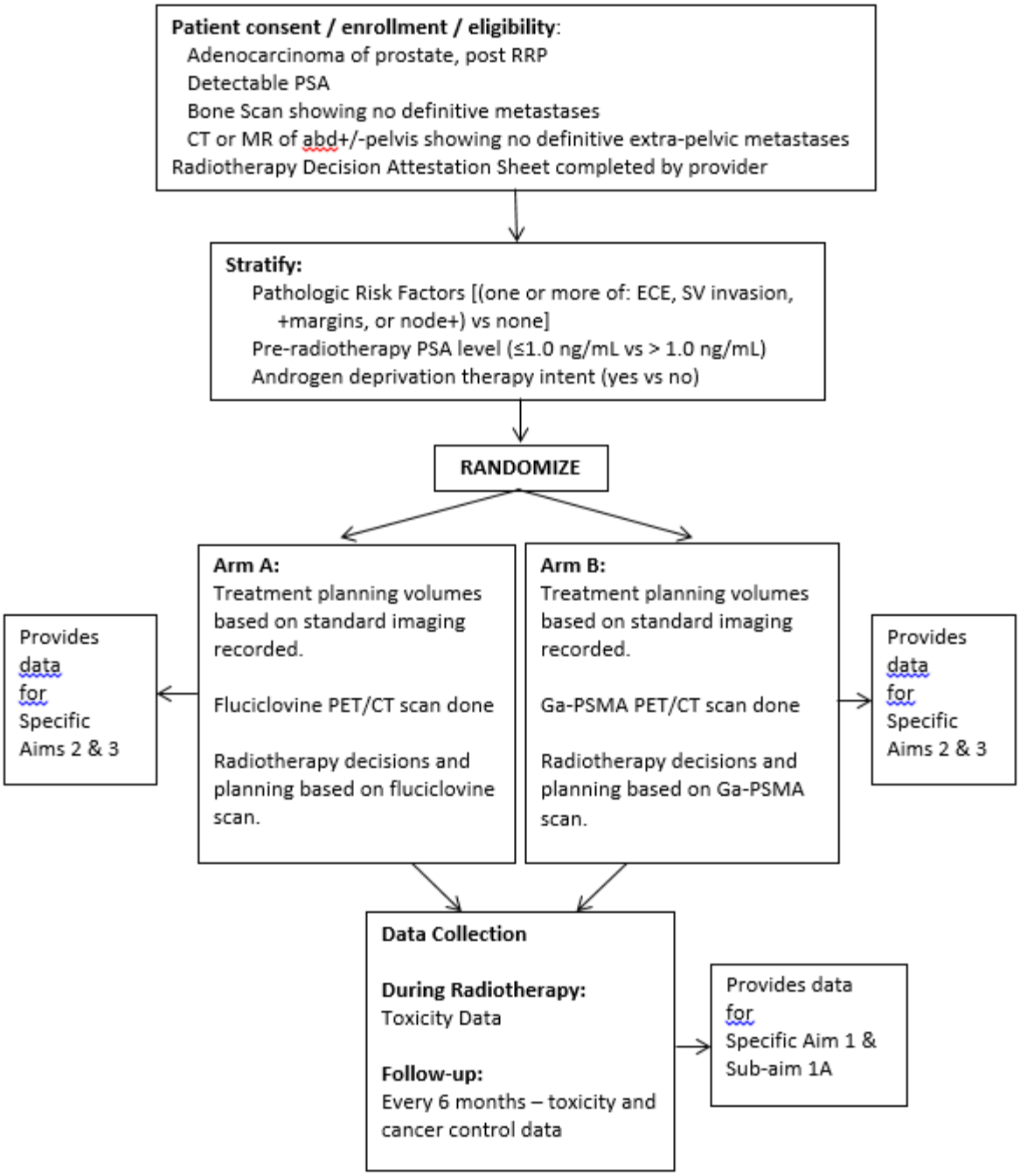
Study Schema

The general schema of the clinical trial is as follows (see adjacent flow-path):
Screen (see inclusion criteria in flow-path).
Stratify by adverse pathological factor, PSA level, and androgen deprivation therapy intent.
Randomize: Arm A: [fluciclovine (^{18}F) PET/CT] or
Arm B: [^{68}Ga PSMA PET/CT] guided radiotherapy.

Findings	**Extrapelvic disease**	**Pelvic nodal uptake (or pN+)**	**Prostate-bed only uptake**	**No uptake**
Action	**No radiotherapy**	**Radiotherapy to prostate bed + pelvic lymph nodes plus boost**	**Radiotherapy only to prostate bed plus boost**	**Radiotherapy only to prostate bed (no boost)**

Decisions will be (a) whether to offer radiotherapy, (b) radiotherapy treatment volume, and (c) boost. Final decisions are based on findings on PET/CT scan. Note also that in each case, the radiotherapy plan will be designed first without PET/CT information. Then, planning CT fusion will determine final treatment plan.

In both arms, regions of molecular PET/CT uptake will be dose-escalated (our current ongoing trial has volume escalation but not dose escalation to areas of fluciclovine (^{18}F) uptake). *The goal is 70.2-76 Gy if the uptake is close to the prostate bed and 54-56 Gy if the uptake is in the upper pelvis. Dose escalation will be done using simultaneous in-field boost, with clinician discretion on dose ability to meet treatment planning constraints. Several prior publications document the feasibility and safety of nodal dose escalation* (74-79).


Patient consent / enrollment / eligibility:
Adenocarcinoma of prostate, post RRP
Detectable PSA
Bone Scan showing no definitive metastases
CT or MR of abd+/-pelvis showing no definitive extra-pelvic metastases
Radiotherapy Decision Attestation Sheet completed by provider
Stratify:
Pathologic Risk Factors [(one or more of: ECE, SV invasion, +margins, or node+) vs none]
Pre-radiotherapy PSA level (≤1.0 ng/mL vs > 1.0 ng/mL)
Androgen deprivation therapy intent (yes vs no)
RANDOMIZE
Arm A:
Treatment planning volumes based on standard imaging recorded.
Fluciclovine PET/CT scan done
Radiotherapy decisions and planning based on fluciclovine scan.
Arm B:
Treatment planning volumes based on standard imaging recorded.
Ga-PSMA PET/CT scan done
Radiotherapy decisions and planning based on Ga-PSMA scan.
Provides data for Specific Aims 2 & 3
Provides data for Specific Aims 2 & 3
Data Collection
During Radiotherapy:
Toxicity Data
Follow-up:
Every 6 months – toxicity and cancer control data
Provides data for Specific Aim 1 & Sub-aim 1A

2.1 Eligibility Checklist

___(Y) 1. Adenocarcinoma of the prostate, post radical-prostatectomy

___(Y) 2. Detectable PSA

___(Y) 3. No definitive findings for skeletal metastasis on technetium 99-m MDP or F-18 PET bone scan

___(Y) 4. No definitive findings of systemic (extrapelvic) metastasis on CT and/or MR scan pelvis (and, if performed, abdomen).

___(Y) 5. ECOG/Zubrod Performance status of 0-2

___(Y) 6. Age over 18

___(N) 7. Contraindications to radiotherapy (including active inflammatory bowel disease or prior pelvic radiotherapy)

___(N) 8. Inability to undergo fluciclovine or Ga-PSMA PET-CT or contraindications to furosemide

___(N) 9. Definitive findings of systemic metastasis on conventional imaging or biopsy

___(N) 10. Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years

___(N) 11. Severe acute co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization in the last 3 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immunocompromised patients

___(Y) 12. Willingness to undergo pelvic radiotherapy.

3.0 Introduction

Prostate cancer is the most common solid malignancy in males in the US. Several treatment options exist for primary treatment, including prostatectomy (12-22). While these are effective for low and favorable intermediate risk disease, recurrence after primary treatment is more frequent in the setting of unfavorable intermediate and high-risk prostate cancer. Radiotherapy has been used with success after prostatectomy as salvage therapy for rising PSA and for adjuvant therapy in patients with high-risk features (23-36). Recently, post-prostatectomy radiotherapy for node positive disease has also been found to be efficacious (37-39). Furthermore, the concept of boosting appropriate regions of cancer involvement has come into focus due to the ability of metabolic imaging to provide relevant guidance (9). In selecting patients for radiotherapy, the location of recurrence informs management. Specifically, if disease is found to be distant, androgen deprivation and/or other systemic therapy becomes the primary treatment. If disease is regional in the pelvis, the pelvic lymph nodes are included in the radiotherapy field. If failure is strictly local (or presumed to be local on the basis of negative imaging), salvage radiotherapy when utilized is typically confined to the prostate bed to minimize potential side effects of pelvic therapy.

Imaging is critically important for assisting patient selection, radiotherapy decisions, and target definition (7, 40-65). Conventional imaging (bone scan, CT, routine MRI) is limited in identifying sites of recurrence. Radioimmunoscintigraphy with ^{111}Indium-capromab pendetide (ProstaScint) had been reported to assist with treatment decisions and volume definition, but was not found to impact biochemical control. Explanations for this deficiency include low resolution and inadequate diagnostic performance (48, 64-67). In the interim, advances in PET radiotracers have resulted in improved accuracy. A synthetic amino acid radiotracer developed at Emory (FACBC or fluciclovine (^{18}F), which is now FDA approved as Axumin) has been reported by our group and others to have significantly improved diagnostic performance compared with ^{111}Indium-capromab pendetide and conventional imaging (6-8, 61-69).

Though novel PET ligands such as fluciclovine and choline have greatly improved our ability to detect recurrent prostate cancer (4), these radiotracers interrogate the metabolome that is upregulated in prostate cancer. Specifically, fluciclovine (^{18}F) uptake is related to increased amino acid transport that has been demonstrated to occur with prostate cancer (70). Both C-11 choline and fluciclovine (^{18}F) are now FDA approved and have become a de-facto standard of care. Yet, there are additional cell level imaging biomarkers that are also upregulated in prostate cancer and may be exploited for imaging. One of these promising new targets is prostate specific membrane antigen (PSMA) (71).

PSMA is a Type 2 transmembrane glycoprotein of the M28 peptidase family and is overexpressed on the cell surface of prostate cancer (72, 73). We have shown *superiority of fluciclovine* (^{18}F) in the detection of prostate cancer compared with ^{111}Indium capromab pendetide (6). Yet, ^{111}Indium capromab pendetide is directed against the intracellular epitope of PSMA, which is an inherent limitation. Preliminary evidence as outlined below suggests that newer generation PSMA PET radiotracers directed against the extracellular epitope of PSMA may possess inherent advantages in sensitivity compared with fluciclovine (^{18}F) especially at lower PSA levels, though each radiotracer has unique strengths and limitations.

The improved diagnostic accuracy demonstrated with molecular techniques and the potential ability to identify which category of recurrence is occurring (local, pelvic, or systemic), has formed the basis of our efforts to exploit molecular imaging with fluciclovine (^{18}F) to positively affect management decisions and achieve improved cancer control. This concept is also central to this proposed effort for additional exploration beyond fluciclovine (^{18}F) with potentially more sensitive novel PSMA agents, combined with the possibility of more effective therapeutic manipulation via radiotherapy boost and with improved selection of patients via a combination of tissue and imaging biomarker predictive modeling.

In our ongoing trial, we have advanced the field by our use of molecular imaging with fluciclovine (^{18}F) to assist in patient selection for radiotherapy, for guiding treatment field decisions, and for modifying radiotherapy targets. This project will extend this work and **fully test a set of novel and clinically relevant hypotheses**.

Study Sites:
Note that this protocol is intended to be open at Emory University Hospital Clifton, Emory St. Joseph's Hospital, Emory University Hospital Midtown, and Grady Memorial Hospital. We will amend this protocol as needed if additional study sites are added.

4.0 Objectives

Our major goal in this proposed investigation is to use advanced molecular imaging to better guide post-prostatectomy decision making.

Specific Aim 1: Improve the outcomes of post-prostatectomy radiotherapy prostate cancer patients via selection and treatment optimization with advanced molecular imaging with dose escalation.
We will conduct a prospective 140 patient trial with subjects randomized (70 in each arm) to either fluciclovine (^{18}F) or ^{68}Ga PSMA PET/CT, in each case boosting areas of PET uptake. The hypothesis is that advanced molecular imaging in either or both arms will increase 2-year disease-free survival by 15% (over the disease-free survival in the current trial without dose-escalation), without added toxicity.

Exploratory Sub-aim 1A: We hypothesize that positive specific tissue biomarker signatures, when combined with standard risk criteria and findings from **molecular imaging with fluciclovine or PSMA PET**, have added value in predicting successful salvage radiotherapy outcomes. To this end, we will build a regression model predictive of outcome (which also includes standard pathologic risk factors and PSA kinetics) in a subset of the estimated 100 recurrence patients for whom we will have access to previously resected primary prostate tissue obtained from our ongoing EDRN.

Specific Aim 2: Establish the role of advanced molecular imaging with fluciclovine (^{18}F) and ^{68}Ga PSMA PET/CT in influencing post-prostatectomy radiotherapy decision-making.
We will analyze the two cohorts of patients in Specific Aim 1, comparing initial (pre-PET/CT) versus final (post-PET/CT) treatment decisions regarding (a) the decision to offer post-prostatectomy radiotherapy, (b) the delineation of extent (bed versus pelvis) and clinical and planning target volumes, and (c) boosting areas of PET/CT uptake.

Specific Aim 3: Establish the role of advanced molecular imaging with fluciclovine (^{18}F) or ^{68}Ga PSMA in altering radiotherapy treatment volumes.
For this technical aim, we will determine the impact of advanced PET/CT on the two patient cohorts with respect to (a) target volumes, and (b) the planned dose delivered to surrounding normal structures (bladder, rectum, and penile bulb), and (c) toxicity profiles.

4.1 Study Endpoints:

Primary endpoint (on which power calculations are based) is:

2-year failure-free survival (Specific Aim 1)
see section 6.5 for definition of failure

Secondary endpoints:

(a) Radiotherapy Decision endpoints (Specific Aim 2)
   a. Decision changes regarding radiotherapy versus no radiotherapy
   b. Decision changes regarding whole-pelvis versus local fields
   c. Total decision changes

(b) Volume-definition and dosimetric endpoints (Specific Aim 3)

a. Prostate bed clinical target volume (CTV) – absolute volume
b. Prostate bed planning target volume (PTV) – absolute volume
c. PTV dosimetric endpoints (V100 and V110)
d. Rectum dosimetric endpoints (V40 and V65)
e. Bladder dosimetric endpoints (V40 and V65)

(c) Toxicity Endpoints – provider-reported (CTCAE v5.0 criteria) [see Appendix 4]
a. Rate of ≥ Grade 2 Acute GU toxicity
b. Rate of ≥ Grade 2 Acute GI toxicity
c. Rate of ≥ Grade 2 Late GU toxicity
d. Rate of ≥ Grade 2 Late GI toxicity

(d) Toxicity Endpoints – patient-reported on EPIC [see Appendix 2]
a. EPIC GU domain (Question 5) score [range 0-12]
b. EPIC GI domain (Question 6) score [range 0-12]
c. EPIC Sexual domain (Question 7) score [range 0-12]
d. EPIC total score [range 0-60]

5.0 PRELIMINARY STUDIES

Scientific Premise and Preliminary Data: Aims 1 and 2

Change in management

Through our ongoing trial**,** we have demonstrated that PET scanning with fluciclovine (^{18}F) results in a statistically significant benefit in altering treatment decisions to offer radiotherapy or not, and to treat pelvic nodes versus treating the prostate bed or not (1-3). In a published preliminary analysis on management decision change, thirty-four (81.0%) of 42 subjects had positive results on fluciclovine. Overall radiotherapy decisions were changed in 17 (40.5%) of 42. Mean PSA, original Gleason score, and prostatectomy-PET interval did not differ significantly between patients with and without radiotherapy decision changes.

Our goal is to expand this work, both to compare how molecular imaging in general (fluciclovine (^{18}F) or ^{68}Ga PSMA), as well as ^{68}Ga PSMA versus fluciclovine (^{18}F), results in more beneficial decision changes. Examples are provided below (Figs 1-3) of category changes with the use of fluciclovine (^{18}F) (3)**:**

(1) Aborting initial plan for salvage radiotherapy:



Fig 1: 72 yo M with pre-radiotherapy PSA of 3.46 ng/mL. The initial plan was radiotherapy to the prostate bed plus pelvic lymph nodes. The fluciclovine (^{18}F) scan showed uptake in the retro-peritoneal nodes (arrows). Radiotherapy was thus aborted; the patient received hormone therapy alone, representing a decision change from radiotherapy to no radiotherapy (i.e., from local to systemic therapy). *From reference (3).*

(2) Changing radiotherapy from prostate bed alone to pelvis:

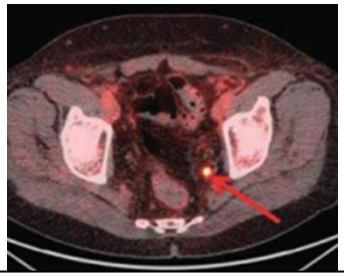


Fig 2: 66 yo M with pre-radiation PSA of 0.19 ng/mL. The initial plan was radiotherapy to prostate bed alone. The fluciclovine (^{18}F) scan showed uptake in the left internal iliac lymph node of 0.5 cm (arrow). Radiotherapy decision was changed to include pelvic lymph nodes, representing a decision change from XRT to the prostate bed alone to XRT to the pelvis [patient is NED post-treatment with available follow-up]. *From reference (3).*

(3) Changing radiotherapy from pelvis to prostate bed:



Fig 3: 60 yo M with pre-radiotherapy PSA of 1.1 ng/mL. The initial plan was radiotherapy to the pelvis + pelvic lymph nodes. The fluciclovine (^{18}F) scan showed uptake in the bilateral seminal vesicle remnants only (arrows), so only the prostate bed was treated. This case represents a decision change from XRT to the pelvis to radiotherapy to the prostate bed alone [patient is NED post-treatment with available follow-up]). *From reference (3).*

In the study population, as shown in Table 1, *(from reference (3))*, radiotherapy field decision was changed in 15 (35.7%) of 42 patients (2 patients did not undergo fluciclovine (^{18}F) PET). Eleven (73.3%) of 15 had fields changed from prostate bed only to both prostate bed and pelvis, while 4 (26.7%) of 15 had fields changed from both prostate bed and pelvis to prostate bed only. Changes in overall radiotherapy decision and field were statistically significant (P < 0.0001). Two (4.8%) of 42 had the decision for radiotherapy withdrawn due to positive extra-pelvic findings; however, the change in the decision to offer radiotherapy or not was not statistically significant (P = 0.15). While not yet formally analyzed, the decision change trends appear to continue with the full cohort of 72 fluciclovine (^{18}F) subjects to date.

Biochemical Control: The continued unmet clinical imaging need

While the primary endpoint of 3 year disease-free survival (DFS) in our ongoing trial has not yet been met, fluciclovine (^{18}F) has been found to be an important tool for radiotherapy decision making and for treatment volume definition. The final analysis (i.e., the impact of fluciclovine (^{18}F) on improving cancer control) is still pending and no formal interim analysis was planned at the onset of the trial. We have now updated our preliminary/unpublished analysis of the failures in both arms. Currently, the mean follow-up of the entire cohort (n=145) is approximately 19 months, and 95 subjects have reached a minimum follow-up of 24 months. There is an overall failure rate of approximately 31% (29/95) with available follow-up. To date, there are 3 more failures in the control (16 failures) versus the fluciclovine (^{18}F) arm (13 failures). This small apparent difference in failures requires validation with longer followup. Mean pre-radiotherapy PSA (3.93 vs 3.45 ng/mL), number of failure patients with adverse prognostic factors (all but 2 failures in each arm) and ultimate treatment fields used (whole pelvis treated in 8/16 failures in the control arm and 8/13 failures in the fluciclovine (^{18}F) arm) are generally similar in both failure groups [also, concurrent ADT was similar (8/16 in the control arm vs 6/13 in the fluciclovine (^{18}F) arm)]. Additionally, median/mean failure times (22.0 months/22.9 months vs 18.0 months/17.8 months) and failure types (12 PSA-only failures and 4 radiologic failures in the control arm, and 11 PSA-only failures and 2 radiologic failures in the fluciclovine (^{18}F) arm) are similar in both control and experimental groups. While the final disease-free survival (DFS) analysis (which will be done when the minimum follow-up of the last enrolled subject reaches 36 months) is pending and will shed light on the subset(s) of subjects for which fluciclovine (^{18}F) may reduce treatment failure, our updated preliminary analysis suggests:

(a) while fluciclovine (^{18}F) has clearly impacted treatment decisions and target volume design, and may in fact result in a small improvement in failure rate subject to validation with longer followup, further advances in imaging guided treatment planning are needed to significantly improve long-term cancer control,

(b) PSA failures often occur early (virtually all failures occurred before 25 months), suggesting a 2-year endpoint should be appropriate for this study population for future trials, and

(c) additional biological prognostic features [over standard PSA and surgical pathology risk features] are needed (i.e., tissue biomarkers in conjunction with imaging for prediction of salvage radiotherapy outcomes).

Table 1 Influence of FACBC on Radiotherapy Treatment and Treatment Field

Pre-Fluciclovine Decision	Post-Fluciclovine Decision			Decision Change, n (%)	P*
Radiotherapy Decision (n = 42)	Offer XRT	No XRT			
Offer XRT	40	2†		2 (4.8)	P = 0.15
No XRT	0	0		0 (0)	
Radiotherapy field (n = 40)‡	Prostate bed only	Prostate bed + pelvis			
Prostate bed only (n = 26)	15	11†		11 (27.5)	P < 0.0001
Prostate bed + pelvis (n = 14)	4†	10		4 (10.0)	
Overall XRT Decision (n = 42)	Prostate bed only	Prostate bed + pelvis	No XRT		
XRT to prostate bed only	15	11†	0	11 (26.2)	P < 0.0001
XRT to prostate bed + pelvis	4†	10	2†	6 (14.3)	
No XRT	0	0	0	0 (0)	

*Statistical significance of overall decision changes calculated using Clopper-Pearson (exact) binomial method.
†Decision Change.
‡Two patients excluded as the final decision was not to give radiotherapy.
XRT indicates radiotherapy.

Thus, our preliminary data for biochemical control, though still in progress, suggests an overall 31% failure rate in the study population, with a potential small advantage for fluciclovine (^{18}F) versus conventional imaging guidance. The motivation and basis for using ^{68}Ga PSMA is more fully described in Section A.1.4 below and relates to a hypothesized greater sensitivity and resultant **potential for further**

improvement in biochemical control with the use of ^{68}Ga PSMA, especially at lower PSA levels which are becoming increasingly relevant to current therapy.

Scientific Premise and preliminary evidence in regards to boost therapy

Molecular imaging to guide radiotherapy dose escalation is an exciting recent development (9). In the prostate cancer arena there are several publications that explore the feasibility and safety of dose escalation to areas of uptake on imaging, both in the intact prostate cancer setting and in the post-prostatectomy setting (9, 74-79). While mature prostate cancer control outcomes series are still pending, the impact of molecular imaging-guided radiotherapy dose escalation at other primary sites including head and neck cancer (80-82), non-small cell lung cancer (83-85), and rectal cancer (86) suggest that cancer control outcomes can be improved upon with this approach. In our current proposal we will be among the first to study this important concept in the post-prostatectomy disease space in a formal clinical trial.

Scientific premise and preliminary data in regards to PSMA radiotracers

Newer generation PSMA directed PET and SPECT radiotracers have generated enthusiasm in the prostate cancer imaging community. The advantage of these radiotracers includes direction against the external epitope of the PSMA glycoprotein which results in a high affinity for prostate carcinoma. Though various motifs have been explored and are undergoing evaluation in clinical trials (71, 87), Gallium-68 based small molecule (low molecular weight) PET radiotracers, specifically ^{68}Ga-PSMA-HBED-CC (^{68}Ga-DKFZ-PSMA-11), have achieved the widest acceptance and utility, especially in Europe. In a recent retrospective study of 319 patients with suspected recurrent prostate cancer, Afshar-Oromieh reported a per patient detection rate of 82.8% with high lesion to background ratio (88). Most importantly, a high detection rate even at very low PSA values has been observed, and that there is superiority to ^{18}F-Fluoromethylcholine and ^{11}C-Choline PET (89, 90). It is this higher sensitivity at lower PSA levels which could provide better discrimination of patients who would benefit from salvage radiotherapy especially at lower PSA trigger points as is currently becoming standard practice.

Fluciclovine (^{18}F) has also demonstrated superiority to ^{11}C-Choline in a 100 intra-patient clinical trial at the University of Bologna, with potential advantage at lower PSA levels and with smaller lymph nodes (91, 92).

Though a formal intra-patient comparison has not been performed for a newer generation PSMA agent and fluciclovine, **recent non-controlled case studies suggest a higher sensitivity and ability to localize disease for ^{68}Ga-PSMA, while also acknowledging a potential advantage for fluciclovine in the prostate bed** due to little to no bladder activity with fluciclovine compared to much higher bladder activity with ^{68}Ga-PSMA (93, 94).

A preliminary retrospective study of ^{68}Ga-PSMA in a recurrence population has shown a change in radiotherapy management in 60.5% of patients (95). Though this retrospective study is not directly comparable to our prospective fluciclovine trial, we have reported, a 40.5% change in radiotherapy decision in a recurrence population (3). In addition, a report from a non-controlled, non-randomized trial without boost or toxicity analysis in patients who underwent ^{68}Ga-PSMA PET to plan salvage radiotherapy after biochemical failure post-prostatectomy (median PSA 0.23 ng/ml) noted 62% scan positivity and 72% therapy response with median followup of 10.5 months (96). Yet, another retrospective non-controlled or randomized analysis of impact of ^{68}Ga-PSMA PET on salvage post-prostatectomy planning (median PSA 0.48 ng/ml) reported 49% positivity rate in a cohort with PSA of <1 ng/ml with 19% disease outside the standard field (97). This latter report compares unfavorably with our published 72% positivity rate in patients with PSA<1 ng/ml in a cohort with median PSA of 0.55 ng/ml and 31.0% disease detected outside the planned field (if analyzed similarly to the above paper) (3). Thus, the literature suggests higher sensitivity for disease detection with ^{68}Ga-PSMA versus fluciclovine PET, but the data seems discrepant regarding a clear advantage of ^{68}Ga-PSMA versus fluciclovine PET in guiding salvage radiotherapy decisions to achieve durable PSA control.

While ^{68}Ga-PSMA-HBED-CC has demonstrated high affinity for the extracellular PSMA receptor and is internalized into the prostate cancer cell, which are advantages with imaging, these PSMA radiotracers exhibit high urinary excretion and bladder activity which can interfere in pelvic lesion detection (98). Both false positive and false negative imaging findings have been reported (99, 100). On the other hand,

despite potentially lower inherent affinity for prostate cancer cells, fluciclovine has little to no bladder excretion, a clear advantage for pelvic imaging, and also may have theoretically superior performance with dedifferentiated disease and loss of the PSMA receptor (101).

Therefore, each radiotracer may have unique advantages and disadvantages. Though our review of the available literature suggests that there is higher affinity and ability to localize distant disease with PSMA, this needs to be proven in a controlled and randomized trial with respect to leveraging potential increased sensitivity to achieve biochemical control. **Thus, we believe there is sufficient scientific premise that the next logical choice is to include <u>both</u> imaging techniques within the context of a well-designed trial with rigorous endpoints.**

<u>Scientific basis and preliminary data with respect to biomarkers</u>

We have defined a 24-gene signature (Sig24) that accurately predicts recurrence, metastasis, and mortality (102, 103). The Sig24 signature was developed using RNAseq of an international multi-center study of 97 patients (103) and validated on an external dataset from Sloan-Kettering Cancer Center (n=140) (104). We also validated this RNA signature on multiple cohorts from the Cleveland Clinic (n=182) and Mayo Clinic (545 and 235 patients, respectively) showing that patients with high-risk scores have a 3.6 fold increase in metastasis risk and 6.5 fold increase in mortality risk in multivariable analyses with a time-dependent AUC of 0.74.

Another 22-gene signature (Decipher), developed by GenomeDx (105-107), has shown similar predictive value for metastasis. In a blinded independent validation study (106) using a case-cohort design from the Mayo Clinic Radical Prostatectomy tumor registry (235 patients) with a median follow-up of 8.09 years, the Decipher signature was successfully validated with an AUC of 0.79 (95% CI 0.68-0.87) for a primary endpoint of clinical metastasis. The Decipher signature is actually generated using an Affymetrix ST GeneChip, and thus provides data genome-wide, and the ability to compute both signatures. In fact, GenomeDx GRIDv2 can generate the predictions of 18 prognostic signatures in prostate cancer using this platform.

We hypothesize that combining positive novel RNA signatures (Sig24 and Decipher) from tissue obtained from the prior prostatectomy together with imaging obtained at biochemical failure will enhance our ability to predict success or failure of salvage therapy over either method alone and standard risk stratification. This approach may result in improved management of patients with recurrent disease due to optimized selection.

Scientific Premise and Preliminary Data Aim 3

We have demonstrated that with the use of fluciclovine (^{18}F) PET in the patient population of post-prostatectomy with rising PSA, there are significant changes in clinical target volumes and planning target volumes (1). Importantly, we have published on the utilization of novel aspects of multimodality image fusion to individualize treatment volumes, and have developed a multi-modality image fusion/registration technique/workflow that can be used for a wide range of radiotracers (2).

First, we have documented a novel registration workflow (2) as demonstrated in figure 4.

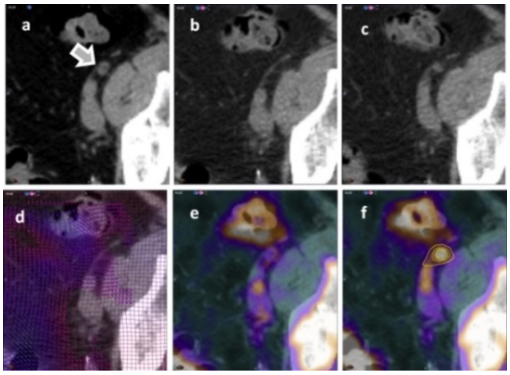


Fig 4: Registration workflow example for (a) a lymph node identified on CT (arrow), (b) rigid registration, (c) deformable registration, (d) displacement field generation, (e) PET/CT rigid registration, and (f) PET/CT deformable registration with iso-SUV levels generated for exporting to the radiotherapy treatment planning system. ***From reference (2).***

Second, we have demonstrated (Figures 5 and 6; Table 2) the impact of PET/CT integration with standard treatment planning (1) (also, the larger PET/CT directed treatment volumes did not increase acute toxicity):

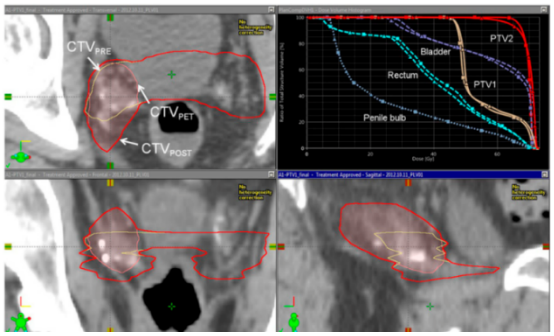


Fig 5: In the adjacent figure, the use of FACBC PET/CT for target design is depicted. For this 69 yo M who had pT3a, GS 7, margin+ disease and rising PSA to 0.17, working plan was treatment to prostate bed. CTV_{PET} (orange) was used to modify CTV_{PRE} (yellow) to generate a CTV_{POST} (red) that is used for treatment planning, with the corresponding PRE and POST dose volume histograms on the targets and normal structures displayed [demonstrating minimal impact on rectum and bladder dose]. *From reference (1).*

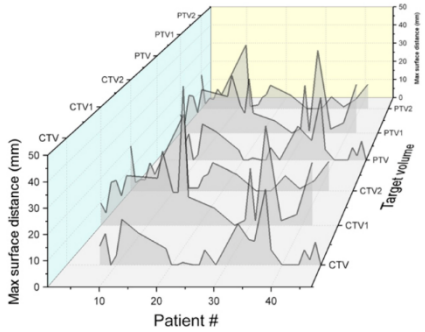


Fig 6: In the adjacent figure, a waterfall plot shows the impact of maximum surface distance over the entire dataset, and shows that for a large proportion (approximately one-third) of patients, there were major changes in target volumes. *From reference (1).*

TABLE 2
Target Volumes and Volumes of Organs at Risk in Experimental Arm Before and After ^{18}F-Fluciclovine PET Registration

Parameter	CTV	PTV	CTV1	PTV1	CTV2	PTV2
Target volume (cm^3)						
Preregistration	137.7 ± 49.0	334.5 ± 79.4	472.8 ± 127.0	1114.8 ± 230.8	129.4 ± 42.9	320.8 ± 77.8
Postregistration	139.6 ± 49.6	339.2 ± 81.4	487.2 ± 132.6	1147.2 ± 237.9	131.4 ± 42.4	324.6 ± 75.5
P	0.034	0.009	0.007	0.002	0.027	0.147
Dice similarity index	0.99467 ± 0.01164	0.99279 ± 0.01099	0.98402 ± 0.03041	0.98673 ± 0.01588	0.99735 ± 0.02878	0.98118 ± 0.03793
Maximum surface distance (mm)	6.02 (0–17.99)	5.94 (0–17.27)	16.51 (0–31.33)	14.33 (0–29.23)	7.25 (0–34.44)	6.99 (0–34.26)
Vector centroid						
Mean difference (*x*, *y*, *z*)	0.00, 0.00, 1.56	0.02, −0.05, 2.50	−0.48, 0.22, 0.43	−0.48, 0.35, 0.99	0.25, 0.44, −1.04	−0.25, 0.19, 0.69
Overall magnitude (mm)	3.69	3.71	2.84	2.90	2.73	2.74
Organs-at-risk volume (cm^3)						
Organ	Rectum, V40	Rectum, V65	Bladder, V40	Bladder, V65	Penile bulb, V40	Penile bulb, V65
Preregistration	45.8 ± 10.2	17.8 ± 8.1	61.7 ± 19.5	33.3 ± 16.0	44.9 ± 30.4	21.6 ± 24.1
Postregistration	45.9 ± 11.9	18.1 ± 8.1	61.7 ± 18.9	33.8 ± 16.8	55.9 ± 34.4	32.6 ± 30.4
P	0.774	0.548	0.940	0.238	0.001	0.002

V40 = volume receiving 40 Gy; V65 = volume receiving 65 Gy.
Number of patients is 46. All *P* values were obtained using 2-tailed paired *t* test. Data in parentheses are range.

Table 2 shows the impact of FACBC PET/CT on target volume differences: all clinical and planning target volumes for the prostate bed if treated alone (CTV/PTV) or [if the lymph nodes were treated), the whole pelvis (CTV1/PTV1) and prostate bed boost (CTV2/PTV2) were significantly different with the integration of FACBC PET volumes (with the exception of PTV2). Analysis of organs at risk (OAR's) revealed no significant difference on bladder and dose endpoints [although penile bulb endpoints were higher in the FACBC arm. *From reference (1).*

We expect the above methodology developed for fluciclovine (^{18}F) will be readily applicable to the integration of ^{68}Ga-PSMA PET/CT, for the aims of the current proposal with respect to determination of impact of PET/CT volumes on treatment planning and on toxicity endpoints.

6.0 Study design and methods

We will undertake a clinical trial of 140 patients post-prostatectomy with detectable PSA levels. Patients may or may not have biopsy proof of local recurrence, but will be under active consideration for salvage radiotherapy based on PSA and other clinical criteria.

Patients will be stratified as follows:

- Adverse Pathological Factor (Margin Status, Extra-capsular Extension, or Seminal Vesical Invasion, pathological node positive) (yes vs no)
- PSA level (pre-radiation): (≤ 1.0 ng/mL vs higher)
- Intended use of Hormone Therapy (yes vs no)

Patients will be randomized to:

Arm A: a conventional molecular imaging group whose treatment decisions will be made based on fluciclovine (FACBC) PET-CT scan; **or**

Arm B: an experimental molecular imaging group in which Ga-PSMA is used to guide radiotherapy decisions and radiotherapy treatment volumes

For patients treated in both arms, we will compare initial (pre-PET) versus final (post-PET) treatment decisions regarding (a) the decision of whether to offer post-prostatectomy XRT, (b) the decision of whether to treat the pelvic lymph nodes in addition to the prostate bed.

This will be accomplished via an intention to treat form that will be filled out prospectively by each treating radiation oncologist, before and after PET-CT

Decisions on (a) whether to offer radiotherapy and (b) radiotherapy volume to be determined are charted

Then either fluciclovine or Ga-PSMA PET-CT scan is done, with radiotherapy decisions as follows:

If extrapelvic uptake:	no radiotherapy
If pelvic uptake or pN1:	radiotherapy to prostate bed + pelvic lymph nodes + boost
If prostate-bed only uptake:	radiotherapy to prostate bed only + boost
If no PET uptake:	radiotherapy to prostate bed only (no boost)

Radiotherapy plan designed first without PET information.
Then PET/planning CT fusion done to determine final treatment plan.

Note that in both arms A and B the use and duration of hormone therapy with radiotherapy is at the discretion of the treating physician.

Follow-up
Each patient (Arms A and B) will be followed for a minimum of two years with PSA levels every 6 months and other clinical parameters to both measure presence and time to PSA failure, as well as manifestation of clinical failure as defined by macroscopic identifiable disease. Outcomes will be compared between groups in aggregate and stratified by PSA level. The endpoint will be failure-free survival after salvage radiotherapy - please see section 6.5 below for failure definition.

6.1 Radiotracer Radiolabeling

Fluciclovine (^{18}F): Since fluciclovine (^{18}F) PET (Axumin) is FDA approved and reimbursed for this clinical indication, **production will take place at a licensed PETNET Solutions radiopharmacy** (located on the Emory Campus). Though Dr. Schuster does hold an IND for fluciclovine (^{18}F) which cross references the commercial product, an IND is not necessary for this trial since off-label research is not being undertaken with this FDA approved and CMS reimbursed radiotracer.

Note that the study will be charged to third party payers and not to the grant. An approximate 85% third party approval rate has been our experience to date and we also anticipate that reimbursement will be even more robust in the next year as fluciclovine has now been included in the NCCN Guidelines for recurrent prostate cancer.

To reiterate, the fluciclovine PET will be a standard of care clinical scan and will not be synthesized by our research radiopharmacy at CSI. In addition, studies performed outside the Emory system will not be accepted for this trial to ensure data integrity.

Human dosimetry data for fluciclovine from FDA package insert: The (radiation absorbed) effective dose resulting from the administration of the recommended activity of 370 MBq (10 mCi) of fluciclovine is 8 mSv (22 microSv/MBq). For an administered activity of 370 MBq (10 mCi), the highest-magnitude radiation doses are delivered to the pancreas, cardiac wall, and uterine wall: 38 mGy, 19 mGy, and 17 mGy, respectively.

^{68}Ga-PSMA-HBED-CC (^{68}Ga-DKFZ-PSMA-11): As of 10/17/22, ^{68}Ga-PSMA-11 (Illucix) will be produced by a commercial radiopharmacy such as Cardinal. Since ^{68}Ga-PSMA-11 (Illucix) is FDA approved for this clinical indication, **production will take place at a licensed radiopharmacy**. Though Dr. Schuster does hold an IND for ^{68}Ga-PSMA-11 which cross references the commercial product, an IND is not necessary for this trial since off-label research is not being undertaken with this FDA approved radiotracer.

Human dosimetry data for Ga-PSMA from Joint EANM and SNMMI Procedure Guideline for Prostate Cancer Imaging: Version 1.0 (85). Based on the available studies, the coefficient for effective dose from 68Ga-PSMA averages is 2.0 × 10−2 mSv/MBq, resulting in an average effective radiation dose of 3 mSv for an administered activity of 150 MBq. For a typical dose of 5 mCi (185 MBq) that we would be administering, the effective dose equivalent would be 3.7 mSv. The organs with the highest dose are urinary bladder wall (0.13-0.173 mSv/MBq) and kidney (0.122-0.262 mSv/MBq).

6. 2. PET Acquisition

Fluciclovine PET-CT imaging: PET-CT images will be acquired on a state-of-the-art PET scanner such as for example the GE Discovery 690 Elite TOF PET-CT (or other equivalent) scanner at Emory University Hospital or acceptable scanners at ESJH or EUHM. We will use our well-established methodology similar to that used for clinical scanning, including NPO except water and medications 4 hours prior to arrival. Approximately 16 oz of oral contrast will be administered on arrival unless contraindicated, (mixture of 13 ml Omnipaque with 16 oz water; or equivalent). No IV contrast will be given. The patient will be advised to refrain from voiding for 30-60 min before radiotracer injection per routine unless contraindicated. Imaging will commence from upper thighs to skull base 4 minutes after IV injection of approximately 10 mCi (8-12 mCi) fluciclovine at 3.5 minutes per bed position (86). The study

is typically carried out over approximately 30 minutes from radiotracer injection to completion of imaging. Images will be reconstructed per PET manufacturer recommendations augmenting by input from our physicists.

^{68}Ga-PSMA PET-CT imaging: PET-CT images will be acquired on a state of the art PET scanner such as those described above using accepted protocol. Patients are not required to be NPO and in fact oral intake of 500 ml water 2 hours before imaging will be advised. Upon arrival, 16 oz of oral contrast will be administered unless contraindicated, (mixture of 13 ml Omnipaque with 16 oz water; or equivalent). No IV contrast will be given. Imaging will commence from upper thighs to skull base after IV injection of approximately 5 mCi (3-7 mCi) ^{68}Ga-PSMA followed by 20 mg IV furosemide (unless contraindicated) as adapted from joint European Association of Nuclear Medicine and Society of Nuclear Medicine and Molecular Imaging (EANM SNMMI) procedure guidelines which also include dosimetry data (85). The study is typically carried out over approximately 90 minutes from radiotracer injection to completion of imaging (60 minute uptake followed by 30 minute imaging). Briefly, an approximately 5 mci (3-7 mCi) dose will be administered IV, followed by 20 mg IV furosemide (unless contraindicated). Then after an uptake period of approximately 60 minutes, the patient will be encouraged to void. A PET-CT will then be completed from upper thighs to skull base at approximately 5 minutes per bed position. We will acquire the first 5-10 patients in list mode and work with our physicist to optimize acquisition times and reconstruction. Final acquisition time will likely be from 3 to 5 minutes per bed position. Images will be reconstructed per PET manufacturer recommendations augmenting by input from our physicists.

6.2.1 FDA Reporting and Laboratory Requirements

Any such conditions for post-marketing reporting as set forth by the FDA will be strictly adhered to.

6.3 Patient Assessment: Image Analysis

Methods.
Both fluciclovine (^{18}F) and ^{68}Ga-PSMA studies will be interpreted independently by two nuclear medicine specialists (to assess inter-observer variability) on a MimVista or similar workstation, with access to prior history but blinded to other imaging. Disagreement and/or equivocal findings will be resolved via consensus which may include review of prior imaging and other history. All studies will be evaluated for well-established positivity criteria based on our experience as well as that adapted from the literature (6, 86-88). Non-physiologic uptake over background in a typical location for prostate cancer metastasis will be considered abnormal, with awareness of sites of typical physiologic activity and physiologic variants. Confidence in interpretation for disease within the prostate bed and outside the bed will be recorded with the following scale on a per patient and lesion basis: 1-defiinitvely negative; 2 -probably negative; 3 - indeterminate; 4 - probably positive; 5 – definitively positive.

Visual analysis will aided by quantitative criteria. SUV (mean, maximum, peak),and total lesion activity of each focus of abnormal uptake will be recorded with a volume of interest tool. SUV max and mean of relevant background structures such as parotid, liver, and blood pool for Ga-PSMA and liver, marrow at L3, and blood pool for fluciclovine will also be recorded. These indices will be used to correlate semi-quantitative activity with PSA free survival, outcome, as well as mRNA signatures in those patients in whom tissue from the original prostatectomy was available. Thus, while qualitative interpretation will be

utilized to guide radiotherapy decisions, semi-quantitative indices will also be used to correlate outcomes from within each group, and in combination with available mRNA signatures, to explore prediction of response to salvage therapy using multivariate analyses.

6.4 Correlation of Histopathology with Imaging:

The object of this study is not to validate these radiotracers with histology as this has already been accomplished by others. Yet, every effort will be made to histologically confirm all fluciclovine (^{18}F) or ^{68}Ga-PSMA positive nodes or other foci if the findings imply the patient has systemic disease, such as extrapelvic nodes or bone, or if results are discordant from clinical impression. Otherwise, positive uptake will be treated as a true positive, unless it can be shown that the focus in question was biopsied and was definitively a false positive or stability demonstrated on prior imaging in case of suspected physiologic variants. We will discuss this eventuality with the patient as part of the consent process. Thus, we may also incidentally have data as to the specificity of each radiotracer, but this will not be the primary focus.

6.5 Patient follow-up

This randomized trial will utilize *advanced molecular imaging as a* vehicle to (a) permit the selection of patients with high PSA levels who would not ordinarily be treated with radiotherapy, (b) improve biochemical control in post-prostatectomy patients treated with radiotherapy, and (c) result potentially in different rates of toxicity than those treated with the current conventional approach. Using a standard definition of failure [serum PSA value of 0.2ng/mL or more above the post-radiotherapy nadir followed by another higher value, a continued rise in the serum PSA despite SRT, initiation of systemic therapy after completion of SRT, or clinical progression] (32), Kaplan-Meier Survival curves will be generated for both Arms A and B and compared. The primary endpoint will be 2-year disease free survival (DFS) survival using this above definition. This follow-up endpoint is appropriate for the current design given our preliminary analysis of failure events above on our current ongoing trial. Follow-up after the 5-year period of the grant, particularly for those patients enrolled in year 4, can be completed by a no-cost grant extension for follow-up only and/or after securing additional funding.

7.0 Participant Selection and Treatment

7.1 Inclusion Criteria

- Adenocarcinoma of the prostate, post radical-prostatectomy
- Detectable PSA
- ECOG/Zubrod Performance Status of 0-2
- No definitive findings for skeletal metastasis on technetium 99-m MDP or F-18 PET bone scan
- No definitive findings of systemic (extrapelvic) metastasis on CT and/or MR scan pelvis (and, if performed, abdomen).
- Willingness to undergo pelvic radiotherapy.

7.2 Exclusion Criteria

- Contraindications to radiotherapy (including active inflammatory bowel disease or prior pelvic XRT)
- Inability to undergo fluciclovine or Ga-PSMA PET-CT
- Age under 18
- Definitive findings of systemic metastasis on conventional imaging or biopsy
- Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years

- Severe acute co-morbidity, defined as follows:
    - Unstable angina and/or congestive heart failure requiring hospitalization in the last 3 months
    - Transmural myocardial infarction within the last 6 months
    - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
    - Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
    - Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immunocompromised patients

7.3 Pre-treatment Evaluations & Registration Procedures

7.3.1 Pre-treatment evaluations (timeline of evaluations assessed by PI):

History and Physical (i.e., Symptom-directed examination)
ECOG/Zubrod Performance Status (see Appendix 1)
Pathology report (from radical prostatectomy)
Bone scan report
CT or MRI pelvis report (and, if performed, abdomen report)
PSA
If ADT intended: Serum Testosterone; Serum AST or ALT
EPIC sheet (see Appendix 2)
Pre-PET-CT Radiotherapy Decision / Attestation Sheet (see Appendix 3)

7.3.2 Registration/Randomization Process

Randomization Process will be done only after all pre-treatment evaluations have been completed and after the decisions on whether to offer radiotherapy (and general target volume), as attested on the pre-PET-CT Radiotherapy Decision /Attestation Sheet the providing physician (see Appendix 3).

Patients will be stratified as follows:

- Adverse Pathological Factor (Margin Status, Extra-capsular Extension, or Seminal Vesical Invasion, pathological node positive) (yes vs no)
- PSA level (pre-radiation): (≤ 1.0 ng/mL vs > 1.0 ng/mL)
- Intended use of Hormone Therapy (yes vs no)

Randomization assignment will be performed by the study statistician through a standard random number generator. The subject will be assigned randomly to one of the two arms:

Arm A: Fluciclovine (FACBC) arm **or Arm B**: Ga-PSMA arm

General treatment methodology of each of these arms is described in section 6.0 above.

After randomization, information as to the enrollment arm will be shared with the PI, treating physician, and subject (ie, the treatment arm will not be masked).

Within 2 months of randomization, subjects will receive a PET-CT (fluciclovine [arm A] or Ga-PSMA [arm B]) scan. Treatment (radiotherapy and/or hormones) will begin within 1 month from the PET-CT (FLUCICLOVINE or Ga-PSMA) scan date.

7.4 PET imaging details

For subjects randomized to arm A, the fluciclovine PET will be performed per standard of clinical care at either EUH, EUHM, or ESJH. Note that the study will be charged to third party payers and not routinely to the grant. An approximate 85% third party approval rate has been our experience to date and we also anticipate that reimbursement will be even more robust in the next year as fluciclovine has now been included in the NCCN Guidelines for recurrent prostate cancer.

For subjects randomized to arm B, the Ga-PSMA scan will be done at EUH. Patients will be responsible for their own travel. The cost of the Ga-PSMA PET study will also be paid from the grant and will not be billed to insurance.

All other diagnostic imaging costs as well as costs of biopsies if any, radiotherapy if any, and systemic therapy if any will be billed to insurance or paid out of pocket by the patient.

A small travel allowance will be provided for completion of the PET scan in both arms.

7.5 Radiation Therapy Details

7.5.1 Dose Specifications

Radiotherapy dose will be specified to the Planning Target Volume (PTV), as described below. For the treatment methods outlined for prostate bed RT (IMRT), ≥ 95% of the PTV should receive the prescribed dose. The total dose to the prostate bed for all treatment arms is 64.8-70.2 Gy at 1.8 Gy per fraction, with a boost to 70.2 to 76.0 Gy to areas of PET-CT uptake, with intent of reducing final dose to maximum allowable to meet normal tissue constraints

7.5.2 Technical Factors [Equipment, energies]
Megavoltage equipment is required with effective photon energies ≥ 6 MV. IMRT is required.

7.5.3 Localization, Simulation, and Immobilization

A urethrogram or MRI is recommended, but not required, to establish the most inferior portion of the prostate bed. Use of contrast, other than for the urethrogram, is discouraged. The placement of contrast in the rectum may cause the rectum to appear more anterior than it will be during treatment. Simulation should be with the rectum as empty as possible (an enema 1-2 hours prior to simulation is encouraged) and with a moderately full bladder (the patient should not be uncomfortable at simulation and probably will have more difficulty maintaining a full bladder during treatment). An overly distended rectum can introduce a systematic positioning error that may increase the probability of missing the CTV.

Immobilization of the hips and feet using a cradle should be considered.

Contrast may be used for simulation but can distort the anatomy slightly and so is not recommended. The bladder should be reasonably full for simulation, keeping in mind that patients may not be able to maintain as full a bladder during radiotherapy. Having a somewhat full bladder at simulation ensures that the CTV will be of maximal dimensions.

A treatment planning CT scan will be required to define the clinical and planning target volumes, and the critical normal structures. The treatment planning CT will be acquired with the patient set up in the same position as for daily treatments. Each patient will be positioned in the supine position. Prone positioning for treatment is not permitted. Rectal balloons for planning and treatment are not permitted. The CT scan of the pelvis should start at or above the iliac crest down to below the perineum (below the ischial tuberosities). All tissues to be irradiated must be included in the CT scan. CT scan thickness should be ≤ 0.3 cm through the region that contains the target volumes. The regions above and below the target volume region may be scanned with slice thickness ≤ 1.0 cm.

7.5.4 Treatment Planning/Target Volumes

7.5.4.1 Prostate Bed Planning

7.5.4.1.1 – CTV – general

The seminal vesicles or remnants thereof, if identified on CT or MRI as being present, will receive the full dose. The immediate periprostatic bed surgical clips should receive the full dose. The CTV will extend from the top of the penile bulb inferiorly, or 1.5 cm below the urethrogram peak if done, to just above the pubic symphysis superiorly (at least for the anterior-most portion of the bladder). Laterally, the CTV will extend from the medial edge of one obturator internus muscle to the other. Anteriorly, the CTV will include the entire bladder neck until above the pubic symphysis, where a gradual reduction off of the anterior bladder is made. Superiorly, above the pubic symphysis, at least the posterior 2 cm of bladder should be included in the CTV, as well as the area between the bladder and rectum, to the anterior rectal wall. The CTV should extend superiorly to cover any clips in the seminal vesicle bed and the seminal vesicle remnants if present and should extend at least 2 cm above the pubic symphysis. Posteriorly, the CTV is defined by the anterior-most aspects of the anus-rectum. The CTV may be increased (not decreased) beyond these limits based on pre-prostatectomy imaging information.

A consensus definition of the prostate bed and an anatomically-based description should be considered in defining the CTV. There has been considerable variability in how the prostate bed has been defined in the past. Although consensus definitions are not based on clinical outcome, they are extremely valuable in making the transition from conventional to conformal volumes. The consensus definition is not much different than the CTV originally described above, but subtle differences are evident and should be considered. Either CTV definition will be accepted in this clinical trial.

1) Superiorly: The prostatic fossa CTV (PF-CTV) should extend superiorly from the level of the caudal vas deferens remnant. In some cases, the vas deferens remnant may be difficult to visualize. In the absence of gross disease or seminal vesicle remnants, the superior limit of the CTV should extend at least 2 cm and need not extend more than 3-4 cm above the level of the pubic symphysis. The consensus definition calls for “inclusion of the seminal vesicle remnants, if present, in the CTV if there is pathologic evidence of their involvement. However, inclusion of any seminal vesicle remnants seen is recommended.

2) Inferiorly: The PF-CTV should extend inferiorly to > 8-12 mm inferior to vesicourethral anastomosis (VUA). With axial CT imaging, the VUA can often be seen in the retropubic region as one slice below the most inferior urine-containing image (the bladder must be modestly full). Magnetic resonance (MR) imaging defines this landmark more clearly with the hyperintense urine signal on T2 images. Inferiorly, the border of the CTV should be at least 8-12 mm below the VUA. A sagittal reconstruction facilitates identification of the position of the VUA and the inferior border of the CTV below it. If visualization of the VUA is problematic due to image quality or surgical clip artifacts, the inferior limit of the CTV can extend

to a level just above the penile bulb (same border as described above). It should be noted that there was considerable discussion about this definition versus extending the inferior border of the CTV to just above the penile bulb; both definitions were deemed acceptable.

3) Anteriorly: Below the superior border of the pubic symphysis, the anterior border is at the posterior aspect of the pubis. The CTV extends posteriorly to the rectum where it may be concave at the level of the VUA. At this level the lateral border extends to the levator ani. Above the pubic symphysis the anterior border should encompass **the posterior 1-2 cm of the bladder wall at the minimum** and posteriorly it is bounded by the mesorectal fascia. At this level the lateral border is the sacro-recto-genito-pubic fascia. This is not well-defined in textbooks. If in question, the lateral border should extend to the obturator internus muscle.

4) Posteriorly: The CTV extends posteriorly to the anterior rectal wall, but may be somewhat concave around the anterior-lateral aspect of the rectum to adequately encompass the prostate bed.

7.5.4.1.2 CTV – Arm A

For patients on Arm A, the CTV as defined in 7.5.4.1.1 above will be contoured and submitted to the Emory Radiation Oncology Department. The Radiation Oncology PI (Dr. Jani) will supervise registration of the fluciclovine scan with the planning CT scan for definition of the prostate bed CTV, which will be defined as the union of the CTV [in section 7.5.4.1.1 above] with the prostate bed uptake seen on the fluciclovine scan.

7.5.4.1.3 CTV – Arm B

For patients on Arm B, the CTV as defined in 7.5.4.1.1 above will be contoured and submitted to the Emory Radiation Oncology Department. The Radiation Oncology PI (Dr. Jani) will supervise registration of the Ga-PSMA scan with the planning CT scan for definition of the prostate bed CTV, which will be defined as the union of the CTV [in section 7.5.4.1.1 above] with the prostate bed uptake seen on the Ga-PSMA scan.

7.5.4.1.4 PTV – Arm A or Arm B

The PTV margins should be 0.8 cm in all dimensions. A reduction of the PTV margin from 0.8 cm to ≥ 0.6 cm to minimize rectal exposure will be considered a variation acceptable. A posterior margin of < 0.6 cm will be considered an unacceptable deviation.

Care should be taken to conform the prescribed dose as closely to the PTV as possible, so as to avoid including the entire width of the rectum in the posterior blocked margin at the bladder neck-rectum interface. The planned dose between 64.8-70.2 Gy (with a boost to 70.2 to 76.0 Gy to areas of PET-CT uptake) will be declared after the patient is planned and all dosimetric parameters finalized.

7.5.4.1.5 Normal Tissue Definitions – Arm A or Arm B

Normal tissues will be outlined as solid structures, including the rectum, bladder and femoral heads. The penile bulb will be outlined as a reference structure. No constraints will be placed on the penile bulb, but doses will be recorded. The rectum will be outlined from the anterior flexion of the rectosigmoid superiorly to the ischial tuberosities inferiorly. The entire bladder should be outlined down to the anastomosis. The DVH calculations will include doses to the entire bladder and the bladder minus the CTV (Bladder - CTV).The femoral heads should be outlined down to the region between the greater and

lesser trochanters. The planning parameters outlined below for IMRT should be used as a guide; formal 3D-CRT normal tissue prostate bed constraints have not been the standard in the past and are not specified here. It should be possible to come close to achieving the constraints outlined for IMRT, at least within the variation range.

7.5.4.1.6 Planning Parameters – Arm A or Arm B

The plan will be deemed acceptable under the following conditions.

PTV: The dose marker levels for bladder and rectum have been modeled after prior studies in men treated definitively with IMRT for prostate cancer. At least 95% of the PTV should receive the prescribed dose; a variation acceptable will be noted if < 95% to 90% of the PTV receives the prescribed dose, and a deviation unacceptable will be noted if < 90% of the PTV receives the prescribed dose. The maximum dose within the PTV, above the prescribed dose, will be 15%; an acceptable variation will be > 15% to ≤ 20% and an unacceptable deviation will be > 20%.

Rectum: Less than or equal to 35% and 55% of the rectum should receive ≥ 65 Gy and ≥ 40 Gy, respectively. An acceptable variation will be noted if up to an additional 10% of the rectal volume at either cutpoint receives above the target doses specified. The inclusion of rectal volumes beyond these constraints will be considered a secondary acceptable variation and the extent of the variation should be recorded. In most patients, these constraints may be easily met and every attempt should be made to achieve the best dose distribution possible. The constraints will be harder to achieve in patients receiving pelvic irradiation.

Bladder: Less than or equal to 50% and 70% of the **bladder minus prostate bed CTV (Bladder - CTV)** should receive ≥ 65 Gy and ≥ 40 Gy, respectively. The criteria for the bladder are relaxed because the dosimetric relationship of volume exposed to the specified marker doses is much less clear and the bladder neck is included in the CTV. Note that the DVH for the entire bladder should be recorded, but the bladder - CTV is the volume that should be used for the calculations described here. An acceptable primary variation will be noted if up to an additional 7.5% of the bladder volume receives above the target doses specified. The inclusion of bladder volumes beyond these constraints will be considered an acceptable secondary protocol variation; it will not be considered a protocol violation. In some patients, the bladder will be relatively empty and the majority will be in the PTV.

Femoral Heads: Less than or equal to 10% of each femoral head should receive ≥ 50 Gy. A variation will be noted if up to an additional 5.0% of either femoral head receives > 50 Gy.

Penile Bulb: The penile bulb will be outlined as a reference structure. No constraints will be placed on the penile bulb, but doses will be recorded.

Small Bowel: See PLNRT section below.

Use of Cone Beam CT and Plan Adjustment: There may be cases in which the target and surrounding normal tissues are found not to be reproducible relative to the simulation CT and consequent plan. Replanning will invalidate the dosimetry and is considered a deviation. If all attempts to reproduce bladder and rectal filling by coaching the patient do not work and replanning is thought to be necessary, the patient should be replanned in the same supine position with the same target volumes as specified per the randomization. The patient will remain on the trial, despite the deviation.

7.5.4.2 Pelvic Lymph Node Radiotherapy (PLNRT) planning

7.5.4.2.1 Pelvic Lymph Node Radiotherapy (PLNRT) planning – General

For patients receiving PLNRT, the prostate bed and pelvic lymph nodes (CTV1/PTV1) will receive 45.0-50.4 Gy at 1.8 Gy per fraction. Once this is completed, a reduction will be made to deliver a total dose of 64.8-70.2 Gy at 1.8 Gy/fraction to the prostate bed (CTV2/PTV2).

The CTV1 will include the obturator, external iliac, proximal internal iliac and common iliac nodes, estimated using the vascular structures, up to the level of L5-S1. The recommended volumes are on the RTOG website under the “Core Lab/Contouring Atlases” menu

(http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePelvicLymphNodes.aspx).

The CTV is described as being 7 mm around the iliac vessels, carving out bowel, bladder and bone, which translates into just contouring the iliac/obturator areas with essentially no extra margin because of the proximity to these structures (this is well-illustrated in the contouring Atlas). Thus, the PTV margins described above are the margins that venture into the potential bowel space, bladder and bone. The remainder of the CTV1, including the prostate bed and seminal vesicle bed are as described above. The CTV2 will include the prostate bed, as described for PBRT above. The PTV1 and PTV2 margins should be a minimum of 0.8 cm in all dimensions. A reduction of the PTV margin from 0.8 cm to ≥ 0.6 cm to minimize rectal exposure will be considered an acceptable variation. A posterior margin of < 0.6 cm will be considered an unacceptable deviation. The maximum dose in the PTV2 (the PTV1 is expected to have greater heterogeneity and no specific constraints are given) above the prescribed dose will be 7%; an acceptable variation will be > 7% to ≤ 12% and an unacceptable deviation >12%. The planned dose will be declared after the patient is planned and all dosimetric parameters finalized A minimum of four treatment fields should be used. The normal tissue outlines will be the same as described above, with the added contouring of the potential space for small/large bowel in the pelvis. The potential bowel space will include the space on either side of the bladder to the medial edge of the lymph node outline laterally, beginning approximately at the top of the prostate bed field to one CT axial imaging level above the most superior level displaying a CTV1 contour. Care should be taken to avoid the presacral lymph node region in the bowel volume.

No specific field arrangement is required, although typically 5-9 fields are used. Rotational IMRT treatments are permitted, as long as the constraints are met. The posterior PTV margin at the bladder neck-rectum interface should not include the entire width of the rectum. A composite plan should be generated showing that at least 95% of the PTV1 and PTV2 receive the prescribed dose; a variation acceptable will be noted if < 95% to 90% of the PTV receives the prescribed dose, and a deviation unacceptable will be noted if < 90% of the PTV receives the prescribed dose. The maximum dose within the PTV2 (the PTV1 is expected to have greater heterogeneity and no specific constraints are given), above the prescribed dose, will be 15%; an acceptable variation will be > 15% to ≤ 20% and an unacceptable deviation > 20%. The other dosimetric parameters for IMRT are the same as for PBRT, except for the addition of a small bowel constraint.

Small/Large Bowel: The volume to be contoured is described above. For the patients receiving PLNRT, ≤ 150 cc of potential bowel space should receive ≥ 45 Gy. A variation will be noted if > 150 cc to 200 cc of potential small bowel space receives ≥ 45 Gy. A secondary variation will be noted if >200 cc receives >45 Gy (see below). Since there are not protocol violations for bowel, treatment volumes should not be dramatically altered to adjust for bowel. In prior protocols, considerable bowel was in the field and patients tolerated treatment well. Thus, these constraints act as a guide.

Overlap of the Bowel with the Prostate Bed PTV: This situation has been one of concern in cases where the high dose PTV overlaps with loops of bowel. Since these patients have had prior surgery, bowel is

not as mobile as for the patient with an intact prostate. However, it should be kept in mind that such compromises were not done in prior studies and that this should be an infrequent occurrence.

Overlap of the Bowel with the Lymph Node PTV: No adjustments in the PTV are permitted. Since the potential bowel contour abuts the lymph node CTV, there should be an overlap with the lymph node PTV. The overlap is expected.

Use of cone beam CT and plan adjustment: There may be cases in which the target and surrounding normal tissues are found to not be reproducible relative to the simulation CT and consequent plan. It should be emphasized that replanning should be avoided if at all possible because this will be considered a deviation. If the patient must be replanned in the opinion of the treating physician, then a deviation will be recorded, but continue to treat the patient per protocol in terms of dose and CTV/PTV volumes.

7.5.4.2.2 Pelvic Lymph Node Radiotherapy (PLNRT) planning – Arm A

For patients on Arm B, the Pelvic Lymph Node Radiotherapy clinical target volumes CTV1 & CTV2 as defined in 7.5.4.2.1 above will be contoured and submitted to the Emory Radiation Oncology Department. The Radiation Oncology PI (Dr. Jani) will supervise registration of the fluciclovine scan with the planning CT scan for definition of the pelvic lymph node and prostate bed CTV's (CTV1/CTV2) which will in each case be defined as the union of the CTV1/CTV2 in section 7.5.5 above with the prostate bed uptake seen on the fluciclovine scan. PTV expansions around this final CTV1/CTV2 will be as in section 7.5.4.2.1 above. A boost to 70.2 to 76.0 Gy to areas of PET-CT uptake close to the prostate bed, and a boost to 54-56 Gy to areas of PET uptake in the upper pelvis will be planned, with intent of reducing final dose to maximum allowable to meet normal tissue constraints.

7.5.4.2.3 Pelvic Lymph Node Radiotherapy (PLNRT) planning – Arm B

For patients on Arm B, the Pelvic Lymph Node Radiotherapy clinical target volumes CTV1 & CTV2 as defined in 7.5.4.2.1 above will be contoured and submitted to the Emory Radiation Oncology Department. The Radiation Oncology PI (Dr. Jani) will supervise registration of the Ga-PSMA scan with the planning CT scan for definition of the pelvic lymph node and prostate bed CTV's (CTV1/CTV2) which will in each case be defined as the union of the CTV1/CTV2 in section 7.5.5 above with the prostate bed uptake seen on the Ga-PSMA scan. PTV expansions around this final CTV1/CTV2 will be as in section 7.5.4.2.1 above. A boost to 70.2 to 76.0 Gy to areas of PET-CT uptake close to the prostate bed, and a boost to 54- 56 Gy to areas of PET uptake in the upper pelvis will be planned, with intent of reducing final dose to maximum allowable to meet normal tissue constraints.

7.5.4.2.4 Critical Structures – Arm A or Arm B

The critical normal structures are the bladder, rectum, small/large bowel above the rectum, and femoral heads. The normal tissues will be contoured and considered as solid organs.

The bladder should be contoured from its base to the dome, excluding the CTV1 (the CTV1 includes the bladder neck).

The rectum should be contoured from the anus (at the level of the ischial tuberosities) to the rectosigmoid flexure (this is roughly at about 10 cm) or for a maximum length of 15 cm if the sigmoid flexure is felt to be higher.

Each femoral head should be outlined down to the interface between the greater and lesser trochanters. Each femoral head should be considered separately.

For the patients who will undergo PLNRT treatment, the external iliac, obturator, internal iliac and common iliac vessels/lymph node regions should be outlined inferiorly from where the external iliacs become the inguinal vessels and superiorly from the level of the common iliacs at L5-S1. The presacral lymph nodes from L5-S1 to S3 should be included.

For the patients who will undergo PLNRT treatment in, the potential bowel space (not individual loops of bowel) where the small and large bowel may fall should be outlined. The borders are the abdominal wall anteriorly, pelvic sidewalls laterally (excluding the pelvic lymph node regions), superiorly to one cut above the last axial CT image on which the lymph nodes are outlined and inferiorly from the level of the top of CTV1 (outlining around the sides of the bladder near the top of the bladder to encompass the bowel that may fall into these regions). Posteriorly, the small bowel potential space should extend to in front of the sacrum, abutting the anterior presacral nodal contours.

The tissue within the skin and outside all other critical normal structures and PTV's is designated as unspecified tissue.

7.5.5 Documentation Requirements

The Radiation Oncology PI (Dr. Jani) will facilitate the review of the CTV, PTV, and designated organs at risk (critical structures). For patients on Arm B of the protocol, the PTV ultimately used to treat the patient (which includes information from the PET-CT/planning CT registration) will be sent back securely to the treating institution. For both arms, the planning CT images, target volume structure set, and treatment plan ultimately used to treat the patient will be stored securely on the Emory Radiation Oncology server.

The treating institution will archive treatment prescription and verification images for later review by the PI if requested. At least one port film from each orthogonal film along with the digital reconstructed radiographs (DRRs) from the treatment planning program shall be acquired and kept for evaluation. Note: Images are required to be taken but not submitted.

7.5.6 Compliance Criteria

7.5.6.1 Dose Heterogeneity
The maximum dose within the PTV, above the prescribed dose, will be 15%; an acceptable variation will be > 15% to ≤ 20% and an unacceptable deviation > 20%. Although, the maximum dose allowable in the PTV(s) will be 15% above the prescribed dose, it is possible in the vast majority of cases to achieve less than 15%.

7.5.6.2 Normal Tissue Deviations
Less than or equal to 35% and 55% of the rectum should receive ≥ 65 Gy and ≥ 40 Gy, respectively. Less than or equal to 50% and 70% of the **bladder minus prostate bed CTV (Bladder - CTV)** should receive ≥ 65 Gy and ≥ 40 Gy, respectively. The criteria for the bladder are relaxed because the dosimetric relationship of volume exposed to the specified marker doses is much less clear and the bladder neck is included in the CTV. Less than or equal to 10% of each femoral head should receive ≥ 50 Gy. A variation acceptable will be noted if up to an additional 5.0% of either the femoral head receives > 50 Gy. For the patients receiving PLNRT, ≤ 150 cc of potential small/large bowel space should receive ≥ 45 Gy. A primary variation will be noted if > 150 cc to 200 cc of potential small/large bowel space receives ≥ 45 Gy. A secondary variation will be noted if > 200 cc of potential small/large bowel space receives ≥ 45 Gy.

7.5.6.3 Radiotherapy Quality Assurance Reviews

The Radiation Oncology PI (Dr. Jani) will facilitate the review of CTV, PTV, designated organs at risk, isodose distributions, treatment plans, and dose-volume histograms (DVH's) of interest for each study subject prior to initiation of radiotherapy.

Specifically the following structures and DVH's will be reviewed and archived on the secure Emory Radiation Oncology server (below are suggested standard names for the structures):

For all patients:
Bladder
Rectum
Small Bowel
Penile_Bulb
R_Femoral_Head
L_Femoral_Head

For Prostate Bed only patients:
CTV
PTV
CTV_final
PTV_final

For Pelvic radiotherapy patients:
Pelvic_Lymph_Nodes
CTV1
CTV2
PTV1
PTV2
Pelvic_Lymph_Nodes_final
CTV1_final
CTV2_final
PTV1_final
PTV2_final

7.5.6.4 Radiation Adverse Events

All patients will be seen weekly by their radiation oncologist during radiation therapy. Any observations regarding radiation reactions will be recorded and should include attention toward the following potential side effects:

Small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, proctitis, or hematochezia;
Bladder complications including urinary frequency/urgency, dysuria, hematuria, urinary tract infection, and incontinence;
Radiation dermatitis.

Clinical discretion may be exercised to treat side effects from radiation therapy as described above. Examples of typical medications used in the management of rectal side effects, such as diarrhea, include

diphenoxylate or loperamide. Bladder or rectal spasms are usually treated with anticholinergic agents or tolterodine. Bladder irritation may be managed with phenazopyridine. Erectile dysfunction is often treated with medical management or mechanical devices.

8.0 Patient Assessments

8.1 Prior to Randomization

History and Physical (i.e., symptom-directed examination)
ECOG/Zubrod Performance Status (see Appendix 1)
Pathology report (from radical prostatectomy)
Bone scan report
CT or MRI pelvis report (and, if performed, abdomen report)
PSA
EPIC sheet (see Appendix 2)
Pre-PET-CT Radiotherapy Decision / Attestation Sheet (see Appendix 3)

8.2 After Randomization but before Radiotherapy

Digital Rectal Examination (DRE) [may also be done prior to randomization]
If randomized to Arm A:
- fluciclovine scan
- CT simulation
- Radiotherapy Treatment Planning

If randomized to Arm B:
- Ga-PSMA scan (& related lab tests)
- CT simulation
- Radiotherapy Treatment Planning

8.3 During Radiotherapy

Adverse event evaluations (see Appendix 4 for AE definitions) on average once weekly during XRT course

8.4 After Radiotherapy

Note: see Appendix 4 for all radiotherapy adverse event definitions, and see Appendix 5 for the Follow-up Data Sheet.

1 month (+/- 2 weeks) follow-up:
- Zubrod PS, PSA, AST/ALT/Serum Testosterone (if on hormones),
- EPIC, adverse event evaluation

6, 12, 18, and 24month (+/- one month) follow-ups:
- Zubrod PS, DRE, PSA, AST/ALT/Testosterone (if on hormones), EPIC, adverse event evaluation; Radiological workup (CT/MR scan, Bone scan, etc.) as clinically indicated

>24 month (+/- two months) follow-up:
- As per clinical routine

Note that if primary endpoint is reached (i.e., 24 months of follow-up is reached, patient is determined to fail treatment [as defined in section 6.5], or the decision to administer radiotherapy is aborted), subsequent follow-up (and specified data collection at the above timepoints) is optional. Also, if subject declines to follow-up after reasonable attempt has been made to contact the subject, data through the most recent follow-up will be used for the primary and secondary endpoints of the study.

For synopsis of study assessments, see Appendix

9.0. Statistical Analysis

Statistical Considerations for Specific Aim 1:

Primary endpoint: As the primary analysis, the chi-square test will be first used to compare the 2 year disease-free survival (DFS) (see section 6.5 above for definition) rates between the two arms. Then a survival analysis will be conducted on DFS. The survivor functions for DFS will be estimated with Kaplan and Meier method and plotted. The logrank test will be used to test the difference in DFS between the two arms. The power and sample size calculation is based on the difference in the 2 year DFS rates for either arm A or B against a historical 2-Year DFS (on the current ongoing study). We estimate that the 2 year DFS rates for either Arm A and Arm B will increase by 15%. This estimate is a combination of boosting the areas of PET/CT uptake and, in the case of ^{68}Ga-PSMA (Arm B) the increased diagnostic accuracy and preliminary PSA control data, as described above. To detect the 15% improvement in DFS, **the estimated sample size of 63 subjects in each arm** will achieve an 81% power at the significance level of 0.05 to detect the difference using a one-sided binomial test. Assuming a drop-out rate of approximately 10% (which was found on the prior R01 study), **we will enroll 70 subjects in each arm (140 subjects total)**.

Multivariate Analysis: For the multivariate analysis of biochemical failure time, a Cox model will be employed to assess the effect of molecular-imaging guided treatment on biochemical failure time after adjusting for patients' other demographic and clinical factors.

Toxicity Analysis: Common Terminology Criteria for Adverse Events (CTCAE) [acute and late] gastrointestinal (GI) and [acute and late] genitourinary (GU) toxicity rates will be charted for arms A and B and compared. Additionally, a multivariate analysis will be done examining all patient demographic, disease, and treatment factors (including fluciclovine (^{18}F) or ^{68}Ga-PSMA use) that influence each of these toxicity endpoints. This will enable determining whether fluciclovine (^{18}F) PET/CT or ^{68}Ga-PSMA guided treatment is tolerable compared to conventional treatment. Chi-square tests will be conducted to compare the distribution of grade (0, 1, 2, or 3) of acute GU/GI toxicity between the two arms. For the multivariate analysis of acute GU/GI toxicity, an ordered logistic model will be employed to assess the effect of fluciclovine (^{18}F) or ^{68}Ga-PSMA guided treatment on the grade of acute GU/GI toxicity after adjusting for patients' other demographic and clinical factors. A survival analysis will be conducted on late GU/GI toxicity. The survivor functions for the time to late GU/GI toxicity (grade ≥2) will be estimated by Kaplan and Meier method and plotted in a graph. The logrank test will be used to test the difference in the overall time to late GU/GI toxicity between the two arms. For the multivariate analysis of late GU/GI toxicity, a Cox model will be employed to assess the effect of fluciclovine (^{18}F) or ^{68}Ga-PSMA guided treatment on the time to late GU/GI toxicity after adjusting for patients' other demographic and clinical factors.

Statistical Considerations for Exploratory Sub-aim 1A:

We hypothesize that combinations of tissue biomarkers available in a subset of patients and molecular imaging will provide more accurate predictions of patient outcomes than either method on its own. Thus, we will perform biomarker analysis of patient samples to develop predictive models that incorporate multiple data types. (*See also Section A.1.5 above*).

We anticipate that there will be **100 patients accrued from treatment failures in part from the current U01 grant for the EDRN and also from patients who had previously undergone prostatectomy at Emory.** We will use the same sets of Decipher and Sig24 tissue RNA biomarkers that are currently being investigated as part of the EDRN study.

For patients enrolled in the study, we will identify those who had prostatectomies at Emory University and locate the relevant formalin-fixed paraffin-embedded (FFPE) tissue blocks. Both Decipher and Sig24 signatures were developed from FFPE tissue specimens, and thus, there should be no issue using fixed tissues. A board-certified GU pathologist (Dr. Osunkoye) will mark the most aggressive lesion from each tumor to use for RNA analysis, and six 5-micron sections will be macrodissected to include the region of interest for each case. Macrodissected tissues will be shipped to GenomeDx for Decipher GRIDv2 analysis to generate predictions for Decipher, Sig24, and the 16 other prognostic prostate cancer signatures in their database.

We will use a logistic regression model and receiver operating characteristic (ROC) analysis to explore whether combinations of Sig24 and/or Decipher tissue RNA biomarkers, together with imaging findings can improve prognosis of post-radiotherapy outcomes in prostate cancer (with additional goal of predicting success or failure within each subset of imaging findings). We will include imaging uptake intensity and location (bed, pelvis, extra-pelvic) as the candidate variables to build a best predictive Cox model of disease free survival (DFS). We will determine which biomarker or combination of biomarkers provides the best prognostic value. Because this is an exploratory aim, we will combine imaging findings of fluciclovine (^{18}F) and ^{68}Ga PSMA into a single group to improve statistical power. We will include type of imaging radiotracer as a covariate to determine whether the type of tracer is a significant predictor of DFS. Secondary analyses will investigate whether data from any subset of genes in the Affymetrix dataset are predictive of radiotracer uptake.

Statistical Considerations for Specific Aim 2:

The Clopper-Pearson (exact) binomial test will be used to compare (a) the decision to offer radiotherapy or not, (b) the decision on treatment of pelvic nodes or not, and (c) the decision to boost or not between the initial (pre- fluciclovine (^{18}F) or ^{68}Ga-PSMA) and final (post- fluciclovine (^{18}F) or ^{68}Ga-PSMA) treatment decisions. This same test will also be used to compare the combined number of decision changes for both decisions together between the initial and final treatment decisions.

Similarly, the number of decision changes for each category [(a) the decision to offer radiotherapy or not, and (b) the decision on treatment of pelvic nodes or not, and (c) the decision to boost or not] will be compared between the fluciclovine (^{18}F) and ^{68}Ga-PSMA arms using the Clopper-Pearson (exact) binomial test.

The hypotheses are that (a) molecular imaging with fluciclovine (^{18}F) or ^{68}Ga-PSMA will result in a significant decision change in each category, and that (b) the number of decision changes will be higher in the ^{68}Ga-PSMA arm versus the fluciclovine (^{18}F) arm. There are 70 subjects in each arm with approximately 5% dropout for this decision analysis. (Note that this is a lower dropout rate than in Aim 1, since this aim does not require followup.) Therefore, the final evaluable minimal sample size of 65 subjects in each arm will achieve at least 80% power at the significance level of 0.05 to detect a difference of 23% in decision changes (35% vs 58%) between the two methods (fluciclovine (^{18}F) vs ^{68}Ga-PSMA), as shown on our current trial (35% is from (3); the 58% supported by reference (95) (in fact, 60.5% in the recurrence sub-population).

Statistical Considerations for Specific Aim 3:

Paired t-test will be used to compare the target volumes (CTV and PTV) and the planned dose delivered to surrounding bladder, rectum, and penile bulb between the initial (pre-PET) and final (post-PET) radiation treatment plans. Spearman's correlation coefficient will be used to measure the correlations of the bladder and rectum dosimetric endpoints (V65, V40) with the grades (0, 1, 2, or 3) of acute GU or GI toxicity. A Wald test will be used to test the significance level of their correlations. A Cox model will be employed to assess the relationship between the time to late GU or GI toxicity (grade ≥2) and the bladder and rectum dosimetric endpoints (V65, V40), respectively. The same approach will be used for both analyses described above [(a) post-molecular vs pre-molecular imaging and (b) fluciclovine (^{18}F) or ^{68}Ga-PSMA].

10.0 Adverse Event Reporting:

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please follow directions for routine reporting provided in the full Data Safety and Monitoring Plan). Additionally, certain adverse events must be reported in an expedited manner to for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

1. **Special note for radiotracers given during this trial**: **The risk of AEs or SAEs from PET radiotracers is exceedingly low. A significant shift from baseline which can be attributable to the radiotracer injection and not the patient's medical condition will be considered an unexpected AE. An event greater than 20 hours post scan for fluciclovine and 10 hours for Ga-PSMA will not be considered an AE since the radiotracer has effectively decayed by 20 hours and 10 hours respectively.** Fluciclovine and Ga-PSMA are FDA approved and a commercial preparation will be used. Reporting will follow relevant FDA guidelines. For commercial doses provided by agreement with Telix Pharmaceuticals Limited through a commercial radiopharmacy per the following contractual Pharmacovigilance instructions:

Emory shall provide a copy of the detailed Clinical Trial protocol to Telix, as amended from time-to-time, as well as a copy of the annual safety reporting (**Safety Reporting**) involving the use of the radiotracer. Emory shall provide an annual report to Telix, summarizing the Adverse Event (**AE**) profile in relation to the use of the radiotracer, specifically noting whether there was attribution of the AE (however serious) to the radiotracer.

In the event of a Serious Adverse Event (SAE) or death occurring any time within 7 days after administration of 68Ga-PSMA-11, and not related to disease progression, Emory shall report to Telix Designated Contact (Dr. Colin Hayward, Chief Medical Officer Email: colin.hayward@telixpharma.com cc: notices@telixpharma,com)

(a) Within seven (7) calendar days of the date of awareness of a life-threatening adverse event or death (**Date of Awareness**), regardless of apparent causality to the use of the Kit.

(b) Within fifteen (15) calendar days of the Date of Awareness, any other SAEs, regardless of apparent causality to the use of the Kit.

(c) Within seven (7) calendar days upon communication of any other safety-related report, issues or queries related to the Kit that are either raised by, or communicated to, regulatory authorities or ethics committees.

(d) Within seven (7) calendar days after submission, the Development Safety Update Report (DSUR) submitted to the FDA.

Serious adverse event (SAE) or reaction is any untoward medical occurrence related to the imaging analysis that: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly / birth defect.

The definition of serious adverse event (experience) also includes *important medical event.* Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Attribution: The determination of whether an adverse event is related to a study imaging agent. The categories are:

Definite: The adverse event is clearly related to the study imaging agent.

Probable: The adverse event is likely related to the study imaging agent.

Possible: The adverse event may be related to the study imaging agent.

Unlikely: The adverse event is doubtfully related to the study imaging agent.

Unrelated: The adverse event is clearly not related to the study imaging agent.

Unexpected Adverse Event**:** An adverse event, the nature or severity of which is not consistent with the applicable product information.

Investigational Agent: A protocol drug administered under an Investigational New Drug Application (IND).

Commercial Agent: An agent not provided under an IND but obtained from a commercial source.

Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study imaging agent (attribution), and the prior experience (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: *Identify the type of event using the NCI Common Toxicity Criteria for Adverse Event Reporting Version 5.0 (CTCAE v5.0).* The CTCAE v5.0 provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE v5.0 can be downloaded from the CTEP home page (**http://ctep.cancer.gov**). Additionally, if assistance is needed, the NCI has an Index to the CTCAE v5.0 that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE v5.0.

Step 2: *Grade the event using the NCI CTCAE v5.0.*

Step 3: *Determine whether the adverse event is related to the protocol imaging agent (investigational or commercial)*. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event*. *Expected* events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected*, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the investigator brochure for an investigational agent or the drug package insert for a commercial agent.

Step 5: *Review Table 1 below to determine if there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents*.

Reporting Methods:

The Principal Investigator is responsible for evaluating all reports of adverse events which occur in patients enrolled on this study and reporting those events which are serious to the Sponsor- Investigator, and the Emory University IRB according to the guidelines below. SAEs must be reported as required by the WCI DSMP.

Expedited reporting requirements: All grade 4-5 adverse events (unexpected and expected) and grade 2-3 adverse events that are unexpected must be reported to Principal Investigator via the AE Form within 24 hours of occurrence.

Routine reporting requirements: All adverse events must be reported via the Toxicity Form and submitted according to the bodies outlined below.

	Grade 2		**Grade 3**		**Grade 4**		**Grade 5[a]**	
Report to	**Unexpected**	**Expected**	**Unexpected**	**Expected**	**Unexpected**	**Expected**	**Unexpected**	**Expected**
Principal Investigator	AE Form[b] Toxicity Form[c]	Toxicity Form[c]	AE Form[b] Toxicity Form[c]	Toxicity Form[c]	AE Form[b] Toxicity Form[c]	AE Form[c] Toxicity Form[c]	AE Form[b] Toxicity Form[c]	AE Form[b] Toxicity Form[c]

Table 1. Outline of Reporting Documents to be Used:

[a] All deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution; and any late death attributed to the agent (possible, probable or definite), should be reported within 10 working days.

[b] Submit to Emory within 24 hours of awareness of occurrence.

c See submission schedule in Section 11.0.

Reporting to Institutional Review Board (IRB): All SAEs must be reported by the Principal Investigator to the Emory University IRB as required by their regulations and the conditions of approval for the protocol.

Reporting to FDA: The Sponsor- Investigator must notify the FDA in a written IND safety report of any adverse event which is both serious and unexpected. In this case, after 10/17/22, we will no longer be operating under an IND. Each written notification must be made as soon as possible but no later than 15 calendar days of first becoming aware of the event. Reports should be submitted using the FDA Form 3500A (available on the FDA website at www.fda.gov/medwatch. Reporting may be done online or via mail or fax.

Any unexpected fatal (Grade 5) or unexpected, life-threatening (Grade 4) adverse event must be reported to the FDA as soon as possible but no later than 7 calendar days of first becoming aware of the event. Reports should be submitted using the FDA Form 3500A via fax at 1-800-332-0178

The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). In this case, after 10/17/22, we will no longer be operating under an IND. This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

11.0 Data Safety Monitoring Plan

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute of Emory University will oversee the conduct of this study. This committee will review all pertinent aspects of study conduct including patient safety, compliance with protocol, data collection and efficacy.

Adverse Events (AE's), Serious Adverse Events (SAE's) [including deaths, hospitalizations, and life-threatening events], and Unanticipated Problems (UP's) will be managed and reported, as required to the IRB, the awarding IC, the NIH Office of Biotechnology Activities, and FDA as required. The trial will be monitored on an ongoing/continual basis to mitigate risks.

The DSMC will review the charts of 10% of patients enrolled to the study and two of the first 5 patients entered to the study. Reviews will occur annually for studies that are low risk or moderate risk. High risk studies will be reviewed every 6 months. The committee reserves the right to conduct additional audits if necessary at any time-point. The Principal Investigator is responsible for notifying the DSMC about the accrual of patients when the first 5 have been entered to the study.

The charter for the Winship DSMC is available upon request to the investigator or other study-related personnel. Additionally, the study team [to include the PI (Dr. Jani) & NIH grant co-PI (Dr. Schuster)] will present all data analyzed to date, record of accrual, and attributable toxicities at the Multidisciplinary Genitourinary Oncology meeting which meets on a regular basis.

Note that our proposed trial is very similar to the trial on our current ongoing clinical trial (5R01CA129356: NCT01666808) which has been audited several times by Winship Cancer Institute of Emory University's DSMC successfully.

As with our ongoing clinical trial, for the current proposal we will adhere strictly to Winship's Data Safety Monitoring Plan which is provided in detail at the following link:

https://winshipcancer.emory.edu/research/clinical-trials-office/data-and-safety-monitoring-committee.html

Data Safety Monitoring Board:

Note that our proposed trial is a randomized Phase II clinical trial that will be conducted completely within the Emory system, so a formal and independent Data Safety Monitoring Board (DSMB) [which is required for multi-site studies or Phase III trials] is not required for our proposal. As described above, the DSMC of Winship Cancer Institute of Emory University will oversee the conduct of our study.

Fidelity to Protocol and Data Integrity:

Clinical trial performance and fidelity to the protocol, particularly with respect to accrual goals, will be monitored both by the DSMC of Winship Cancer Institute of Emory University, as well as at Emory monthly inter-disciplinary genito-urinary clinical trials meetings. Integrity of the data will be maintained by rigorous peer-review internally by all of the clinical co-investigators (in Radiation Oncology, Radiology/Nuclear Medicine, Urology, Pathology, and Medical Oncology). As described in the protocol, dual-reading of the PET-CT scans will be done by the Nuclear Medicine PI and co-investigators. Additionally, radiotherapy treatment plan quality assurance will be reviewed at weekly chart rounds that the Radiation Oncology PI and co-investigators routinely attend.

12.0 References

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13.0 Appendices

Appendix 1: ECOG/Zubrod Performance Scale
Appendix 2: EPIC
Appendix 3: Pre-PET-CT Radiotherapy Decision Sheet
Appendix 4: RTOG/CTCAE Toxicity Grading
Appendix 5: Follow-up Data Sheet
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Appendix 1:

ECOG/ ZUBROD PERFORMANCE SCALE

0 - Fully active, able to carry on all predisease activities without restriction

1 - Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work

2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited self-care, confined to bed or chair 50% or more of waking hours

4 - Completely disabled. Cannot carry on self-care. Totally confined to bed

5 - Death

Appendix 2:

Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) Questionnaire.

Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP)

A Clinical Tool to Measure Urinary, Bowel, Sexual and Vitality/Hormonal Health **Date:** ___ /___ /___

Patients: Please answer the following questions by checking the appropriate checkbox. All questions are about your health and symptoms in the **LAST FOUR WEEKS**. Select one answer for each question.

1. Overall, how much of a problem has your urinary function been for you?
☐ No problem ☐ Very small problem ☐ Small problem ☐ Moderate problem ☐ Big problem

2. Which of the following best describes your urinary control?
0 ☐ Total control 1 ☐ Occasional dribbling 2 ☐ Frequent dribbling 4 ☐ No urinary control ____

3. How many pads or adult diapers per day have you been using for urinary leakage?
0 ☐ None 1 ☐ One pad per day 2 ☐ Two pads per day 4 ☐ Three or more pads per day ____

4. How big a problem, if any, has urinary dripping or leakage been for you?
0 ☐ No problem 1 ☐ Very small problem 2 ☐ Small problem 3 ☐ Moderate problem 4 ☐ Big problem ____

*CLINICIANS: **ADD** the answers from questions **2-4** to calculate the **Urinary Incontinence Symptom Score (out of 12):*** ☐

5. How big a problem, if any, has each of the following been for you?	**No problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**	
a. Pain or burning with urination	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____
b. Weak urine stream/incomplete bladder emptying	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____
c. Need to urinate frequently	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____

*CLINICIANS: **ADD** the answers from questions **5a-5c** to calculate the **Urinary Irritation/Obstruction Symptom Score (out of 12):*** ☐

6. How big a problem, if any, has each of the following been for you?	**No problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**	
a. Rectal pain or urgency of bowel movements	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____
b. Increased frequency of your bowel movements	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____
c. Overall problems with your bowel habits	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____

*CLINICIANS: **ADD** the answers from questions **6a-6c** to calculate the **Bowel Symptom Score (out of 12):*** ☐

7. How would you rate your ability to reach orgasm (climax)?
0 ☐ Very good 1 ☐ Good 2 ☐ Fair 3 ☐ Poor 4 ☐ Very poor to none ____

8. How would you describe the usual quality of your erections?
0 ☐ Firm enough for intercourse 1 ☐ Firm enough for masturbation and foreplay only 2 ☐ Not firm enough for any sexual activity 4 ☐ None at all ____

9. Overall, how much of a problem has your sexual function or lack of sexual function been for you?
0 ☐ No problem 1 ☐ Very small problem 2 ☐ Small problem 3 ☐ Moderate problem 4 ☐ Big problem ____

*CLINICIANS: **ADD** the answers from questions **7-9** to calculate the **Sexual Symptom Score (out of 12):*** ☐

10. How big a problem, if any, has each of the following been for you?	**No problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**	
a. Hot flashes or breast tenderness/enlargement	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____
b. Feeling depressed	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____
c. Lack of energy	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____

*CLINICIANS: **ADD** the answers from questions **10a-10c** to calculate the **Vitality/Hormonal Symptom Score (out of 12):*** ☐

*CLINICIANS: Add the five domain summary scores to calculate the **Overall Prostate Cancer QOL Score (out of 60):*** ☐

Appendix 3:

Pre-PET-CT Radiotherapy Decision / Attestation Sheet

Note: This form must be completed prior to randomization.

Pathologic Stage: T_____ N_____ M_____

Margin positive (y/n)_____ Extra-capsular Extension (y/n) _____ Seminal Vesical Invasion(y/n)_____

Highest post-prostatectomy PSA: Value_____ Date_____

Most recent PSA: Value_____ Date_____

DRE date & Findings_____

CT or MRI scan shows no extrapelvic disease (y/n)_____ Scan date_____

Bone scan shows no skeletal metastases (y/n)_____ Scan date_____

Please answer the below provider-related questions:

1. Are you planning to offer the patient pelvic radiotherapy (check only one): Yes_____ No/Undecided_____

If Yes, which of the following general target volumes are you planning to treat (check only one):

Prostate bed alone _____ OR Prostate bed plus regional lymph nodes ____

If No/Undecided, please provide reason below:

Wish to observe PSA _____ Likely futile_____

Other (please explain): _____

2. Are you planning to offer the patient androgen deprivation therapy? Yes_____ No_____

If Yes, what is intended duration ?_____

3. All other pretreatment evaluations (Symptom-directed Exam, Zubrod, path report, bone scan report, CT/MR report, PSA, EPIC, [LFT's/testosterone only if hormones intended]) have been completed:

Yes_____ No_____ If no, please explain_____

Provider signature_____ **Date**_____

Appendix 4:

RTOG/CTCAE Definitions

CTCAE version 5.0 can be found at the following link:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

The common side effects related to pelvic radiotherapy are gastrointestinal and urinary in this PDF.

Appendix 5:

Follow-up Data Sheet

Note: This form must be provided at each of 1, 6, 12, 18, and 24 month post-radiotherapy.

Follow-up Visit _____ months post-radiotherapy _____ Date

Symptom-directed examination completed _____ (y/n)

DRE completed (not needed at 1 month follow-up)? _____ (y/n)

If completed, is DRE Normal? _____ (y/n)

ECOG/Zubrod Performance Status (0-5) _____

PSA (ng/mL): Value_____ Date_____

GU Toxicity Grade _____ (0-4)

GI Toxicity Grade _____ (0-4)

Insert EPIC sheet here.

Other Toxicity? If so, list type(s) and grade(s)_____

Did patient receive or is patient receiving androgen deprivation therapy ? ___(y/n)

If yes, below are needed (if androgen deprivation therapy spans current follow-up period):

Testosterone: Value_____ Date_____

AST: Value_____ Date_____

or ALT: Value_____ Date_____

Any evidence of clinical progression or started additional non-ADT systemic therapy since last visit ? _____ (y/n)

If clinical progression, provide details (CT scan, bone scan, biopsy, etc) including dates:

_____

If chemotherapy started, provide details of type and start date?_____

Provider signature_____ Date_____

Appendix 6. Study Parameter Table [see also sections 8.1-8.4 for details]

Assessment	Pre-XRT (may be required for eligibility)	During XRT	Follow-up After XRT					Long-term follow up
		Weekly	1 month	6 months	12 months	18 months	24 months	As per routine
Symptom-Directed Exam	x	x	x	x	x	x	x	x
DRE	x			x	x	x	x	x
ECOG PS	x		x	x	x	x	x	x
Prostatectomy Report	x							
PSA	x		x	x	x	x	x	x
Bone Scan	x							x
CT or MRI pelvis+/- abdomen	x							x
EPIC-CP	x		x	x	x	x	x	x
Radiotherapy Decision Sheet (RDS)	x							
AST or ALT	If H intended		If on H	If on H	If on H	If on H	If on H	If on H
Serum Testosterone	If H intended		If on H	If on H	If on H	If on H	If on H	If on H
fluciclovine scan (only after RDS completed)	Only Arm A							
Ga-PSMA scan (only after RDS completed)	Only Arm B							
CT simulation	x							
XRT plan registration	x							
AE evaluation		x	x	x	x	x	x	x