Advanced Molecular Imaging with anti-3-[18F]FACBC PET-CT to Improve the Selection and Outcomes of Prostate Cancer Patients Receiving Post-prostatectomy Radiotherapy

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Advanced Molecular Imaging with *anti*-3-[18F]FACBC PET-CT to Improve the Selection and Outcomes of Prostate Cancer Patients Receiving Post-prostatectomy Radiotherapy

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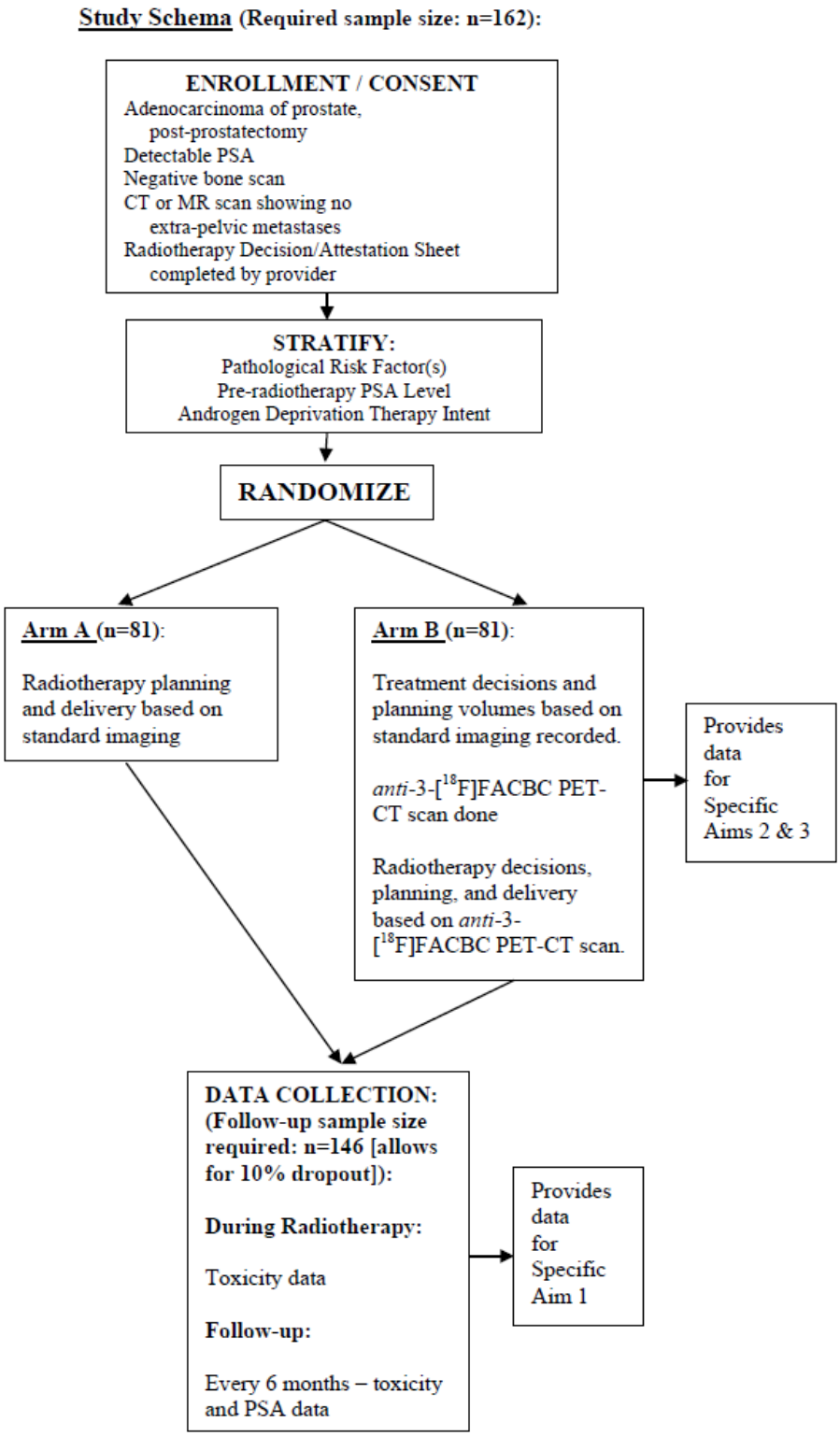
1.0 Abstract

Our overall goal is to improve the long term biochemical free survival of patients with recurrent prostate carcinoma by altering the current decision algorithm through the ability of advanced molecular imaging to guide the appropriate selection of patients who will benefit from salvage radiotherapy. Approximately 50% of patients who have undergone post-prostatectomy radiotherapy after Prostate Specific Antigen (PSA) failure or biopsy proven prostate bed recurrence manifest subsequent systemic disease, in part, because conventional imaging methods fail to adequately differentiate prostatic from extraprostatic recurrence. In the post-prostatectomy setting, both under-treatment and over-treatment occur based on existing strategies, and appropriately directing radiotherapy is an unmet public health need in this population. We plan to leverage advanced molecular imaging with the positron emission tomography (PET) radiotracer *anti*-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid (*anti*-3-[^{18}F]FACBC) which in preliminary data is able to differentiate prostatic from extra-prostatic recurrence even at low PSA levels. Doing so will enable more appropriate selection of patients who will benefit from salvage radiotherapy and to achieve durable response at higher PSA levels than previously believed.

We hypothesize that if patients are appropriately selected for salvage radiotherapy with the aid of newly available advanced molecular imaging with *anti*-3-[^{18}F]FACBC PET-CT, a significantly higher proportion will achieve long-term cure and at higher PSA levels than via conventional treatment algorithms. We also hypothesize that the use of advanced molecular imaging will alter post-prostatectomy radiotherapy algorithms both in decision to treat and in planning volumes.

To test these two hypothesis, we plan to conduct a prospective randomized clinical trial in which patients will be treated with salvage radiotherapy after conventional imaging methods in the control arm (A) and with the addition of *anti*-3-[^{18}F]FACBC PET-CT in the trial arm (B). We will explore the role of *anti*-3-[^{18}F]FACBC PET-CT in (1) controlling prostate cancer that would otherwise generally not be treated with post-prostatectomy radiotherapy, and improving prostate cancer control in patients that would generally be considered for radiotherapy, (2) guiding radiotherapy decisions, both in the overall decision to offer radiotherapy and in the decision to guide the general radiation field (prostate bed versus pelvis), and (3) influencing the target volume and overlap of normal structures when planning and delivering radiotherapy. The work will have significant implications for improving the outcomes of post-prostatectomy patients, not just for the use of *anti*-3-[^{18}F]FACBC but for the application of novel imaging to guide post-prostatectomy radiotherapy.

2.0 Schema –


Study Schema (Required sample size: n=162):
ENROLLMENT / CONSENT
Adenocarcinoma of prostate, post-prostatectomy
Detectable PSA
Negative bone scan
CT or MR scan showing no extra-pelvic metastases
Radiotherapy Decision/Attestation Sheet completed by provider
STRATIFY:
Pathological Risk Factor(s)
Pre-radiotherapy PSA Level
Androgen Deprivation Therapy Intent
RANDOMIZE
Arm A (n=81):
Radiotherapy planning and delivery based on standard imaging
Arm B (n=81):
Treatment decisions and planning volumes based on standard imaging recorded.
anti-3-[18F]FACBC PET-CT scan done
Radiotherapy decisions, planning, and delivery based on anti-3-[18F]FACBC PET-CT scan.
Provides data for Specific Aims 2 & 3
DATA COLLECTION:
(Follow-up sample size required: n=146 [allows for 10% dropout]):
During Radiotherapy:
Toxicity data
Follow-up:
Every 6 months – toxicity and PSA data
Provides data for Specific Aim 1

2.1 Eligibility Checklist

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

___(Y) 2. Detectable PSA

___(Y) 3. Negative technetium 99-m MDP or F-18 PET bone scan for skeletal metastasis

___(Y) 4. CT and/or MR scan of abdomen and pelvis which does not suggest presence of metastatic disease outside of the pelvis

___(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 *anti*-3-[^{18}F]FACBC PET-CT

___(N) 9. Metastatic disease outside of pelvis on any 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 tumor, with approximately 200,000 new cases diagnosed per year. Several different local therapies are available for treatment, including surgery and radiotherapy (1). Significant advances have been made in the technical aspects of surgery and of radiotherapy which have improved both the cancer control outcomes as well as the morbidity of treatment.

Despite these significant advances, approximately 30% of patients treated with definitive local therapy experience recurrent disease (2, 3). Recurrent disease after prostatectomy usually manifests with rising PSA. The PSA level is often of limited use in the differentiation of local from extra-prostatic recurrence, though the rate of PSA rise may have some value (4).

The differentiation of local from regional from distant recurrence is of critical importance since salvage techniques can cure disease confined to the surgical field. If pelvic nodal involvement is suspected, radiation fields can be extended to include the pelvic nodes (5-7). If a patient is not a candidate for salvage radiotherapy, he will likely be treated with systemic long term hormonal therapy which is expensive and result in significant morbidity, also leading to increased healthcare expenditures. Hormonal therapy, particularly long-term hormone therapy, can cause vasomotor symptoms, depression, loss of cognitive function, sexual dysfunction, loss of muscle mass, weight gain, shrinkage of genitalia, breast tenderness/gynecomastia, osteoporosis, risk of bone fracture, changes in lipid profile, glucose intolerance and cardiovascular complications (8-11). This morbidity of long-term hormones can be avoided if the PSA can be controlled with radiotherapy.

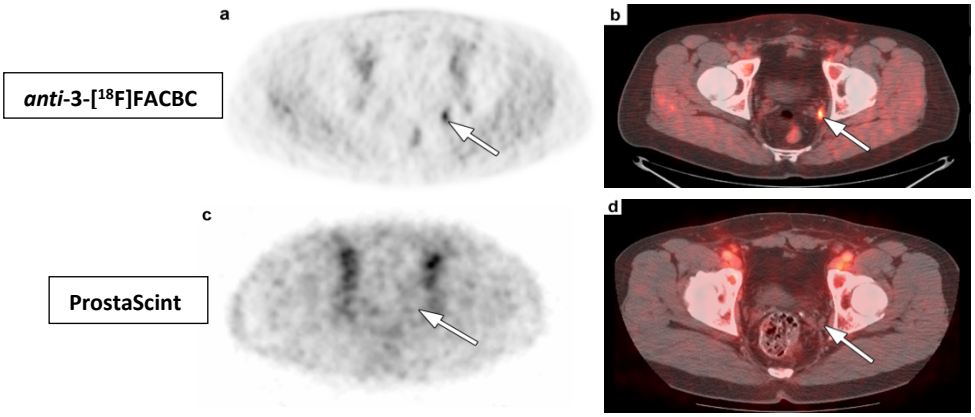
Appropriate patient selection for radiotherapy is important. The decision to offer radiotherapy in the post-prostatectomy setting is somewhat controversial and based on many factors, including pre-prostatectomy disease factors, post-prostatectomy PSA nadir, PSA velocity, and absolute PSA level (12-25). The last item, the absolute PSA, is perhaps the most commonly used, so that in face of an elevated PSA greater than 2.0 ng/ml, patients may not be offered potential curative radiotherapy because of the belief that the recurrence has a high probability of being systemic. In a recent study by Schuster et al (submitted, Journal of Clinical Oncology) based on data from the NIH sponsored clinical trial of *anti*-3-[^{18}F]FACBC with recurrent prostate carcinoma (5R01CA129356), 3/13 patients in the cohort of those with PSA >10 ng/ml were true negative for extraprostatic spread, and thus could have been potential candidates for salvage radiotherapy. Similarly, with low PSA values, patients may be offered radiation therapy. Yet, occult prostate carcinoma may be extraprostatic even at these PSA levels, and thus radiotherapy would be futile or could have been modified to include the pelvic nodes. In this same study, 4/12 patients in the cohort of those with PSA <2.0 ng/ml had occult metastatic disease outside of the prostate bed undiscovered on conventional imaging. If these patients had been offered salvage therapy, it would likely have been ineffective since disease had spread beyond normal fields of local therapy.

Thus, imaging plays a central role in the differentiation of prostatic from extraprostatic recurrence. Conventional methodology to detect extra-prostatic nodal involvement including computed tomography (CT), magnetic resonance imaging (MR), transrectal ultrasound, and ^{111}Indium-capromab-pendetide (ProstaScint) (EUSA Pharma, Langhorne, PA) suffer from poor diagnostic performance with approximately 20-50% reported sensitivity (12, 26-33). ProstaScint had been studied to potentially select patients for salvage radiotherapy after PSA relapse with discouraging results (12, 34). Bone scanning with Tc-99mMDP is highly sensitive for the detection of bone metastasis, but there is low yield with PSA less than 10 ng/ml (35). To date, no established imaging test has demonstrated a role in a prospective setting in improving outcomes of post-prostatectomy radiotherapy. For this reason, newer methods such as diffusion weighted MR (DWMR) and positron emission tomography (PET) with molecular radiotracers are currently under study for the characterization of post therapy recurrence (36-44). The choline

PET radiotracers have also been suggested as a means to individualize post-prostatectomy treatment decisions (41). Yet the sensitivity of most imaging techniques including choline based radiotracers is dependent upon PSA level, doubling time, and velocity (41, 45, 46).

One PET radiotracer which has shown promise in the staging and restaging of patients with prostate carcinoma is *anti*-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid (*anti*-3-[^{18}F]FACBC) which is a synthetic amino acid analog with little renal excretion and transport via sodium dependent and independent pathways (47-49). In a recent study, *anti*-3-[^{18}F]FACBC demonstrated higher accuracy compared with ^{111}Indium-capromab-pendetide in the restaging of patients with suspected recurrent prostate carcinoma (50). The figure below demonstrates the ability of *anti*-3-[^{18}F]FACBC PET-CT to detect extraprostatic involvement in a patient with negative ProstaScint.

Post radical prostatectomy PSA 1.1. *anti*-3-[^{18}F]FACBC (a and b) and ^{111}Indium-capromab-pendetide (c and d). Intense uptake on axial *anti*-3-[^{18}F]FACBC (arrow in a) and fused images (arrow in b) in 5 mm left obturator lymph node biopsy proven recurrence. No uptake in same region on ^{111}Indium-capromab-pendetide (arrow in c) and fused images (arrow in d).



Most importantly, as noted in our preliminary data below, anti-3-[^{18}F]FACBC PET-CT maintains excellent diagnostic performance in the differentiation of prostatic from extra-prostatic recurrence across all PSA levels.

Our central hypothesis is if patients are appropriately selected for salvage radiotherapy with the aid of newly available advanced molecular imaging with *anti*-3-[^{18}F]FACBC PET-CT, a significantly higher proportion will achieve long-term cure and at higher PSA levels than via conventional treatment algorithms**.** We will use *anti*-3-[^{18}F]FACBC as an imaging vehicle to appropriately select patients in order to (1) control prostate cancer that would otherwise generally not be treated with post-prostatectomy radiotherapy, and improve prostate cancer control in patients that would generally be considered for radiotherapy, (2) guide radiotherapy decisions, both in the overall decision to offer radiotherapy and in the decision to guide the general radiation field (prostate bed versus pelvis), and (3) influence the target volume and overlap of normal structures when planning and delivering radiotherapy. The work will have significant implications for improving the outcomes of post-prostatectomy patients and for the application of novel imaging to guide post-prostatectomy radiotherapy.

Study Sites:
Note that this protocol is intended to be open initially at Emory University Hospital Clifton, Emory University Hospital Midtown, and Grady Memorial Hospital. The protocol is also intended to be open and available to the members of the Georgia Center for Oncology Research and Education (Georgia CORE – an organization which intends to increase the available cancer trials in the state of Georgia). Though Georgia CORE has provided written support [for the NIH R01 grant in support of this current protocol] to assist in trial accrual, as a formal contract between Emory CTO and Georgia CORE for this clinical is currently pending, we will amend this protocol at a later date once this formal contract is finalized.

4.0 Objectives

Imaging techniques have typically been evaluated in terms of diagnostic performance verified usually with biopsy or clinical follow-up; truth as an endpoint has usually been that of histology. *anti*-3-[^{18}F]FACBC PET-CT has been studied in this regard as well (47, 50). There have been retrospective analyses and reviews analyzing the role of ProstaScint which ultimately were negative for the utility of anti-PSMA antibody imaging in prostate control outcomes. In fact the study PI's have considerable expertise in exploring the role of ProstaScint (51-54) and in comparison of ProstaScint to *anti*-3-[^{18}F]FACBC PET-CT (50). There are ongoing prospective trials examining the role of androgen deprivation and field size (Radiation Therapy Oncology Group [RTOG] Protocol #0534), systemic therapy (RTOG Protocol #0622), and the timing of radiotherapy (MRC RADICALS Trial [Protocol NCT00541047] and Trans-Tasmanian Radiation Oncology Group [Protocol NCT00860652]) but no current prospective trials evaluating the role of advanced molecular imaging. Our study will involve a prospective randomized trial examining the impact of a novel imaging technique in guiding post-prostatectomy radiotherapy outcomes, decision making, and treatment planning.

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

<u>Specific Aim 1</u>: To improve the outcomes of post-prostatectomy radiotherapy prostate cancer patients using advanced molecular imaging with *anti*-3-[^{18}F]FACBC PET-CT

We hypothesize that the high failure rate of salvage radiotherapy in the post-prostatectomy patient population is secondary to lack of adequate imaging to identify extraprostatic spread of recurrent tumor which would preclude radiotherapy or result in modification of radiotherapy fields. Thus, a patient who normally would be considered for salvage radiation therapy because of a low PSA value may be spared needless radiotherapy if carcinoma is discovered outside the pelvis through the use of advanced molecular imaging techniques. Similarly, a patient who may otherwise not have been considered for salvage radiotherapy may be able to undergo potential curative salvage techniques because of the high negative predictive value of advanced molecular imaging. Our preliminary data strongly suggests that *anti*-3-[^{18}F]FACBC PET-CT is the correct imaging vehicle for these decisions where others have failed.

<u>Specific Aim 2</u>: To establish the role of advanced molecular imaging with *anti*-3-[^{18}F]FACBC PET-CT in influencing post-prostatectomy radiotherapy decision-making.

As described above, the use of diagnostic imaging to guide radiotherapy is in its infancy. Current field design for prostate carcinoma radiotherapy mainly relies on the planning CT scan, with no novel imaging added beyond the bone scan and diagnostic CT scan and MRI in some situations. Adding imaging with advanced molecular methods will not only affect decisions to provide salvage radiotherapy, but also influence therapy fields, extending the potentially curative benefits of salvage techniques. For example, if internal iliac nodes are identified to be malignant with the use of *anti*-3-[^{18}F]FACBC PET-CT, those areas could have radiation fields extended or targeted with IMRT to increase likelihood of biochemical control.

<u>Specific Aim 3</u>: To establish the role of advanced molecular imaging (with *anti*-3-[^{18}F]FACBC) in altering radiotherapy treatment volumes.
<u>Utilizing novel aspects of multimodality image fusion to individualize treatment volumes</u>

As our study will evaluate the role of a PET radiotracer in post-prostatectomy radiotherapy, there are several novel aspects of multi-modality image fusion that will be explored in this study. Successful completion of this process will pave the way for multi-modality registration of other novel radiotracers in the future.

4.1 Study Endpoints:

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

3-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 v4.0 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

Preliminary Data for Specific Aims 1 and 2:

In a recent study published by our group in Radiology (50) *anti*-3-[^{18}F]FACBC has been shown to have high sensitivity and specificity in the detection of extraprostatic extension of recurrent prostate carcinoma. Briefly, in this study, *anti*-3-[^{18}F]FACBC PET-CT was compared with ^{111}Indium-capromab-pendetide (ProstaScint) performed within 6 weeks of each other in 50 patients. *anti*-3-[^{18}F]FACBC PET-CT demonstrated significantly higher sensitivity in the detection of recurrent prostate carcinoma in the prostate bed, but more importantly in 17 patients in whom there was definitive consensus as to presence or absence of extraprostatic disease, **there was 100% accuracy of *anti*-3-[^{18}F]FACBC PET-CT in the detection of extraprostatic recurrence, while the sensitivity of ProstaScint was 10%**.

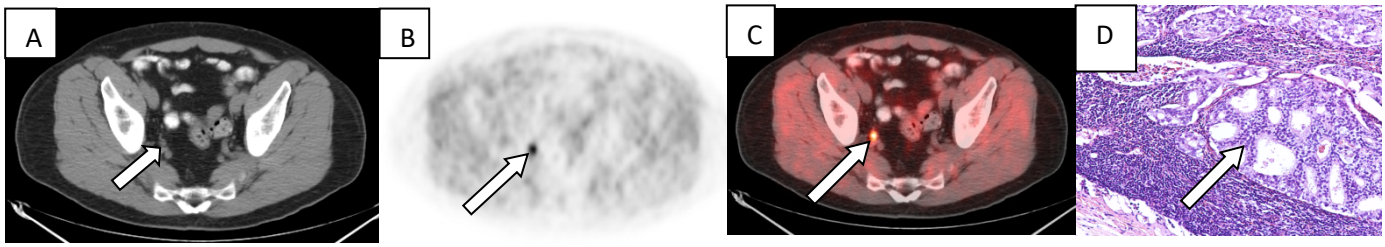
In a more recent analysis of a larger cohort, (submitted JCO), 117 patients with suspected recurrent prostate carcinoma were studied with *anti*-3-[^{18}F]FACBC PET-CT. In the 46 patients in whom there was definitive consensus on the presence or absence of extraprostatic disease, sensitivity to detect extraprostatic disease was 96.2% [CI: 80.4%, 99.9%], specificity 95.0% [CI: 75.1%, 99.9%], accuracy 95.7% [CI: 85.2%, 99.5%], PPV 96.2% [CI: 80.4%, 99.9%] and NPV 95.0% [CI: 75.1%, 99.9%]. **Diagnostic performance for extraprostatic detection remained high at all PSA levels**. The table below is a breakdown of diagnostic performance by PSA levels. Of the 26/46 patients with proof of extraprostatic disease, 21 had node only, 3 had bone, 2 had both bone and nodal involvement. Lymph node sizes detected ranged from 4 mm to 2.3 cm (mean 1.2 cm ± 0.6) [typically, nodes smaller than 1.0 cm would not be deemed suspicious in the pelvis on cross sectional imaging]. Both observers were in initial agreement 115/117 (98.3%) with kappa (SE) of 0.957 (0.03) for presence or absence of extraprostatic disease. **Most importantly, in further analysis of data for this proposal, all 6 recurrent post-prostatectomy patients subsequently treated with local salvage radiotherapy based on negative *anti*-3-[^{18}F]FACBC PET-CT for extra-prostatic disease achieved durable PSA nadir. In one of these patients, PSA at restaging, pre-salvage radiotherapy was 6.9 ng/ml.**

Table 1. Extraprostatic Disease Detection Diagnostic Performance (JCO submitted)

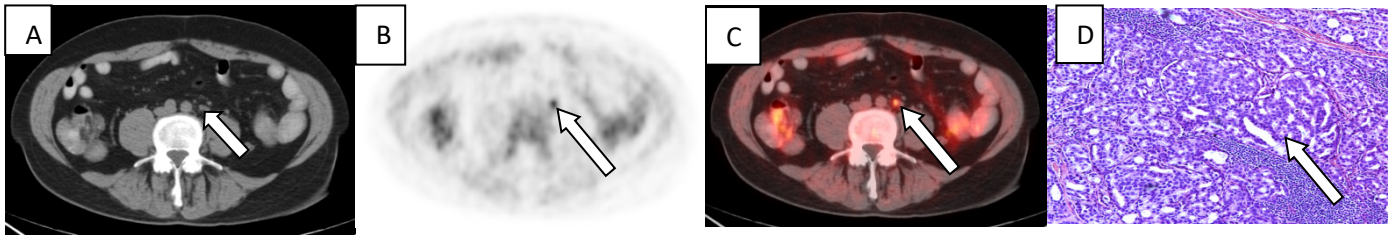
PSA (ng/ml)	<2	≥2 and <5	≥5 and <10	≥10	All PSA
True Positive	4	5	7	9	25
True Negative	8	4	4	3	19
False Positive	0	0	0	1	1
False Negative	0	0	1	0	1
Total	12	9	12	13	46
Sensitivity	100%	100%	87.5%	100%	96.2%
Specificity	100%	100%	100%	75%	95.0%
Accuracy	100%	100%	91.7%	92.3%	95.7%
PPV	100%	100%	100%	90%	96.2%
NPV	100%	100%	80%	100%	95.0%

Thus, this preliminary data demonstrates excellent diagnostic performance of *anti*-3-[^{18}F]FACBC PET-CT in the recurrent disease setting justifying its utility in guiding management decisions. Below are two representative cases in which *anti*-3-[^{18}F]FACBC PET-CT can detect occult disease and potentially guide treatment decisions both at low and high PSA levels:

Case 1: 68 year old patient post external beam radiation therapy and prostatectomy with rising PSA to 1.9 ng/ml and no abnormal findings in the prostate bed. CT (A) demonstrates 8 x 6 mm right internal iliac node (short arrow) with abnormal uptake on *anti*-3-[^{18}F]FACBC PET (B) and fused PET-CT image (C) (long arrows) which was confirmed metastasis by CT guided biopsy. H&E stained section of the lymph node (40X) (D) demonstrates metastatic adenocarcinoma (arrow) from a prostate primary.



Case 2: 60 year old patient post EBRT, brachytherapy with rising PSA to 28.7 ng/ml and biopsy positive prostate bed. CT (A) demonstrates 1 cm left common iliac (short arrow) with abnormal uptake on *anti*-3-[^{18}F]FACBC PET (B) and fused PET-CT image (C) (long arrows) which was confirmed metastasis by laparoscopic biopsy. H&E stained section of the lymph node (40X) (D) demonstrates metastatic adenocarcinoma (arrow) from a prostate primary.



Preliminary Data for Specific Aim 3:

Dr. Jani and Dr. Schuster (co-PI's on the current proposal) and Dr. Fox (Co-I on the current proposal) have worked together on a case report **[Jani AB, Fox TH, Whitaker D & Schuster D. Clinical Nuclear Medicine 2009]** (55) in which the impact of *anti*-3-[^{18}F]FACBC PET-CT on radiotherapy treatment planning was analyzed in the setting of an intact prostate. For this case report, a rigid-body registration was performed, followed by a deformable image registration in order to fuse the *anti*-3-[^{18}F]FACBC PET-CT with the radiotherapy planning CT. The results are shown below. Figure 1 depicts for a representative axial slice (a) the radiotherapy planning CT, (b) the *anti*-3-[^{18}F]FACBC PET-CT, and (c) the registered image. Figure 2 shows how the *anti*-3-[^{18}F]FACBC image could then be contoured on three levels (A) upper, (B) mid, and (C) lower on the radiotherapy planning CT to define (GTV_{FACBC} [pink]). Finally, Figure 3 shows (A) an mid-level axial representation of the radiotherapy isodose curves of the treatment plan and (B) corresponding dose-volume histograms of the planning target volumes (red, green and aqua, corresponding to various phases of the treatment), bladder (blue), and rectum (brown)

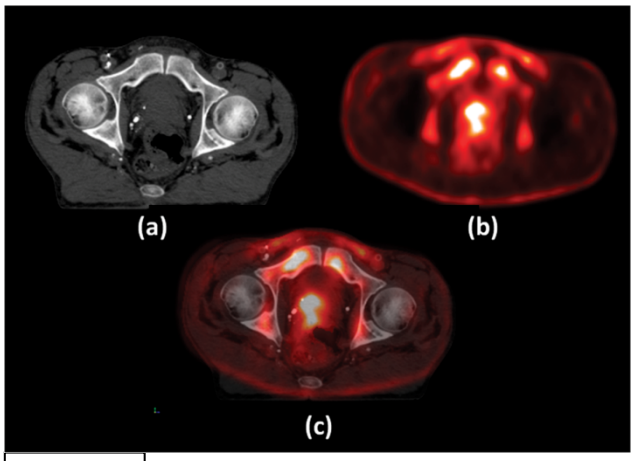


Figure 1

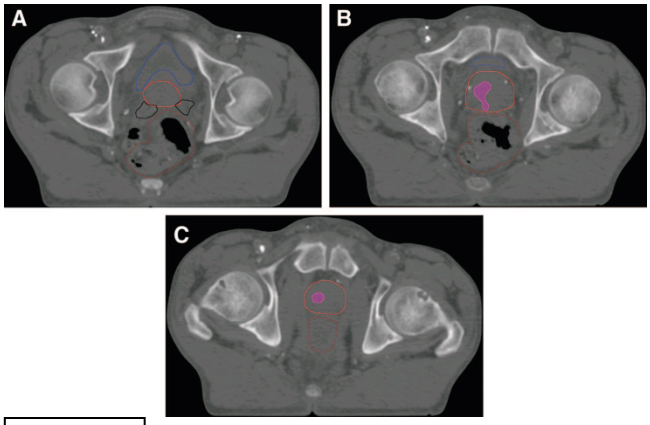


Figure 2

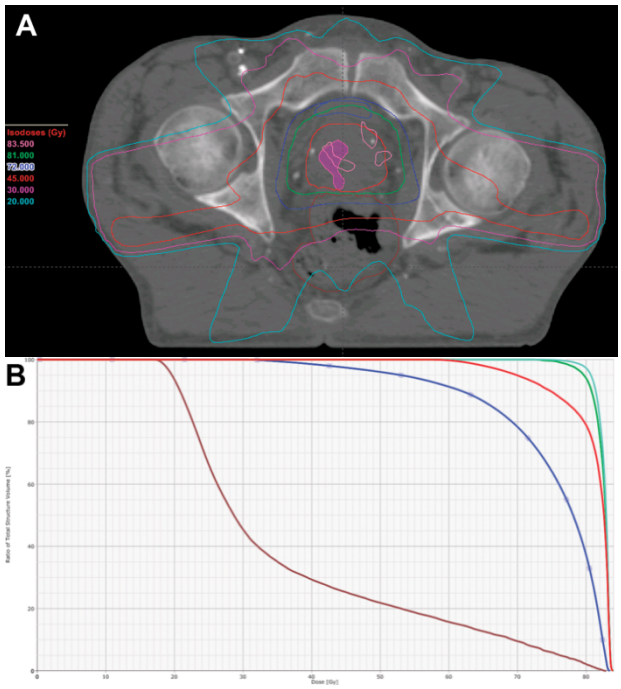


Figure 3

As shown in Figures 1 through 3 above, the process of registering and using the *anti*-3-[^{18}F]FACBC PET-CT information to design a radiotherapy treatment plan in the setting of an intact prostate has been established. For the current proposal, the rigid and deformable image methods will need to be modified for the prostate bed as the patient population under study is post-prostatectomy. The aim of registration is to establish an exact point-to-point correspondence (coordinate system transformation) between the voxels of the *anti*-[^{18}F]FACBC PET-CT with the CT simulation dataset, making direct comparison possible. A rigid coordinate transformation is when only translations in three orthogonal directions and rotations in three directions are allowed. The use of rigid registration may not provide accurate results since the patient can be positioned differently between imaging scans as well the internal organs can change position and shape. In the case of prostate imaging, this may be due to changes in volume for internal organs such as bladder and rectum. Deformable or elastic registration methods can be employed for these situations but it is not a trivial matter. Deformable image registration extracts structures from one image and elastically deforms it to fit the second image. With the deformable registration methods, the optimization algorithm is locally defined and calculated in small iterative steps using splines to mathematically represent the surfaces.

Several computational models for deformable registration have been proposed with the most commonly used being the fluid-flow approach, BSpline, and the finite element approach (FEM). Each model is applied to a particular image registration problem depending and being restricted to the type of assumptions made concerning the nature of the images to be registered. Especially relevant to the CT-CT registration problem addressed in this proposal is the BSpline technique (56-58) combined with the Mattes formulation of the mutual information metric. The performance and characteristics of the BSpline model have been intensively studied (56, 58, 59) the model being applied to CT-CT (60-62) or 2D-3D (63) registrations with an accuracy of 3 mm.

In the BSpline model, the input image is divided into a grid with N^3 cells. The corner of a lattice cell is referred to as a node and is indexed by i (i=1, 2, …N^3). The displacement of a node i is specified by a vector $\mathbf{x}_i$ and the displacement vectors, $\{\mathbf{x}_i\}$, of a collection of nodes characterize the tissue deformation. The displacement at a location $\mathbf{x}$ on the image is deduced by fitting a polynomial expressed using the basis spline (BSpline) to the grid nodes $\mathbf{x}_i$. One of the main advantages of using the spline model is that the deformation is interpolated between grid points, making it stable to pixel-level noise. Unlike other spline models, the B-Splines are locally controlled. That is, the displacement of an interpolation point is influenced only by that of the closest grid points and changing a lattice node only affects the transformation regionally, making it efficient in describing local deformations. Due to these features, the B-Spline model should perform well for fusing post-prostatectomy CT images.

Generally speaking, the input to the image registration model are two images, whose content has to be correlated. The task is to find the coefficients of a transformation matrix, $T(\mathbf{x})$, that maps an arbitrary point $\mathbf{x}$ on one image to the corresponding point $\mathbf{x}'$ on the second image so that the best possible match, as measured by the registration metric, is achieved. The metric is a usually constructed from the voxel intensities in the two images based on the image content, its choice for ranking different possible matching differentiating one algorithm from the others and being fundamental to the success of the image registration. As the metric we will select the Mattes implementation of the mutual information MI metric due to its speed, simplicity and stability to noise in the input images. The Mattes implementation does not use all voxels in the input images, rather it evaluates a random sample of the voxels and uses interpolation to evaluate the joint histogram, creating histograms that are less noisy if used as criteria for the optimization Mattes) Since only a percent of the input image voxels are used, the metric is faster than the metrics that are evaluated on the whole image.

In the BSpline model, node displacements are adjusted iteratively to minimize the metric. The limited memory BFGS algorithm L-BFGS is a good candidate to optimize the system here, for its superior performance in dealing with high-dimensionality problems. To facilitate the optimization it is preferable that both the deformable model and the metric are differentiable (60). This condition is satisfied for the system that we are dealing with, as demonstrated in a previous mathematical work (64). Additionally, it is possible that L-BFGS may produce unrealistic deformations in finding the minimum of the metric. Similar to previous investigators (60), we will use the bounded version of L-BFGSB, where variables representing deformation magnitude are restricted to within certain limits.

Depending on initial registration results, changes will be accommodated in the BSpline model to increase accuracy and decrease computation times. Since noise and artifacts in the input images affect accuracy (56), a current trend is to restrict the deformations only to relevant image regions to increase algorithm stability by decreasing the number of control points. Additionally this approach permits a simple alternative to classical multi-modality metrics for the cases voxel intensities in the input images do not build a balanced histogram for evaluating the joint information (61).

All calculations will be implemented using an open-source software toolkit named the Insight Toolkit (ITK), which consists of template-based codes for a large number of image visualization, segmentation and registration classes. The programs contained in ITK are easily extendable, making it an ideal platform for the development of image registration methods. A special filter permits connecting registration results to other medical software through the DICOM protocol. Potential indicators of the correctness of the deformation field are differential operators such as Jacobian, and vectors representations of the warping map. The Jacobian is computed from the deformation field as a measure of the local tissue expansion or contraction, with negative values implicating that the transformation map has gone singular, an indication of an unrealistic situation. It is an efficient and intuitive clinical tool for the understanding of the deformation field as it summarizes in a simple number the local characteristics of the deformation field.

Once registered to the radiotherapy planning CT scan, the process of formally comparing pre- *anti*-3-[^{18}F]FACBC vs post- *anti*-3-[^{18}F]FACBC treatment plans (for Specific Aim 3 of the current study) is well-known. Dr. Jani has led a prior team that has done this very analysis (using radioimmunoscintigraphy with ProstaScint) of volumetric and dosimetric comparisons of target volumes and their impact on dosimetry of surrounding structures, in prior publications (51, 54), and these methods can be readily extended to the *anti*-3-[^{18}F]FACBC volumes.

6.0 Study design and methods

We will undertake a clinical trial of 162 patients post-prostatectomy with detectable PSA levels. **Note that patients with <u>any</u> detectable PSA will be eligible, 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 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): (≤ 2.0 ng/mL vs > 2.0 ng/mL)
- Intended use of Hormone Therapy (yes vs no)

Patients will be randomized to:

Arm A: a control group whose treatment decisions will be made based on conventional imaging - bone scan and abdominopelvic CT scan; **<u>or</u>**

Arm B: a trial group in which *anti*-3-[^{18}F]FACBC PET-CT is used to guide radiotherapy decisions and radiotherapy treatment volumes

For patients treated in Arm B, we will compare initial (pre- *anti*-3-[^{18}F]FACBC) versus final (post- *anti*-3-[^{18}F]FACBC) 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 *anti*-3-[^{18}F] FACBC PET-CT

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

Then an *anti*-3-[^{18}F]FACBC 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
If prostate-bed only uptake:	radiotherapy to prostate bed only
If no FACBC uptake:	radiotherapy to prostate bed only

Radiotherapy plan designed first without *anti*-3-[^{18}F]FACBC information.
Then *anti*-3-[^{18}F]FACBC/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

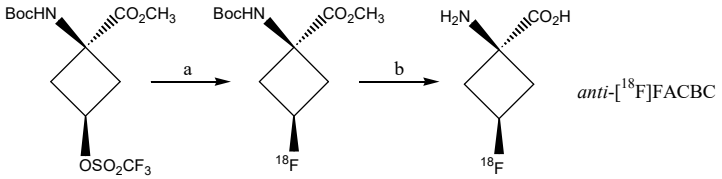
Each patient (Arms A and B) will be followed for a minimum of three years with PSA levels every 6 months and other clinical parameters to both measure presence and time to PSA failure, as well as manifestation of clinical failure as defined by macroscopic identifiable disease. Outcomes will be compared 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 *anti*-3-[^{18}F]FACBC Radiolabeling

Methods. We will prepare *anti*-3-[^{18}F]FACBC by the GE FastLab Cassette System. Alternatively, by the automated synthesis developed by J. McConathy and M.M. Goodman (65) as outlined in Figure 3. The automated radiosynthesis of *anti*-3-[^{18}F]FACBC will be carried out in a chemical process control unit (CPCU) with a computer interface. The two-step reaction sequence will involve incorporation of no-carrier-added potassium [18F]fluoride into a protected triflate precursor and deprotection using aqueous hydrochloric acid. The crude reaction mix will be passed in series through ion-retardation resin, an alumina-N SepPak®, an HLB cartridge and a 0.22 μm sterile filter, and the resulting aqueous solution will be collected in a dose vial. The radiochemical purity of the product will be determined by TLC. Additional chemical solvent purity will be measured by Gas Chromatography (GC). The total time for synthesis of *anti*-3-[^{18}F]FACBC after delivery of 18[F]fluoride will be ~70 minutes, and the average decay-corrected yield of *anti*-3-[^{18}F]FACBC will be 24 ± 4 % (n = 40 runs, average ± standard error) in over 99% radiochemical purity . This procedure will provide 140-200 mCi of anti-[18F]FACBC at the end of synthesis. We have prepared greater than 30 batch productions for tumor imaging in volunteer subjects.

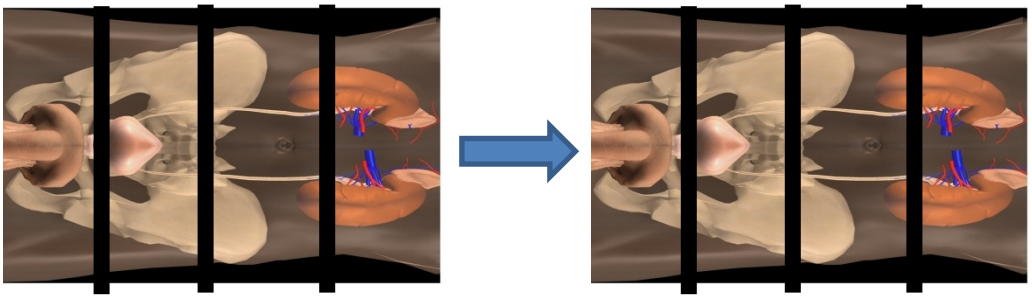
Figure 3. Synthesis of anti-FACBC



a)K^{18}F, K_{222}, K_2CO_3; 90C b) 4 NHCl, 120 C

6. 2. PET Acquisition

We have previously reported on the preparation of *anti*-3-[^{18}F]FACBC (65). The radiotracer will be produced under the auspices of investigational new drug (IND) application 72,437. A GE FastLab cassette system will be employed. Scanning will conducted on a GE Discovery MV690 PET-CT scanner with time of flight capabilities and interpreted on a workstation utilizing MIMvista 5.2 (Cleveland, OH) software. All patients will fast for 4-6 hours before the *anti*-3-[^{18}F]FACBC scan. After a CT scan of the abdomen and pelvis (80-120 mA; 120 kVp) with oral and without IV contrast, *anti*-3-[^{18}F]FACBC (10 mCi; 370 MBq) will be injected IV over 2 minutes. At 5 minutes, 4 consecutive 2.5 minutes per frame acquisitions (z axis FOV is: 15cm with 3 cm overlap per table position) will be obtained starting from the prostate level of the pelvis and extending superiorly to the diaphragm. At 16 minutes, this process will be repeated. Thus, 4-15.5 minute, and 16-27.5 minute acquisitions from the pelvis extending superiorly to the abdomen at the diaphragm will be obtained (Figure 1). This imaging schema is based on analysis of our data to date in which early and delayed uptake to 30 minutes yields the most diagnostic information. Imaging will be carried out with either HD mode and respiratory gating or TOF mode with or without respiratory gating. This timing is based upon our experience for best criteria in dual time point imaging to diagnose prostatic recurrence (50). Imaging above the diaphragm will not be carried out to best approximate standard of care CT scans of the abdomen and pelvis. Isolated prostate carcinoma metastasis above the diaphragm rarely occur.



Minutes: 5-7.5 8-10.5 11-13.5 14-15.5 16-18.5 19-21.5 22-24.5 25-27.5

Figure 16: CT of abdomen and pelvis followed by injection of anti-[18F]FACBC then PET scanning as above.

Summary of PET-CT Scanning Procedure

1) The patient will be placed in the tomographic gantry for a CT scan of the abdomen-pelvis (80-120 mA) to be utilized for anatomic imaging and correction of emission data (approximately 1 minute).
2) The patient will then receive a bolus of *anti*-[^{18}F]FACBC injected IV over 1-2 minutes
3) The dosage will be approximately 10.0 mCi (370 MBq).
4) At 5 minutes after initial injection (3 minutes after injection ceases), a 2.5 minute per bed position PET acquisition will start at the pelvis with the inferior aspect of the acquisition to include the entire prostate or prostate bed.
5) 4 bed positions will be obtained which should cover pelvis through abdomen to the diaphragm.
6) This sequence will be repeated once.
7) The entire study including injection of radiotracer should take approximately 30 minutes.

6.2.1 FDA Reporting and Laboratory Requirements

(3) The patient will be called by the study nurse within one week of the scan to determine if there were any adverse events and the record of the phone conversation will be recorded in the patient chart.

6.3 Patient Assessment: Image Analysis

Methods. The methods of image analysis to be used for the *anti*-[^{18}F]FACBC PET-CT are as follows:
1) Images will be reconstructed with iterative technique (2 iterations, 28 subsets) and hardware fused (PET to CT) on a MimVista 5.2 or similar workstation which enables SUV (mean, maximum, total lesion activity) as well as standard size measurements of lesions. An edge seeking conformational volume of interest tool (PET Edge, MIMvista, Cleveland, OH) will typically utilized. If this is not possible due to anatomy a 1 cm ROI will be utilized.
2) Visual inspection of the PET-CT images by 2 board certified nuclear medicine imagers who will be blinded to all history and other imaging. Each reader will assess images individually and any disagreement will be resolved by consensus. Thus, Z score will be calculated.
3) For *anti*-3-[^{18}F]FACBC, uptake will be defined according to the following criteria in relation to background structures: mild (above blood pool but less than marrow), moderate (above or equal

to marrow but less than liver), and intense (equal to or above liver). Visual analysis will aided by quantitative criteria of SUV_{max} lesion/SUV_{mean} background. Maximum and mean SUV of each focus of abnormal uptake as well as background structures including liver, marrow at L3, aorta, and bladder will be recorded. For prostate beds as well as extra-prostatic sites such as lymph nodes and bone, abnormal moderate or intense focal uptake over background marrow which persist from early to delayed images will be considered prospectively positive. These criteria were used to analyze data in our study of *anti*-[^{18}F]FACBC in recurrent disease (66).
4) Confidence in interpretation for disease within the prostate bed and outside the bed will be recorded with the following scale on a per patient basis and any all recordable lymph nodes: 1- defiinitvely negative; 2 -probably negative; 3 - indeterminate; 4 - probably positive; 5 – definitively positive.
5) In summary, we will record both visual and semi-quantitative analysis of the prostate bed, positive lymph nodes (greater than blood pool), and other structures such as skeletal foci on early and delayed time frames. We will use maximum and mean SUV as well as standard bidimensional size measurements. We will also record similar measurements on background structures such that we may derive uptake ratios.

6.4 Correlation of Histopathology with Imaging:

Every effort will be made to histologically confirm all *anti*-3-[^{18}F]FACBC positive nodes or other foci. Any positive uptake per above 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.

6.5 Patient follow-up

This randomized trial will us utilizing *anti*-3-[^{18}F]FACBC as an imaging 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 in different rates of toxicity than those treated with the current conventional approach.

Using standard definition of failure [serum PSA value of 0.2ng/mL or more above the postradiotherapy nadir followed by another higher value, a continued rise in the serum PSA despite radiotherapy (RT), initiation of systemic therapy after completion of RT, or clinical progression] (21), Kaplan-Meier Survival curves will be generated for both Arms A and B and compared – the primary endpoint will be 3-year failure-free survival.

This follow-up endpoint is appropriate for the current design as an adequate event rate at 3-years was noted in one of the original salvage XRT series (67). Follow-up after the 5-year period of the grant, particularly for those patients enrolled in year 3, can be completed by a minimal-cost grant extension for follow-up only.

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
- Negative technetium 99-m MDP or F-18 PET bone scan for skeletal metastasis
- CT or MR scan of abdomen and pelvis which does not suggest presence of metastatic disease outside of the pelvis
- Willingness to undergo pelvic radiotherapy.

7.2 Exclusion Criteria

- Contraindications to radiotherapy (including active inflammatory bowel disease or prior pelvic XRT)
- Inability to undergo *anti*-3-[^{18}F]FACBC PET-CT
- Age under 18
- Metastatic disease outside of pelvis on any 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:

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
PSA
If ADT intended: Serum Testosterone; Serum AST or ALT
EPIC sheet (see Appendix 2)
Pre-FACBC 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-FACBC 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): (≤ 2.0 ng/mL vs > 2.0 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: Standard/Control Arm
Arm B: FACBC 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). While ideally masking would be done (for both physicians and subject), in an imaging study this is not feasible (it not generally not possible to obtain a 'sham' FACBC scan and the study investigators would not be in equipoise if an FACBC scan were obtained on all subjects and this information were to be withheld these subjects).

Within 1 month of randomization, subjects on arm A will begin treatment (radiotherapy and/or hormones), and subjects on arm B will receive an FACBC scan. For subjects on arm B, treatment (radiotherapy and/or hormones) will begin within 1 month from the FACBC scan date.

7.4 FACBC details

For subjects randomized to arm B, the FACBC scan will be done at Emory. This has been described in detail including post-scan laboratory test required by the FDA above in sections 6.1-6.4 above. Patients will be responsible for their own travel. A travel allowance of approximately $100 per patient will be provided upon completion of all laboratory follow-up. The patient does not have to return to Emory for their follow-up laboratory work, but may provide this to the study nurse via fax, secure email, or mail.

The cost of the FACBC 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.

7.5 Radiation Therapy Details

(modeled after Radiation Therapy Oncology Group Protocol 0534:
http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0534)

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.

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 – Arm A

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 sacrorectogenitopubic 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 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 FACBC 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 FACBC scan.

7.5.4.1.3 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 will be declared after the patient is planned and all dosimetric parameters finalized.

7.5.4.1.4 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 anastamosis. 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.

7.5.4.1.5 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 (64.8-70.2 Gy); 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 enrolled on Arm 3 (those 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 – Arm A

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 (64.8-70.2 Gy), 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 of 64.8-70.2 Gy 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 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 FACBC 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 FACBC scan. PTV expansions around this final CTV1/CTV2 will be as in section 7.5.4.2.1 above.

7.5.4.2.3 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 FACBC/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 study chair 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

For Pelvic radiotherapy patients:
Pelvic_Lymph_Nodes
CTV1
CTV2

PTV1
PTV2

Additionally, for Arm B only (final volumes including FACBC information registered to planning CT scan):

For Prostate Bed only patients:
CTV_final
PTV_final

For Pelvic radiotherapy patients:
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
PSA
EPIC sheet (see Appendix 2)
Pre-FACBC 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:
- CT simulation
- Radiotherapy Treatment Planning

If randomized to Arm B:
- FACBC 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, 24, 30, and 36 month (+/- 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

>36 month (+/- two months) follow-up:
- As per clinical routine

Note that if primary endpoint is reached (i.e., 36 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 3 year biochemical failure rates between the two arms. Then a survival analysis will be conducted on biochemical failure time. The survivor functions for biochemical failure will be estimated with Kaplan and Meier method and plotted in a graph. The logrank test will be used to test the difference in the biochemical failure between the two arms. The power and sample size calculation is based on the difference in the 3 year biochemical failure rates between the two arms. We estimate that the 3 year biochemical control rates are 50% and 70% for the Arm A and Arm B, respectively. The 50% rate with conventional imaging (Arm A) has been reported in all salvage patients treated with a median PSA of 2.0 ng/mL(14-16, 21-23). The estimated improvement in biochemical failure (in Arm B) comes from the sensitivity data from the preliminary results of Aim 1 below (an estimated 25/46 (54%) true positive rate [see Table 1 in the "Preliminary Data for Specific Aim 1" subsection] would be expected to translate conservatively into a failure rate difference of 20% advantage in biochemical control at 3 years (over those treated without the aid of *anti*-3-[^{18}F]FACBC guidance). In the study, a total of 162 patients will be accrued and randomized to the two groups (Arm A and Arm B) with a ratio of 1:1. At the significance level of 0.05, the sample size of 73 patients per group will achieve a power of at least 80% to detect the difference (50% vs 70%) between the two groups using chi-square test.

Secondary endpoints:
PSA Analysis: Although stratification during enrollment will be done by PSA < 2.0 or PSA ≥ 2.0, during analysis, cohorts in arms A and B will be stratified by PSA <0.2; ≥0.2 and <1.0; ≥1.0 and <2.0; ≥2.0 and <5.0, ≥5.0 and <10.0, ≥10 ng/mL. We will continuously monitor the accrual to ensure enough patients in each strata (as was done in the prior RO1 trial); also, no more than 50% of patients in each arm will have PSA < 2.0 – this will ensure that enough high-risk patients are included. Stratification groups may be conglomerated or subdivided to achieve adequate statistical power depending on accrual figures. This will allow us to determine (a) whether patients with high PSA (a population with a relatively low chance of success with radiotherapy) can be controlled with radiotherapy guided by *anti*-3-[^{18}F]FACBC, and (b) whether for a given PSA level (in each individual or combined strata) whether *anti*-3-[^{18}F]FACBC guided radiotherapy improves biochemical control. Patients will also be analyzed per risk level stratification groups as above; this analysis will serve as the basis for design of a larger trial in the future which more closely examines the strata.
Multivariate Analysis: For the multivariate analysis of biochemical failure time, a Cox model will be employed to assess the effect of *anti*-3-[^{18}F]FACBC guided treatment on biochemical failure time after adjusting for patients' other demographic and clinical factors. To confirm that the use of *anti*-3-[^{18}F]FACBC PET-CT permits the selection of patients with high PSA levels who would not ordinarily be treated with radiotherapy, a chi-square test will also be conducted to compare frequency of patients with high PSA levels between the two arms.
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 and EPIC scores (for GU, GI, and Sexual axes, in addition to total scores) for arms A and B and compared. Additionally, a multivariate analysis will be done examining all patient demographic, disease, and treatment factors (including *anti*-3-[^{18}F]FACBC use) that influence each of these

toxicity endpoints. This will enable determining whether *anti*-3-[^{18}F]FACBC PET-CT guided treatment is tolerable compared to conventional treatment. For provider-reported toxicity, the Chi-square test will be conducted to compare the distribution of the grade (0, 1, 2, or 3) of acute GU or GI toxicity between the two arms, respectively. For the multivariate analysis of acute GU or GI toxicity, an ordered logistic model will be employed to assess the effect of *anti*-3-[^{18}F]FACBC guided treatment on the grade of acute GU or GI toxicity after adjusting for patients' other demographic and clinical factors. A survival analysis will be conducted on late GU or GI toxicity. The survivor functions for the time to late GU or 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 or GI toxicity between the two arms. For the multivariate analysis of late GU or GI toxicity, a Cox model will be employed to assess the effect of *anti*-3-[^{18}F]FACBC guided treatment on the time to late GU or GI after adjusting for patients' other demographic and clinical factors.For patient-reported toxicity, a similar analyses to that described above will be done using EPIC scores rather than CTCAE grades.

Analysis of Treatment Decisions Data

For Specific Aim 2, we will analyze patients treated in Arm B (of the randomized trial in Specific Aim 1 above) and compare initial (pre- *anti*-3-[^{18}F]FACBC) versus final (post- *anti*-3-[^{18}F]FACBC) treatment decisions regarding (a) the decision of whether to offer post-prostatectomy radiotherapy, (b) the decision of whether to treat the pelvic lymph nodes in addition to the prostate bed. We will also explore the cost-effectiveness of *anti*-3-[^{18}F]FACBC (and *anti*-3-[^{18}F]FACBC PET-CT based decision changes) in guiding post-prostatectomy treatment.

In determining the impact of *anti*-3-[^{18}F]FACBC PET-CT on the decision to offer radiotherapy, as shown in the schema of the randomized trial for Specific Aim 1 above, the radiotherapy treatment decision will be charted before the *anti*-3-[^{18}F]FACBC is completed. Then, the final decision based on the *anti*-3-[^{18}F]FACBC PET-CT will also be charted as determined by the strict protocol-defined use of *anti*-3-[^{18}F]FACBC. Then, the total number of decision changes (changes from offering radiotherapy to not, and not offering to offering radiotherapy) will be noted and compared. Similarly, in determining the impact of *anti*-3-[^{18}F]FACBC on the decision to treat pelvic lymph nodes (versus prostate bed alone), as shown in the schema of the randomized trial for Specific Aim 1 above, the radiotherapy treatment field decision will be charted before the *anti*-3-[^{18}F]FACBC PET-CT is done. Then, the final treatment field decision based on the *anti*-3-[^{18}F]FACBC will also be charted as determined by the strict protocol-defined use of *anti*-3-[^{18}F]FACBC. Then, the total number of decision changes (changes to treating regionally to include the pelvic nodes, and changes to treating the prostate fossa alone) will be noted and compared. In addition to the individual decisions regarding the decision to treat and the region to treat, these decisions will be examined (weighing each decision change equally) in composite to determine the total number of decision changes and the overall impact of *anti*-3-[^{18}F]FACBC PET-CT on decision-making.

Analysis of Data for Cost Effectiveness

A cost-effectiveness analysis based on these decision changes will also be done. As *anti*-3-[^{18}F]FACBC is used to guide decision making, the simple cost of *anti*-3-[^{18}F]FACBC PET-CT is not the only item under consideration, as the employment of *anti*-3-[^{18}F]FACBC can guide the decision on whether to offer radiotherapy and may influence the biochemical control rate and need for salvage (hormone) therapy. The two major factors that will influence the overall cost of treatment when using *anti*-3-[^{18}F]FACBC are the number of decision changes to offer versus not offer radiotherapy (and resultant salvage hormone therapy), and the biochemical failure rate difference (Arm B versus Arm A in the randomized trial).

Estimates will be made for (a) the cost of radiotherapy, (b) the cost of hormone therapy, and (c) the cost of *anti*-3-[^{18}F]FACBC. A model will be constructed which assumes (a) failures

are treated with hormone therapy, (b) decisions to abort radiotherapy imply using hormone therapy. In this manner the cost-effectiveness of *anti*-3-[^{18}F]FACBC for post-radical prostatectomy radiotherapy can be determined. Avoiding futile radiotherapy will also be factored into the data analysis as cost-saving.

Statistical considerations for Specific Aim 2:

The McNemar test will be used to compare (a) the decision to offer radiotherapy or not and (b) the decision on treatment of pelvic nodes or not between the initial (pre- *anti*-3-[^{18}F]FACBC) and final (post- *anti*-3-[^{18}F]FACBC) treatment decisions, respectively. The Stuart-Maxwell test will be also used to compare the combined number of decision changes for both decisions together between the initial (pre- *anti*-3-[^{18}F]FACBC) and final (post- *anti*-3-[^{18}F]FACBC) treatment decisions. The cost-effectiveness of *anti*-3-[^{18}F]FACBC (and *anti*-3-[^{18}F]FACBC based decision changes) in guiding post-prostatectomy treatment will be further explored by comparing the cost of radiotherapy, the cost of hormone therapy, and the cost of *anti*-3-[^{18}F]FACBC PET-CT with t-test.

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- *anti*-3-[^{18}F]FACBC) and final (post- *anti*-3-[^{18}F]FACBC) radiation treatment plans. Spearman's correlation coefficient will be estimated 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, respectively, and 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.

For this technically-oriented aim, we will analyze patients treated in Arm B (of the randomized trial in Specific Aim 1 above) and compare initial (pre- *anti*-3-[^{18}F]FACBC PET-CT) versus final (post- *anti*-3-[^{18}F]FACBC PET-CT) radiation treatment plans. We will determine the impact of *anti*-3-[^{18}F]FACBC PET-CT on (a) target volumes – the clinical target volume (CTV) and planning target volume (PTV), and (b) the planned dose delivered to surrounding normal structures (bladder, rectum, and penile bulb).

Prostate bed CTV (CTV-pre) will first be defined by CT without any *anti*-3-[^{18}F]FACBC PET-CT information – this will enable blinding of the *anti*-3-[^{18}F]FACBC PET-CT information when first designing the treatment plan. Then the *anti*-3-[^{18}F]FACBC PET-CT scan [using iso-SUV level of 2.2 (55)] will be registered to the planning CT scan using deformable registration to define the final CTV used for treatment planning (CTV-post) [see proposed details of this registration under "Preliminary Data for Specific Aim 3" subsection below]. CTV-pre and CTV-post will be compared, as will (using standard expansion from CTV to planning target volume [PTV] in both arms) PTV-pre and PTV-post. In the above manner the impact of *anti*-3-[^{18}F]FACBC PET-CT in influencing target volumes can be determined.

CTV-pre will be expanded using uniform guidelines to define PTV-pre. CTV-post will be expanded to define PTV-post. For each patient 2 plans will be generated – one using PTV-pre and a second using PTV-post. Dose volume histograms for the normal structures (rectum, bladder, and penile bulb) using standard dosimetric endpoints (V65 [%volume receiving ≥ 65 Gy], V40) and compared (51, 52). Additionally, the bladder and rectum dosimetric endpoints will be correlated with observed rates of GU and GI toxicity (which are both components of the clinical outcomes study in Specific Aim 1 above), respectively.

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.

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). In this case, this will be FACBC.

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 4.0 (CTCAE v4.0).* The CTCAE v4.0 provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE v4.0 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 v4.0 that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE v4.0.

Step 2: *Grade the event using the NCI CTCAE v4.0.*

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 FDA, 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.

Table 1. Outline of Reporting Documents to be Used:

	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]

[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 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 Principal Investigator must notify the FDA in a written IND safety report of any adverse event which is both serious and unexpected. 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

11.0 Data Safety Monitoring Plan

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute 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. The committee 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 PI will also notify the DSMC of the study status within 2 months before the next annual review is due. 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 monthly basis (and is chaired by Dr. Omer Kucuk). This body will serve as the DSMC for study sites that are external to Emory, and will produce a written document every 6 months in which the decision to proceed or to halt the study will be made based upon standard clinical and scientific standards.

12.0 References

1. Jani AB, Hellman S. Early prostate cancer: clinical decision-making. Lancet. 2003;361(9362):1045-53.PMID=12660074.
2. Mohler J, Bahnson RR, Boston B, Busby JE, D'Amico A, Eastham JA, et al. NCCN clinical practice guidelines in oncology: prostate cancer. J Natl Compr Canc Netw. 2010;8(2):162-200.PMID=20141676.
3. Ward JF, Blute ML, Slezak J, Bergstralh EJ, Zincke H. The long-term clinical impact of biochemical recurrence of prostate cancer 5 or more years after radical prostatectomy. J Urol. 2003;170(5):1872-6.PMID=14532796.
4. Partin AW, Pearson JD, Landis PK, Carter HB, Pound CR, Clemens JQ, et al. Evaluation of serum prostate-specific antigen velocity after radical prostatectomy to distinguish local recurrence from distant metastases. Urology. 1994;43(5):649-59.PMID=7513108.
5. Pilepich MV, Winter K, Lawton CA, Krisch RE, Wolkov HB, Movsas B, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys. 2005;61(5):1285-90.PMID=15817329.
6. Lawton CA, Michalski J, El-Naqa I, Buyyounouski MK, Lee WR, Menard C, et al. RTOG GU Radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2009;74(2):383-7. PMCID: 2905150.PMID=18947938.
7. Da Pozzo LF, Cozzarini C, Briganti A, Suardi N, Salonia A, Bertini R, et al. Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: the positive impact of adjuvant radiotherapy. Eur Urol. 2009;55(5):1003-11.PMID=19211184.
8. Jani AB. The effectiveness of combining hormone therapy and radiotherapy in the treatment of prostate cancer. Expert Opin Pharmacother. 2004;5(12):2469-77.PMID=15571465.
9. Jani AB, Kao J, Heimann R, Hellman S. Hormone therapy and radiotherapy for early prostate cancer: a utility-adjusted number needed to treat (NNT) analysis. Int J Radiat Oncol Biol Phys. 2005;61(3):687-94.PMID=15708246.
10. Jani AB, Basu A, Abdalla I, Connell PP, Krauz L, Vijayakumar S. Impact of hormone therapy when combined with external beam radiotherapy for early-stage, intermediate-, or high-risk prostate cancer. Am J Clin Oncol. 2003;26(4):382-5.PMID=12902891.
11. Nanda A, Chen MH, Braccioforte MH, Moran BJ, D'Amico AV. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. JAMA. 2009;302(8):866-73.PMID=19706860.
12. Choo R. Salvage Radiotherapy for Patients with PSA Relapse Following Radical Prostatectomy: Issues and Challenges. Cancer Res Treat. 2010;42(1):1-11. PMCID: 2848745.PMID=20369045.
13. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer - A randomized clinical trial. Jama-J Am Med Assoc. 2006;296(19):2329-35.PMID=ISI:000241998700020.
14. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant Radiotherapy for Pathological T3N0M0 Prostate Cancer Significantly Reduces Risk of Metastases and Improves Survival: Long-Term Followup of a Randomized Clinical Trial. J Urology. 2009;181(3):956-62.PMID=ISI:000263321800007.
15. Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K, Da Pozzo L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet. 2005;366(9485):572-8.PMID=ISI:000231227300029.
16. Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Storkel S, et al. Phase III Postoperative Adjuvant Radiotherapy After Radical Prostatectomy Compared With Radical Prostatectomy Alone in pT3 Prostate Cancer With Postoperative Undetectable Prostate-Specific

Antigen: ARO 96-02/AUO AP 09/95. Journal of Clinical Oncology. 2009;27(18):2924-30.PMID=ISI:000267133300010.
17. Swindle P, Eastham JA, Ohori M, Kattan MW, Wheeler T, Maru N, et al. Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. J Urol. 2005;174(3):903-7.PMID=16093984.
18. Schild SE, Buskirk SJ, Wong WW, Halyard MY, Swanson SK, Novicki DE, et al. The use of radiotherapy for patients with isolated elevation of serum prostate specific antigen following radical prostatectomy. J Urology. 1996;156(5):1725-9.PMID=ISI:A1996VM11700048.
19. Hudson E, Kynaston H, Varma M, Carter A, Staffurth J, Barber J, et al. Radiotherapy after radical prostatectomy for adenocarcinoma of the prostate: a UK institutional experience and review of published studies. Clin Oncol-Uk. 2008;20(5):353-7.PMID=ISI:000256581200007.
20. Stephenson AJ, Scardino PT, Eastham JA, Bianco FJ, Jr., Dotan ZA, DiBlasio CJ, et al. Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. Journal of Clinical Oncology. 2005;23(28):7005-12. PMCID: 2231088.PMID=16192588.
21. Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. Journal of Clinical Oncology. 2007;25(15):2035-41. PMCID: 2670394.PMID=17513807.
22. Swanson GP, Goldman B, Tangen CM, Chin J, Messing E, Canby-Hagino E, et al. The Prognostic Impact of Seminal Vesicle Involvement Found at Prostatectomy and the Effects of Adjuvant Radiation: Data From Southwest Oncology Group 8794. J Urology. 2008;180(6):2453-7.PMID=ISI:000260982200057.
23. Swanson GP, Hussey MA, Tangen CM, Chin J, Messing E, Canby-Hagino E, et al. Predominant treatment failure in postprostatectomy patients is local: Analysis of patterns of treatment failure in SWOG 8794. Journal of Clinical Oncology. 2007;25(16):2225-9.PMID=ISI:000247010400014.
24. Jani AB, Kao J. Postprostatectomy adjuvant versus salvage radiotherapy: a complication-adjusted number-needed-to-treat analysis. Cancer. 2005;103(9):1833-42.PMID=15756656.
25. Trock BJ, Han M, Freedland SJ, Humphreys EB, DeWeese TL, Partin AW, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. Jama. 2008;299(23):2760-9.PMID=18560003.
26. Kelloff GJ, Choyke P, Coffey DS. Challenges in clinical prostate cancer: role of imaging. AJR Am J Roentgenol. 2009;192(6):1455-70.PMID=19457806.
27. Kundra V, Silverman PM, Matin SF, Choi H. Imaging in oncology from the University of Texas M. D. Anderson Cancer Center: diagnosis, staging, and surveillance of prostate cancer. AJR Am J Roentgenol. 2007;189(4):830-44.PMID=17885053.
28. Schoder H, Larson SM. Positron emission tomography for prostate, bladder, and renal cancer. Semin Nucl Med. 2004;34(4):274-92.PMID=15493005.
29. Fowler JE, Jr., Brooks J, Pandey P, Seaver LE. Variable histology of anastomotic biopsies with detectable prostate specific antigen after radical prostatectomy. J Urol. 1995;153(3 Pt 2):1011-4.PMID=7531783.
30. Brassell SA, Rosner IL, McLeod DG. Update on magnetic resonance imaging, ProstaScint, and novel imaging in prostate cancer. Curr Opin Urol. 2005;15(3):163-6.PMID=15815192.
31. Sartor O, McLeod D. Indium-111-capromab pendetide scans: an important test relevant to clinical decision making. Urology. 2001;57(3):399-401.PMID=11248605.
32. Lange PH. PROSTASCINT scan for staging prostate cancer. Urology. 2001;57(3):402-6.PMID=11248606.

33. Seltzer MA, Barbaric Z, Belldegrun A, Naitoh J, Dorey F, Phelps ME, et al. Comparison of helical computerized tomography, positron emission tomography and monoclonal antibody scans for evaluation of lymph node metastases in patients with prostate specific antigen relapse after treatment for localized prostate cancer. J Urol. 1999;162(4):1322-8.PMID=10492189.
34. Liauw SL, Weichselbaum RR, Zagaja GP, Jani AB. Salvage radiotherapy after postprostatectomy biochemical failure: does pretreatment radioimmunoscintigraphy help select patients with locally confined disease? Int J Radiat Oncol Biol Phys. 2008;71(5):1316-21.PMID=18234446.
35. Kane CJ, Amling CL, Johnstone PA, Pak N, Lance RS, Thrasher JB, et al. Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy. Urology. 2003;61(3):607-11.PMID=12639656.
36. Hong H, Zhang Y, Sun J, Cai W. Positron emission tomography imaging of prostate cancer. Amino Acids. 2010;39(1):11-27. PMCID: 2883014.PMID=19946787.
37. Takahashi N, Inoue T, Lee J, Yamaguchi T, Shizukuishi K. The roles of PET and PET/CT in the diagnosis and management of prostate cancer. Oncology. 2007;72(3-4):226-33.PMID=18176088.
38. Beer AJ, Eiber M, Souvatzoglou M, Schwaiger M, Krause BJ. Radionuclide and hybrid imaging of recurrent prostate cancer. Lancet Oncol. 2010.PMID=20599424.
39. Apolo AB, Pandit-Taskar N, Morris MJ. Novel tracers and their development for the imaging of metastatic prostate cancer. J Nucl Med. 2008;49(12):2031-41.PMID=18997047.
40. Bouchelouche K, Tagawa ST, Goldsmith SJ, Turkbey B, Capala J, Choyke P. PET/CT Imaging and Radioimmunotherapy of Prostate Cancer. Semin Nucl Med. 2011;41(1):29-44.PMID=21111858.
41. Picchio M, Briganti A, Fanti S, Heidenreich A, Krause BJ, Messa C, et al. The Role of Choline Positron Emission Tomography/Computed Tomography in the Management of Patients with Prostate-Specific Antigen Progression After Radical Treatment of Prostate Cancer. Eur Urol. 2010.PMID=20869161.
42. Plathow C, Weber WA. Tumor cell metabolism imaging. J Nucl Med. 2008;49 Suppl 2:43S-63S.PMID=18523065.
43. Eiber M, Beer AJ, Holzapfel K, Tauber R, Ganter C, Weirich G, et al. Preliminary results for characterization of pelvic lymph nodes in patients with prostate cancer by diffusion-weighted MR-imaging. Invest Radiol. 2010;45(1):15-23.PMID=19996762.
44. Ravizzini G, Turkbey B, Kurdziel K, Choyke PL. New horizons in prostate cancer imaging. Eur J Radiol. 2009;70(2):212-26. PMCID: 2702141.PMID=18993004.
45. Giovacchini G, Picchio M, Coradeschi E, Bettinardi V, Gianolli L, Scattoni V, et al. Predictive factors of [(11)C]choline PET/CT in patients with biochemical failure after radical prostatectomy. Eur J Nucl Med Mol Imaging. 2010;37(2):301-9.PMID=19756592.
46. Mertens K, Slaets D, Lambert B, Acou M, De Vos F, Goethals I. PET with (18)F-labelled choline-based tracers for tumour imaging: a review of the literature. Eur J Nucl Med Mol Imaging. 2010;37(11):2188-93.PMID=20544193.
47. Schuster DM, Votaw JR, Nieh PT, Yu W, Nye JA, Master V, et al. Initial Experience with the Radiotracer Anti-1-Amino-3-18F-Fluorocyclobutane-1-Carboxylic Acid with PET/CT in Prostate Carcinoma. J Nucl Med. 2007;48(1):56-63.PMID=17204699.
48. Oka S, Hattori R, Kurosaki F, Toyama M, Williams LA, Yu W, et al. A Preliminary Study of Anti-1-Amino-3-18F-Fluorocyclobutyl-1-Carboxylic Acid for the Detection of Prostate Cancer. J Nucl Med. 2007;48(1):46-55.PMID=17204698.
49. Okudaira H, Shikano N, Nishii R, Miyagi T, Yoshimoto M, Kobayashi M, et al. Putative Transport Mechanism and Intracellular Fate of Trans-1-Amino-3-18F-Fluorocyclobutanecarboxylic Acid in Human Prostate Cancer. J Nucl Med. 2011;52(5):822-9.PMID=21536930.

50. Schuster DM, Savir-Baruch B, Nieh PT, Master VA, Halkar RK, Rossi PJ, et al. Detection of Recurrent Prostate Carcinoma with anti-1-Amino-3-18F-Fluorocyclobutane-1-Carboxylic Acid PET/CT and 111In-Capromab Pendetide SPECT/CT. Radiology. 2011;259(3):852-61. PMCID: 3099047.PMID=21493787.
51. Jani AB, Spelbring D, Hamilton R, Blend MJ, Pelizzari C, Brendler C, et al. Impact of Radioimmunoscintigraphy on definition of clinical target volume for radiotherapy after prostatectomy. Journal of Nuclear Medicine. 2004;45(2):238-46.PMID=ISI:000189082500033.
52. Jani AB, Blend MJ, Hamilton R, Brendler C, Pelizzari C, Krauz L, et al. Radioimmunoscintigraphy for postprostatectomy radiotherapy: Analysis of toxicity and biochemical control. Journal of Nuclear Medicine. 2004;45(8):1315-22.PMID=ISI:000223188300021.
53. Jani AB, Blend MJ, Hamilton R, Brendler C, Pelizzari C, Kranz L, et al. Influence of radioimmunoscintigraphy on postprostatectomy radiotherapy treatment decision making. Journal of Nuclear Medicine. 2004;45(4):571-8.PMID=ISI:000220729700014.
54. Su A, Blend MJ, Spelbring D, Hamilton RJ, Jani AB. Postprostatectomy target-normal structure overlap volume differences using computed tomography and radioimmunoscintigraphy images for radiotherapy treatment planning. Clin Nucl Med. 2006;31(3):139-44.PMID=16495731.
55. Jani AB, Fox TH, Whitaker D, Schuster DM. Case study of anti-1-amino-3-F-18 fluorocyclobutane-1-carboxylic acid (anti-[F-18] FACBC) to guide prostate cancer radiotherapy target design. Clin Nucl Med. 2009;34(5):279-84.PMID=19387202.
56. Rueckert D, Sonoda LI, Hayes C, Hill DL, Leach MO, Hawkes DJ. Nonrigid registration using free-form deformations: application to breast MR images. IEEE Trans Med Imaging. 1999;18(8):712-21.PMID=10534053.
57. Rohlfing T, Maurer CR, Jr., O'Dell WG, Zhong J. Modeling liver motion and deformation during the respiratory cycle using intensity-based nonrigid registration of gated MR images. Med Phys. 2004;31(3):427-32.PMID=15070239.
58. Rohlfing T, Maurer CR, Jr., Bluemke DA, Jacobs MA. Volume-preserving nonrigid registration of MR breast images using free-form deformation with an incompressibility constraint. IEEE Trans Med Imaging. 2003;22(6):730-41.PMID=12872948.
59. Loeckx D, Maes F, Vandermeulen D, Suetens P. Non-rigid image registration using a statistical spline deformation model. Inf Process Med Imaging. 2003;18:463-74.PMID=15344480.
60. Mattes D, Haynor DR, Vesselle H, Lewellen TK, Eubank W. PET-CT image registration in the chest using free-form deformations. IEEE Trans Med Imaging. 2003;22(1):120-8.PMID=12703765.
61. Schreibmann E, Chen GT, Xing L. Image interpolation in 4D CT using a BSpline deformable registration model. Int J Radiat Oncol Biol Phys. 2006;64(5):1537-50.PMID=16503382.
62. Loeckx D, Maes F, Vandermeulen D, Suetens P. Temporal subtraction of thorax CR images using a statistical deformation model. IEEE Trans Med Imaging. 2003;22(11):1490-504.PMID=14606682.
63. Zhang X, Zheng G, Langlotz F, Nolte LP. Assessment of spline-based 2D-3D registration for image-guided spine surgery. Minim Invasive Ther Allied Technol. 2006;15(3):193-9.PMID=16785186.
64. Bernard O, Friboulet D, Thevenaz P, Unser M. Variational B-spline level-set: a linear filtering approach for fast deformable model evolution. IEEE Trans Image Process. 2009;18(6):1179-91.PMID=19403364.
65. McConathy J, Voll RJ, Yu W, Crowe RJ, Goodman MM. Improved synthesis of anti-[18F]FACBC: improved preparation of labeling precursor and automated radiosynthesis. Appl Radiat Isot. 2003;58(6):657-66.PMID=12798374.

66. Schuster D, Savir-Baruch B, Nieh P, Master V, Halkar R, Rossi P, et al. Detection of Recurrent Prostate Carcinoma with anti-1-Amino-3-F-18-Fluorocyclobutane-1-Carboxylic Acid PET/CT and In-111-Capromab Pendetide SPECT/CT. Radiology. 2011;259(3):852-61.PMID=WOS:000290898100026.
67. Stephenson AJ, Shariat SF, Zelefsky MJ, Kattan MW, Butler EB, Teh BS, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA. 2004;291(11):1325-32.PMID=15026399.

13.0 Appendices

Appendix 1: ECOG/Zubrod Performance Scale
Appendix 2: EPIC
Appendix 3: Pre-FACBC Radiotherapy Decision Sheet
Appendix 4: RTOG/CTCAE Toxicity Grading
Appendix 5: Follow-up Data Sheet
Appendix 6: Study Parameters Table

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-FACBC 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 4.0 can be found at the following link:

http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

The common side effects related to pelvic radiotherapy are gastrointestinal (pages 28-54 of the above PDF), and urinary (pages 147-152 of above PDF).

Appendix 5:

Follow-up Data Sheet

Note: This form must be provided at each of 1, 6, 12, 18, 24, 30, and 36 months 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	1mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	As per routine
Symptom-Directed Exam	x	x	x	x	x	x	x	x	x	x
DRE	x			x	x	x	x	x	x	x
Performance Status	x		x	x	x	x	x	x	x	x
Prostatectomy Report	x									
PSA	x		x	x	x	x	x	x	x	x
Bone Scan	x									x
CT or MRI pelvis	x									x
EPIC	x		x	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	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	If on H	If on H
FACBC scan & related labs (only after RDS completed)	Arm B only									
CT simulation	x									
XRT plan registration	x									

AE evaluation		x	x	x	x	x	x	x	x	x

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