SUMMARY OF CHANGES

Protocol Amendment #6

LCCC 1908: Image-Adapted Target Volumes Using 68Ga-HBED-CC PSMA-PET/MRI for Unfavorable-Risk Prostate Cancer Patients Receiving Radiation

AMENDMENT INCORPORATES:

_X_ Editorial, administrative changes
__ Scientific changes
__ Therapy changes
__ Eligibility Changes

Rationale for amendment: The purpose of this amendment is to update the protocol to support early closure of study due to low patient accrual and subsequent lack of funding. It is also important to note that 68Ga-HBED-CC PSMA-PET/MRI is no longer investigational.

Editorial, administrative changes:

Section 6.6	Language added to reflect circumstances of patient removal from the study
Section 10.3	Language added to reflect circumstances of early termination of the study

THE ATTACHED VERSION DATED July 24, 2024 INCORPORATES THE ABOVE REVISIONS

SUMMARY OF CHANGES

Protocol Amendment #5

LCCC 1908: Image-Adapted Target Volumes Using 68Ga-HBED-CC PSMA-PET/MRI for Unfavorable-Risk Prostate Cancer Patients Receiving Radiation

AMENDMENT INCORPORATES:

_X_ Editorial, administrative changes
_X_ Scientific changes
__ Therapy changes
__ Eligibility Changes

Rationale for amendment: The purpose of this amendment is to update the protocol with respect to the ^{68}Ga-PSMA-11 radiotracer that was once investigational and is now a commercial product. Accordingly, the language within the protocol was amended. The appendix was also updated with the most recent version of the PCSI questionnaire.

Editorial, administrative changes:

___	Mechanical edits made throughout
Section 6.2	Language added referencing package insert
Section 11.2___	List of required documents updated

Scientific changes:

Section 6.1.1.1 ___	The ^{68}Ga-PSMA-11 radiotracer will now be via a commercial kit. Language regarding the synthesis and quality control of [68Ga]-PSMA removed.
Section 6.2	Investigational PSMA tracer language removed
Appendix A.5	Updated PCSI: QoL questionnaire added.

THE ATTACHED VERSION DATED April 14, 2023 INCORPORATES THE ABOVE REVISIONS

LCCC 1908: Image-Adapted Target Volumes Using 68Ga-HBED-CC PSMA-PET/MRI for Unfavorable-Risk Prostate Cancer Patients Receiving Radiation

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LCCC 1908: Image-Adapted Target Volumes Using 68Ga-HBED-CC PSMA-PET/MRI for Unfavorable-Risk Prostate Cancer Patients Receiving Radiation

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: Michael Repka, MD

PI Signature: via IRBIS certification

Date: _____

Protocol Version Date: July 24, 2024

LIST OF ABBREVIATIONS

ADT	androgen-deprivation therapy
BRIC	Biomedical Research Imaging Center
CK	CyberKnife
CRF	case report form
CTCAE	common terminology criteria for adverse events
CTV	clinical target volume
DIL	dominant intra-prostatic lesion
EBRT	external beam radiation therapy
EPIC	expanded prostate cancer index composite
EQD_2	equivalent dose in 2 Gy per fraction
^{68}Ga	gallium 68
GI	gastrointestinal
GU	genitourinary
INR	International Normalized Ratio
mpMRI	multi-parametric magnetic resonance imaging
PCSI	prostate cancer symptom indices
PET	positron emission tomography
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
PT	Prothrombin time
PTT	Partial thromboplastin time
PTV	planning target volume
SBRT	stereotactic body radiation therapy
SIB	simultaneous integrated boost
XRT	radiation therapy

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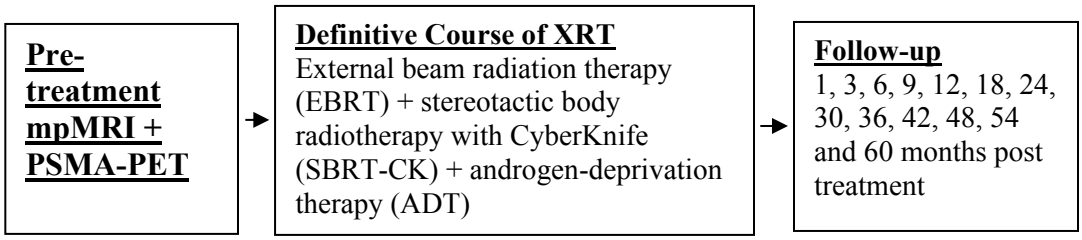
1.0 STUDY SCHEMA

The purpose of this study is to determine the feasibility and toxicity of using prostate-specific membrane antigen-positron emission tomography (PSMA-PET) and multi-parametric magnetic resonance imagining (mpMRI) to guide target volumes for patients with unfavorable-risk prostate cancer receiving radiation. The study schema is shown in **Figure 1**.

Figure 1. Study Schema



2.0 BACKGROUND AND RATIONALE

2.1 Study Overview

Title of the study	Image-Adapted Target Volumes Using ^{68}Ga-HBED-CC PSMA-PET/MRI for Unfavorable-Risk Prostate Cancer Patients Receiving Radiation
Short description of the study	PSMA-PET/MRI Unfavorable-Risk Target Volume Pilot Study
Indication	Primary radiation therapy for localized prostate cancer
Primary objective of the study	To determine the safety of using PSMA-PET/MRI to define radiotherapy targets, while meeting all the current planning criteria.
Secondary objectives of the study	To further describe the adverse events associated with using PSMA-PET/MRI to define radiotherapy target volumes in subjects with unfavorable-risk prostate cancer. To evaluate biochemical control after radiotherapy in subjects who have received PSMA-PET/MRI to define radiotherapy target volumes.

	To measure patient-reported quality of life prior to radiation therapy and over time in subjects with prostate cancer who have received PSMA-PET/MRI to define radiotherapy target volumes. To determine the proportion of screened subjects who are enrolled on the study.
Exploratory objectives of the study	[redacted]
Study design	One study arm, Phase II
Inclusion criteria	Written informed consent obtained to participate in the study and HIPAA authorization for release of personal health information. Male subjects ≥ 18 years of age Histologically confirmed prostate adenocarcinoma Unfavorable intermediate or high-risk, based on the NCCN criteria[31] (Appendix A.1), with appropriate staging (e.g. bone scan) Subject has adequate performance status as defined by ECOG performance status of 0-2. (Appendix A.2) Subject is willing and able to comply with the protocol as determined by the Treating Investigator. Subject speaks English (quality of life instrument is validated in English)
Exclusion criteria	Contraindications for MRI

	Other prior or concomitant malignancies with the exception of: • Non-melanoma skin cancer • Other cancer for which the subject has been disease free for ≥5 years before the first study treatment and of low potential risk for recurrence. Inflammatory bowel disease
Number of patients	42
Primary endpoints	The planning criteria that will be used are the current standard of care and standard practice at UNC and includes defined treatment volumes with a prescribed dose while respecting the dose constraints to all organs at risk. The primary endpoint is grade 3+ late genitourinary toxicity and gastrointestinal toxicity as classified and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 at 12 months after radiation therapy.
Secondary endpoints	Grade 3+ acute and late genitourinary and gastrointestinal toxicity will be defined according to CTCAE, version 5.0 during radiation therapy and at 1, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months post radiotherapy. Biochemical control will be defined according to the Phoenix criteria33 (PSA rise of 2 ng/mL over nadir) at 2 and 5 years after radiation therapy. Patient reported quality of life will be measured using the Expanded Prostate Cancer Index Composite (EPIC-26) and the Urinary Obstruction/Irritation scale of the validated Prostate Cancer Symptom Indices (PCSI). Patient reported quality of life will be measured before the start of radiation therapy at 1, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months post radiotherapy. The total number of subjects enrolled on the study will be compared to the total number of screened subjects.

	The feasibility of meeting dose constraints will be defined as the proportion of subjects who meet the following dose constraint criteria:
	• SBRT-CK boost dose prescription: 6.5Gy x 3
	  ○ PTV: V19.5Gy > 95%
	  ○ PTVmax > 150%, CI < 1.8
	  ○ CTV: V19.5Gy > 99%
	  ○ DIL: V24.0Gy > 99%
	• SBRT-CK boost dose constraints:
	  ○ Rectum
	  ▪ V21.1Gy< 5 %
	  ▪ V18.9Gy< 20 %
	  ▪ V17.5Gy< 10 %
	  ▪ V16.2Gy< 40 %
	  ▪ V10.2Gy< 60 %
	  ▪ V9.3Gy< 40 %
	  ▪ V19.5Gy< 1cc
	  ▪ Max<21.2Gy
	  ○ Bladder
	  ▪ V21.1Gy< 5 %
	  ▪ V19.5y< 5 cc
	  ▪ V9.3Gy< 40 %
	  ▪ Max<21.2Gy
	  ○ Prostatic Urethra
	  ▪ V19.5Gy > 95%
	  ▪ V22Gy < 0.03cc
	  ○ Membranous Urethra
	  ▪ V18 Gy < 50%
	  ○ Large bowel
	  ▪ V15Gy< 1cc
	  ○ Small bowel
	  ▪ V15Gy< 1cc
	  ○ Penile bulb
	  ▪ V15Gy< 3cc
	Performance of PSMA-PET/MRI to PSMA PET/CT as defined as:
	• Rate of identification and delineation of DIL
	  ○ Compared to a gold standard of image-guided prostate biopsy
	• Rate of identification of positive pelvic nodes

	• Rate of identification of distant metastatic disease in the pelvis Rate of identification of positive pelvic nodes by PSMA-PET and therefore the proportion of patients who have pelvic nodes included in the radiation field.
Schedule	• Start: January 2023 • Recruitment period: 24 months • Provisional conclusion: January 2026 for primary endpoint Study will terminate with the completion of the last follow-up in the last enrolled patient, unless study ends
Participating centers	Single center

2.2 Study Synopsis

The goals of this pilot trial are to:

1. Test the safety and feasibility of designing the radiation treatment plan so that the entire prostate receives the prescribed dose of radiation in addition to the visible tumor in the prostate (as detected by mpMRI and/or PSMA-PET (i.e. dominant intra-prostatic lesion (DIL))) receiving any inevitable intrinsic plan "hot spots" or areas of dose above the prescription
2. Test the safety and feasibility of designing the radiation treatment plan so that the pelvic lymph nodes are covered (or not covered) depending on whether visible tumor is detected by mpMRI and/or PSMA-PET imaging.

It should be noted that the prescription dose given in this study will be no different than current practice and that all radiation plans have hot spots. This study will focus the hot spots on regions determined by mpMRI + PSMA-PET to have visible tumor as opposed to the current practice where hot spot regions are randomly located in the target. Additionally, it should be noted that it is not a consensus as to whether pelvic nodes should be treated in addition to the prostate in this unfavorable risk population and that practice patterns as to whether the pelvic notes are treated differ. Simply, this study aims to determine if mpMRI and PSMA-PET imaging can help optimize 1) the location of the high dose region of SBRT-CK and 2) pelvic lymph node coverage. As all radiation plans designed and delivered to the patient as part of this trial will follow current standards on respecting dose constraints to organs surrounding the prostate and pelvic lymph nodes, including urethra, bladder, small bowel, and rectum, we do not expect the toxicities to differ from those observed in standard of care practices.

Of note, the imaging agent, PSMA, has usage guideline-dictated by other countries and we do not anticipate any toxicity or safety issues as they relate to the PSMA

itself. To our knowledge, there have been no reported substantive adverse effects due to its use.[1,2]

The feasibility questions: Is it possible to design "smarter" radiation plans for enrolled patients that covers the entire prostate (standard), respects all dose constraints to surrounding organs (standard), and also preferentially place the inevitable hot spots at the image-identified lesion within the prostate, all without violating the standard dose constraints for the normal tissues (organs at risk)? Furthermore, is it possible to more intelligently make the decision of whether or not to treat the pelvic lymph nodes with guidance from imaging results?

The safety question: Does delivering this treatment to the patient lead to increased side effects (compared to historical data)?

2.3 Investigational Imaging Background

Interest in using ^{68}Ga-PSMA PET/CT in the setting of unfavorable risk and biochemically recurrent prostate cancer has increased tremendously since it was introduced in 2012.[3] Regarding radiation field design, PSMA-PET has been shown to influence the radiation planning in nearly 50% of patients with high risk disease (includes patients with recurrent disease as well as those at initial presentation).[4,5] In a prospective study of 108 unfavorable risk prostate cancer patients at initial presentation, PSMA-PET imaging influenced treatment design in 21% of patients.[6] Further, Dewes et al. conducted a retrospective study of 15 patients and evaluated the utility of PSMA-imaging and if it influenced the radiation treatment target volumes. They found the radiation concept changed in 33% of all patients, leading to relevant changes in the planning target volumes, including an additional irradiation of the pelvic lymph nodes due to tracer uptake in 25% of patients.[7] Therefore it is likely PSMA-PET/CT can be useful in radiation field design.

Corfield et al. conducted a systematic review of ^{68}Ga-PSMA PET for primary staging of high-risk prostate cancer and concluded, based on 12 studies of 322 patients, it outperforms traditional imaging modalities.[8] Their study included the results from Budaus et al. who conducted a retrospective study of 608 lymph nodes removed from men with high risk prostate cancer who had preoperative ^{68}Ga-PSMA-PET/CT scans and compared them to histologic findings after radical prostatectomy with lymph node dissection. They found the sensitivity, specificity, positive predictive value, and negative predictive value of ^{68}Ga-PSMA-PET/CT for lymph node metastasis detection were 33.3%, 100%, 100%, and 69.2%, respectively.[9] In a recent systematic review and meta-analysis, the following predictive ability of PSMA-PET imaging for primary staging purposes was found. Incorporating the results of five different studies with a total of 244 high and intermediate risk prostate cancer patients, on a per-lesion analysis the summary sensitivity and specificity were 75% and 99%, respectively. On a per-patient analysis the summary sensitivity and specificity were 77% and 97%, respectively.[10]

Regarding nodal radiation, there are three published large randomized controlled trials looking at the role of pelvic nodal irradiation in nonmetastatic prostate cancer which have proved inconclusive.[11–13] More recently, a randomized study conducted at a single institution in India (POP-RT, Murthy et al., JCO 2021) demonstrated improvements in biochemical failure free survival, disease free survival, and distant metastasis free survival with the addition of pelvic radiotherapy in patients with a nomogram-predicted risk of occult nodal metastasis exceeding 20%.[14] There are two more trials currently underway (NCT01368588; PEACE 2 - GETUG - AFU 23) with estimated primary completion dates in 2025-2027.[15,16] Collectively, these studies demonstrate the clinical equipoise in this area (whether or not to include nodes in the treatment field), which has been an area of intense debate for at least two decades (Nguyen & D'Amico, JCO 2008; Roach, JCO 2008).[17,18]

Regarding defining intraprostatic lesions, ^{68}Ga-PSMA-PET alone has not been perfect. One meta-analysis found in seven studies that PSMA-expressing lesions were identified in only 203 of 273 patients (74%).[19] However, this number appears to be confounded by lymph node detection rates. When looking at PSMA-PET defined DILs alone, the detection rates could be over 95%,[20] and may be even higher in high-risk disease which have greater PSMA-PET avidity.[21] Three separate studies have shown that MRI and PSMA can deliver complimentary information on the localization of DILs.[22–24] Therefore, it is likely PSMA PET-MRI is advantageous to PSMA PET-CT alone in identifying DILs. In a slice-by-slice analysis with histopathology, the sensitivity for PSMA PET alone, mpMRI alone, and PSMA PET-MRI combined, was 75%, 70%, and 82%, respectively for prostate cancer tumor detection. The specificity was 87%, 82%, and 67%, respectively.[25] Others have also found PSMA-PET/MRI to be superior to multiparametric MRI alone in detecting prostate cancer.[26]

The concept of biological-guided (e.g. with PET) dose escalation (e.g. to DILs) is not new,[27] but has never been done with in combination with SBRT-CK. A feasibility study such as the current study under investigation will be the first step to investigating this question. Based on other studies, know that dose escalation in prostate cancer improves progression free survival.[28,29]

Other nations have been quicker to explore ^{68}Ga-PSMA-PET/CT imaging for prostate cancer and guideline standards have been developed in Europe in regards to the recommendation, performance, interpretation and reporting of PSMA-PET/CT for prostate cancer imaging. One such endorsed use is for primary staging in high-risk disease before planning external beam radiation.[1] Additionally, the Australian and New Zealand Radiation Oncology Genito-Urinary group recommends considering PSMA-PET in the setting of recurrent disease post-prostatectomy at low PSA levels because of its sensitivity over other imaging modalities.[2]

Importantly, for all of these studies, the impact on patient-reported quality of life of this approach has not been described.

Furthermore, in published literature, probability of tumor control for prostate cancer has been associated with radiation dose. Martinez et al.[30] showed that a dose of $EQD_2 > 100$ Gy (using $\alpha / \beta = 1.2$ Gy) had a significant effect on the recurrence rate of prostate cancer. Converting this EQD2 dose to clinical practice, as relevant for the current pilot trial, we will increase area of visible tumor to receive at least EQD2 > 100 Gy.[30]

2.4 Rationale

Radiation therapy is a standard curative option for patients with localized prostate cancer. At UNC, patients with unfavorable intermediate and high-risk prostate cancer are offered radiation usually given with a long course (18 months) of androgen deprivation therapy. The radiation can be given as moderately hypoefractionated radiotherapy alone, or with with a combination of conventionally fractionated external beam radiation therapy (EBRT) (25 daily treatments) and boost utilizing stereotactic body radiotherapy (SBRT) with CyberKnife (CK). Our standard practice is to include the pelvic nodes in our treatment field, although as previously discussed this topic is controversial. These are standard treatment options according to NCCN guidelines.[31] With current standard radiation doses, 5-year recurrence-free survival is reported to be 83% (unfavorable risk disease). Additionally, when the radiation fields are designed, the primary tumor location within the prostate is not typically taken into account, rather, the entire prostate is treated uniformly.

The availability of the PET-MRI facility at UNC (Biomedical Research Imaging Center, BRIC) uniquely allows us to examine these clinically-relevant questions using an mpMRI/PSMA-PET scan. Patients participating on this trial will have, using the same injection, an mpMRI/PSMA-PET scan and a PSMA-PET/CT scan, both of which will be used to help with radiation design. The long-term goal of this line of research is to allow smarter radiation design in the future that more specifically targets the tumor(s), therefore maximizing the therapeutic window (by focusing treatment more where there is cancer and not treating where there is no cancer). There is significant long-term potential for this research as imaging continues to improve and PSMA-PET/mpMRI becomes more widely adapted. UNC's PET-MRI is one of only a few in the country, which positions UNC to be a leader in the development of this technology. This study will also help create new knowledge in terms of comparability of PET/MR and PET/CT, and how the information gained on PET/MR could potentially be transferred to PET/CT, the latter of which is more widely available.

Image-adapted prostate irradiation

Currently, all radiation treatment is designed to treat the entire prostate to a prescribed dose. However, improvements in imaging, such as with multi-parametric MRI (mpMRI) and PSMA-PET, which can be used to visualize tumor locations within the prostate, allow exploration of smarter radiation designs that concentrate the inevitable heterogeneous hot spots in a radiation plan on the area(s)

of visible tumor. Specifically, mpMRI has already revolutionized the way prostate biopsies are performed to diagnose or follow men with prostate cancers. Historically, prior to the availability of mpMRI when prostate tumors cannot be visualized, biopsies are done with random sampling of the prostate. More recently, clinical trials have shown that mpMRI-guided prostate biopsies are better than random sampling biopsies in diagnosing high-grade, clinically relevant prostate cancer.[32] This same targeted approach of diagnosis can be adapted to radiation treatment.

Image-adapted pelvic nodal irradiation
Currently, patterns of practice vary as to whether the pelvic lymph nodes are included in the radiation field for men with unfavorable risk prostate cancer. The NCCN simply states "prophylactic nodal radiation can be considered".[31] Improvements in imaging may allow the exploration of smarter radiation design by better identifying the subset of men who would stand to benefit from the inclusion of pelvic lymph nodes in the radiation field. Specifically, mpMRI and PSMA-PET may better identify lymph node involvement, and thus their inclusion in the radiation fields.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

3.1.1 To determine the safety of using PSMA-PET/MRI to define radiotherapy targets, while meeting all the current planning criteria.

Hypothesis: Using PSMA-PET/MRI to define radiotherapy targets in patients with unfavorable-risk prostate cancer does not increase toxicity at 1 year after radiation, relative to historical controls.

3.2 Secondary Objectives

3.2.1 To further describe the adverse events associated with using PSMA-PET/MRI to define radiotherapy target volumes in subjects with unfavorable-risk prostate cancer.

3.2.2 To evaluate biochemical control after radiotherapy in subjects who have received PSMA-PET/MRI to define radiotherapy target volumes.

3.2.3 To measure patient-reported quality of life prior to radiation therapy and over time in subjects with prostate cancer who have received PSMA-PET/MRI to define radiotherapy target volumes.

3.2.4 To determine the proportion of screened subjects who are enrolled on the study.

3.3 Exploratory Objectives

3.3.1 [redacted]

3.3.2 [redacted].

4.0 STUDY ENDPOINTS

4.1 Primary

The planning criteria that will be used are the current standard of care and standard practice at UNC and includes defined treatment volumes with a prescribed dose while respecting the dose constraints to all organs at risk. The primary endpoint is grade 3+ late genitourinary toxicity and gastrointestinal toxicity as classified and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 at 12 months after radiation therapy.

4.2 Secondary

4.2.1 Grade 3+ acute and late genitourinary and gastrointestinal toxicity will be defined according to CTCAE, version 5.0 during radiation therapy and at 1, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months post radiotherapy. Additionally, this will be reported as a cumulative incidence over the entire 5-year course of the study.

4.2.2 Biochemical control will be defined according to the Phoenix criteria[33] (PSA rise of 2 ng/mL over nadir) at 2 and 5 years after radiation therapy.

4.2.3 Patient reported quality of life will be measured using the Expanded Prostate Cancer Index Composite (EPIC-26) and the Urinary Obstruction/Irritation scale of the validated Prostate Cancer Symptom Indices (PCSI). Patient reported quality of life will be measured before the start of radiation therapy at 1, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months post radiotherapy.

4.2.4 The total number of subjects enrolled on the study will be compared to the total number of screened subjects.

4.2.5 The feasibility of meeting dose constraints will be defined as the proportion of subjects who meet the following dose constraint criteria:

- SBRT-CK boost dose prescription: 6.5Gy x 3
  - PTV: V19.5Gy > 95%
  - PTVmax > 150%, CI < 1.8
  - CTV: V19.5Gy > 99%
  - DIL: V24.0Gy > 99%

- SBRT-CK boost dose constraints:
  - Rectum
    - V21.1Gy< 5 %
    - V18.9Gy< 20 %
    - V17.5Gy< 10 %
    - V16.2Gy< 40 %
    - V10.2Gy< 60 %
    - V9.3Gy< 40 %
    - V19.5Gy< 1cc
    - Max<21.2Gy
  - Bladder
    - V21.1Gy< 5 %
    - V19.5y< 5 cc
    - V9.3Gy< 40 %
    - Max<21.2Gy
  - Prostatic Urethra
    - V19.5Gy > 95%
    - V22Gy < 0.03cc
  - Membranous Urethra
    - V18 Gy < 50%
  - Large bowel
    - V15Gy< 1cc
  - Small bowel
    - V15Gy< 1cc
  - Penile bulb
    - V15Gy< 3cc

4.2.6 Performance of PSMA-PET/MRI to PSMA PET/CT as defined as:

- Rate of identification and delineation of DIL (e.g. sensitivity and specificity)
  - Compared to a gold standard of image-guided prostate biopsy
- Rate of identification of positive pelvic nodes
- Rate of identification of distant metastatic disease in the pelvis

4.2.7 Rate of identification of positive pelvic nodes by PSMA-PET and therefore the proportion of patients who have pelvic nodes included in the radiation field.

5.0 PATIENT ELIGIBILITY

5.1 Inclusion Criteria

Each subject must meet all of the following inclusion criteria to participate in this study.

5.1.1 Written informed consent obtained to participate in the study and HIPAA authorization for release of personal health information.

5.1.2 Male subjects ≥ 18 years of age

5.1.3 Histologically confirmed prostate adenocarcinoma

5.1.4 Unfavorable intermediate or high-risk, based on the NCCN criteria[31] (Appendix A.1), with appropriate staging (e.g. bone scan).

5.1.5 Subject has adequate performance status as defined by ECOG performance status of 0-2. (Appendix A.2)

5.1.6 Subject is willing and able to comply with the protocol as determined by the Treating Investigator.

5.1.7 Subject speaks English (quality of life instrument is validated in English)

5.2 Exclusion Criteria

All subjects meeting any of the following exclusion criteria at baseline will be excluded from study participation.

5.2.1 Contraindications for MRI

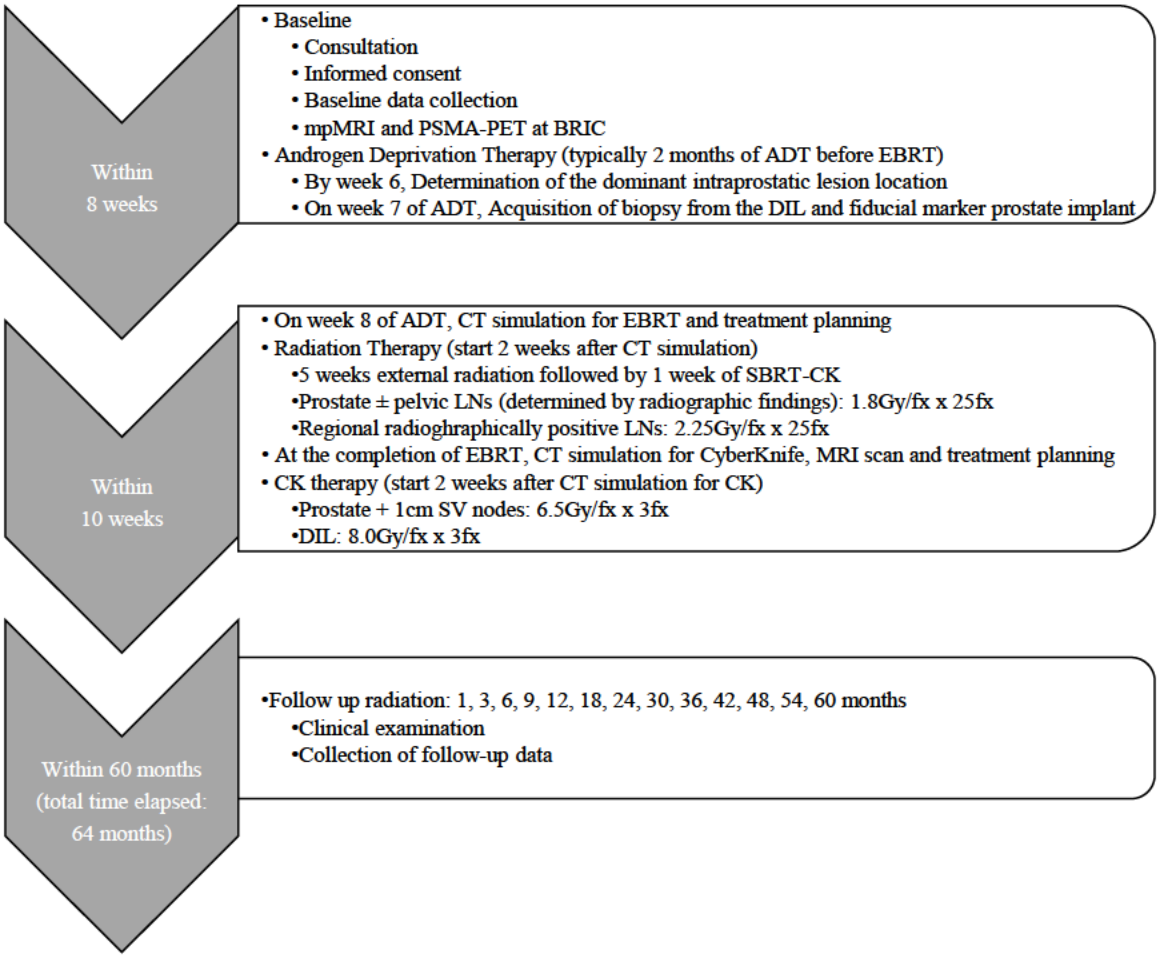
5.2.2 Other prior or concomitant malignancies with the exception of:

- Non-melanoma skin cancer
- Other cancer for which the subject has been disease free for ≥5 years before the first study treatment and of low potential risk for recurrence.

5.2.3 Inflammatory bowel disease

6.0 TREATMENT PLAN

6.1 Treatment Overview



6.1.1 Subsection for Radiation Delivery Details

6.1.1.1 Preparation process for radiotherapy

6.1.1.1.1 PET CT and MRI

1. The subject will start ADT on the day of or after PSMA-PET/MRI. ADT can be administered at UNC or at Subject's local providers. Prior to radiation planning, the subject will have three MRI-compatible fiducials placed into the prostate by an urologist or radiation oncologist. These will be used for image registration purposes.

2. 1-2 weeks after fiducial placement, the subject will undergo PSMA-PET/MRI (pelvis) scan at the BRIC. The subject will be injected with ~0.07 mCi/kg body weight ^{68}Ga-PSMA-11. Subject will undergo a PET/MR of the pelvis

with simultaneous acquisition of multi-parametric (mp)MR sequences and PET about 60 minutes after radiotracer injection (Siemens Biograph mMR). During the uptake period of 60 minutes, the subject should drink at least 500 mL of fluid (water or fluid of choice). The subject should void immediately prior to PET/MR acquisition. The MR sequences to be acquired are shown in A.6 Sequences of the mpMRI protocol). PET/MR acquisition takes about 30 minutes. Intravenous contrast will be administered for the mpMRI. All PET images will be reconstructed with corrections for attenuation, dead time, random events, and scatter, using iterative ordered-subsets expectation maximization. PET images in PET/MR will be acquired in list mode and reconstructed for several time points after scan start time and durations adjusted for radioisotope decay: e.g. 0-5 min, 5-10 min, 15-21 min and 21-28 min. No Lasix will be used for the PSMA-PET/MRI imaging acquisition. For the first five protocol subjects, if real-time reconstruction does not produce satisfactory images, the option to have the subject void (i.e. urinate) and re-image will be considered.

a. 68Ga-PSMA PET scans co-registered with MRI scan with IV contrast. 68Ga-PSMA PET scans will be performed with co-registration with MR with contrast before starting radiation therapy. A commercial PSMA kit will be used to source the 68Ga-PSMA radiotracer and will be infused into the subject at the BRIC facility. These images with be acquired on the PET/MR scanner available at the Biomedical Research Imaging Center (BRIC). PET/MR will of the pelvis. Subjects will remain in a quiet room for 60 minutes after injection of the 68Ga-PSMA to allow for uptake of the tracer and excretion of non-localized radioactivity. Subjects will then undergo a PET/MR scan of the pelvis including multiparametric MR. Participants must have their 68Ga-PSMA PET scan performed at UNC-CH.

b. **Administration, scanning and analysis of [68Ga]-PSMA.** Initially, a venous line will be established for the administration of ^{68}Ga-PSMA, irrespective of whether the patient already has a central line (e.g. Mediport, Port-a-cath, PICC line). In other words, these central lines will NOT be used for infusion of the radionuclide agent. Intravenous administration of ^{68}GA-PSMA [0.07 mCi/kg ± 10%] will be administered under the supervision of Dr. Amir Khandani or another qualified nuclear medicine physician from the Nuclear Medicine Department. 68Ga-PSMA PET/MR imaging will commence 60 minutes following injection.

3. Per UNC standard practice patients with high-risk disease will undergo elective pelvic nodal irradiation. Patients with unfavorable-intermediate risk disease will receive elective nodal irradiation at the discretion of the treating physician (e.g. secondary to suspicious imaging findings or high nomogram predicted incidence of occult nodal disease). If the PSMA imaging alone shows suspicious pelvic nodes, a biopsy of the suspicious node will be offered, and upon confirmation, these may be included in the external beam radiation treatment field.

4. Because the PSMA-PET/MRI may find distant disease that may otherwise not have been found, if the use of the PSMA-PET or MRI information suggests that the patient has M1 disease, the patient will be re-referred to the UNC multidisciplinary Urologic Oncology clinic for consultation to discuss 1) the implication of these findings, 2) what additional systemic agents should be used in their treatment regimen, if any, and 3) how these findings may impact the utility of this study. This would not exclude them from the study.

6.1.1.1.2 External Beam Radiation Therapy

1. Patients will undergo a radiation planning CT and preferably, in those patient to get pelvic nodes treated, with intravenous contrast if clinically available. This will be done roughly 8 weeks after ADT. Patients will undergo a planning CT. Standard departmental protocol will be followed for simulation, including eligibility for intravenous contrast, patient immobilization, with a comfortably full bladder.

6.1.1.1.3 SBRT with CyberKnife

1. SBRT with the use of CyberKnife will occur roughly 6 weeks after initiation of EBRT. Standard departmental protocol will be followed for CK-SBRT preparation. Patients with seminal vesicle involvement are eligible and seminal vesicles will be covered with CK-SBRT only as clinical indicated.

2. The fusion of the PSMA PET/mpMRI scans with the planning CT will be carried out in the treatment planning software; the fiducials will be used for soft tissue registration. Initially, the T2w MRI sequence will be registered with the planning CT by mutual information registration via fiducials. If necessary, manual adjustments may also be applied during image registration. The PSMA-PET and rest of the MRI and PET-CT scans will share the registration between the T2w MRI scan and planning CT.

3. The GTV-MRI will be outlined as a joint effort between a radiologist and the treating radiation oncologist on the basis of the PI-RADs v2 criteria.[34-35] Additionally, the GTV-PET will be contoured again jointly between the radiologist and radiation oncologist by 30% of the SUVmax value.[24] This will be done by taking into account all additional information (including tumor localization in the diagnostic biopsy and physical exam [palpation]). An additional volume (GTV-union) is created from both GTVs.

4. The GTVs (i.e. DILs), will be biopsied as a joint effort between the treating radiation oncologist and a urologist. Two cores will be taken per GTV.

5. Contouring of the prostate, rectum, and urethral will be performed per UNC standard practice and SBRT with CyberKnife will be performed per UNC standard practice.

6. Per UNC standard practice, if the CT or the MRI imaging shows suspicious pelvic nodes, these will be included in the radiation treatment field. If the PSMA imaging alone shows suspicious pelvic nodes, a biopsy of the suspicious node will be offered, and upon confirmation, these may be included in the radiation treatment field.

7. Because the PSMA-PET/CT may find distant disease that may otherwise not have been found, if the use of the PSMA-PET or MRI information suggests that the patient has M1 disease, the patient will be re-referred to the UNC multidisciplinary Urologic Oncology clinic for consultation to discuss 1) the implication of these findings, 2) what additional systemic agents should be used in their treatment regimen, if any, and 3) how these findings may impact the utility of this study. This would not exclude them from the study.

6.1.1.2 Definition of Target Volumes

Gross Tumor Volume (GTV)

- GTV1 = fusion of the prostate GTV-PET and prostate GTV-MRI
- GTV2 = fusion of nodal GTV-PET and nodal GTV-MRI

Clinical Target Volume (CTV)

- CTV1 = Prostate + seminal vesicles
- CTV2 = Pelvic lymph nodes as defined by RTOG contouring guide[36]
- CTV3 = Prostate + up to 1 cm of the involved seminal vesicles

Planning Target Volume (PTV)

- PTV1 = CTV1 + 7 mm (except posteriorly with a only 5mm expansion)
- PTV2 = CTV2 + 7 mm
- PTV3 = GTV2 + 5 mm
- PTV4 = CTV3 + 2 mm isotropically (but 5 mm on the side of disease) – Rectum
- PTV5 = GTV1 + 0 mm – Urethra/Bladder/Rectum

6.1.1.3 Radiation therapy planning

The irradiation technique will be a combination of EBRT and SBRT. The highest planning priority will be to satisfy the restrictions of the bowel, rectum and bladder (see below).

Dose on target volumes:

- PTV1: EBRT prescription dose of 45 Gy in 1.8 Gy/fraction for 25 fractions.
- PTV2: EBRT prescription dose 45 Gy in 1.8 Gy/fraction for 25 fractions
- PTV3: EBRT prescription with simultaneous integrated boost (i.e. dose painting) to 56.25 Gy in 2.25 Gy/fraction for 25 fractions

- PTV4: SBRT-CK prescription dose of 19.5Gy in 6.5Gy/fraction in 3 fractions.
- PTV5: SBRT-CK prescription dose of 24.0Gy in 8.0Gy/fraction in 3 fractions (satisfying first the dose constraints of the urethra, bladder and rectum). The maximum dose in PTV3 should be at least 3 mm away from rectum and bladder.

The planning priorities will be:

1. Compliance with standard planning criteria for external beam radiation and SBRT-CK in terms of prostate dose coverage and restrictions on normal tissue (urethra, bladder and rectum) (**Table 2**).
2. After #1 is met, an attempt will be made to place areas of increased dose heterogeneity, or hot spots, in PTV4+5.

Table 2 Dose Prescription and Normal Tissue Constraints used at UNC-Chapel Hill.

Structure	Goal (doses in Gy)
External Beam	
PTV1, PTV2	At least 95% of volume at 45 Gy
PTV3	At least 95% of volume at 56.26 Gy
Bladder	At most 40Gy average dose
Rectum	At most 10cm^3 volume at 40 Gy
Femoral Heads	At most 0.1cm^3 volume at 45 Gy
Femoral Heads	At most 40 Gy at 10% volume
Small bowel	At most 0.1cm^3 at 45 Gy
CyberKnife therapy	
PTV4	V19.5 Gy > 95%
PTV5	V24.0 Gy > 99% (satisfying first the dose constraints of the urethra, bladder and rectum)
Rectum	V21.1Gy < 5 % V18.9Gy < 20 %

	V17.5Gy < 10 %
	V16.2Gy < 40 %
	V10.2Gy < 60 %
	Max < 21.2 Gy
	V20.1Gy < 1cc
Bladder	V21.1Gy < 5 %
	V19.5y < 5 cc
	V9.3Gy < 40 %
	V19.5 Gy < 5cc
	Max < 21.2 Gy
Large Bowel	V15Gy < 1cc
	Max *** Gy (assuming a/b of large bowel to be 3 and *** cGy max dose from first course); BED would result in Max dose <60Gy in 1.8Gy/fx
Small Bowel	V15Gy < 1cc
	Max *** Gy (assuming a/b of large bowel to be 3 and *** cGy max dose from first course); BED would result in Max dose <54 Gy in 1.8Gy/fx
Penile bulb	V15Gy< 3cc
Testicles/	Max <1.1Gy
Membranous Urethra	V18 Gy < 50%
Prostatic Urethra	V19.5Gy > 95%
	V22Gy < 0.03cc

6.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluated for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events Table (Section 8.1). Patients will be evaluated during their external beam radiation therapy at least once/week while on treatment. Acute toxicity (<3 months) and/or late radiation associated toxicity (>3 months) will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0 (if appropriate). Treatment holds and delays and dose adjustments will be made according to the system showing the greatest degree of toxicity per these metrics. Neither dose modifications or treatment delays are anticipated and priority will be given to honoring normal tissue dose constraints (5.1.1.3).

For further information regarding PSMA please refer to the package insert:
Galium Ga 68 PSMA-11 Injection

6.2.1 Radiation Dose Delays/Dose Modifications

For acute radiation toxicities, treatment breaks should be kept to a minimum. An effort will be made to complete the radiotherapy on schedule without significant treatment breaks, as prolongation of treatment is known to contribute to treatment failure. The need for radiotherapy breaks due to severe acute toxicity will be determined by the treating radiation oncologist. Patients on treatment are evaluated weekly by the radiation oncologist.

6.3 Supportive Care/Symptom Management

Patients who develop any adverse event while on study will receive standard of care treatment. Radiation and hormone therapy are already standard of care treatments for these patients. Standard of care treatments for known potential adverse events from these treatments are well established.

6.4 Definition of Dose Limiting Toxicity

A dose-limiting toxicity is defined as all Grade 3 or above acute toxicities attributed to the treatment under study. The accrual will be halted if the number of patients with dose-limiting toxicities equals to or exceeds a rate of 30%.

6.5 Duration of Follow Up

All patients will be followed for up to 5 years after radiation, or until death, whichever occurs first, after removal from study treatment for determination of study endpoints. Patients removed from study treatment for unacceptable adverse events (AEs) will be followed for resolution or stabilization of the AEs. All patients (including those withdrawn for AEs) should be followed after removal from study treatment as stipulated in the protocol.

6.6 Removal of Patients from Protocol Therapy

In case a patient decides to prematurely discontinue protocol therapy (“refuses treatment”), the patient should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in the medical record. Patients may also be removed from the study at any time per PI discretion due to unexpected reactions, lack of study compliance or for study closure.

6.7 Subjects Lost to Follow-Up

Subject will be considered lost to follow-up if he fails to return for three scheduled visits and is unable to be contacted by the study site staff.

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

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the

assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.

Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.8 Study Withdrawal

If a patient decides to withdraw from the study (and not just from protocol therapy) an effort should be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, the investigator should attempt to establish as completely as possible the reason for the study withdrawal.

- The patient should be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet the long term follow up (e.g., biochemical control or survival) objectives outlined in the protocol.
- A complete final evaluation at the time of the patient's study withdrawal should be obtained with an explanation of why the patient is withdrawing from the study.
- If the patient is noncompliant and does not return for an end of study follow up assessment, this should be documented in the case report form (CRF).
- If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the CRF.

7.0 EVALUATIONS AND ASSESSMENTS

7.1 Clinical Assessments

Clinical assessments will be performed as outlined in the Time and Events Table in Section 8.1.

7.1.1 Demographics

Demographic information (date of birth, gender, race) will be recorded at screening.

7.1.2 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history (e.g., tobacco use), and information regarding underlying diseases will be recorded at screening and a focused medical history on symptoms/toxicity will be performed thereafter.

7.1.3 Physical Examination

A complete physical examination including height (at screening only), weight, performance status (ECOG) and vital signs (e.g**.,** temperature, heart rate, respiratory rate, pulse oximetry and blood pressure) will be performed by either the investigator or a sub-investigator who is a physician at screening and the first study visit.

Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits.

New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

7.1.4 Adverse Events

Events should be assessed per NCI-CTCAE criteria 5.0. Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to study treatment will be recorded in the case report form. A dose-limiting toxicity is defined as all Grade 3 or above acute toxicities attributed to the treatment under study. The accrual will be halted if the number of patients with dose-limiting toxicities equals to or exceeds a rate of 30%.

7.1.5 Disease Assessment

Patients' disease will be assessed with prostate-specific antigen (PSA) test draws. PSA will be obtained at within three months prior to study enrollment and then at each follow up (1, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months post treatment).

7.2 Clinical Laboratory Assessments

7.2.1 Hematology

Blood will be obtained at screening and sent to the clinical site hematology lab for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count), coagulations (International Normalized Ratio (INR) or prothrombin time (PT) and partial thromboplastin time (PTT)).

7.2.2 Blood Chemistry Profile

Blood will be obtained at screening and sent to the clinical site chemistry lab for a complete metabolic panel (serum sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), albumin and LDH).

7.2.3 Pathology

At time of fiducial markers placement, GTVs (i.e. DILs) will be biopsied by the treating radiation oncologist and a urologist. Two cores will be taken per GTV and placed in buffered formalin containers. This is a research only biopsy and will be used to evaluate the sensitivity and specificity of PSMA-PET/MRI vs PSMA-PET/CT. It will not require any additional visits or cost for the subject. These samples will be collected and accessioned with coded identifiers by the Tissue Procurement Facility (TPF). Specimen processing, embedding and histologic sectioning will be performed by the Translational Pathology Laboratory (TPL) and slides interpreted by the collaborating pathologist.

7.3 Patient Reported Outcomes (Quality of life assessment)

Quality of life (QOL) will be measured using the EPIC-26 instrument according to the time points delineated in the Time and Events Table (Section 8.1).[37] Expanded Prostate Cancer Index Composite (EPIC-26) is a validated prostate cancer-specific health-related QOL (HRQOL) instrument that measures urinary, bowel, sexual, and hormonal symptoms related to prostate cancer treatments, including prostatectomy, radiotherapy, and hormonal therapy. Summary and subscale scores were derived by content and factor analyses. Test-retest reliability and internal consistency were high for EPIC urinary, bowel, sexual, and hormonal domain summary scores (each $r \geq 0.80$ and Cronbach's alpha ≥ 0.82) and for most domain-specific subscales. Correlations between function and bother subscales within domains were high ($r > 0.60$). Correlations between different primary domains were consistently lower, indicating that these domains assess distinct HRQOL components.

Another scoring protocol to assess the quality of life is the Prostate Cancer Symptom Indices (PCSI). This assessment will be performed per timing described in the Time and Events Table (Section 8.1). The PCSI has 4 domains: urinary obstruction and irritation (5 items), urinary incontinence (3 items), sexual dysfunction (5 items), and bowel problems (6 items). Each domain is scored from

0 to 100, with a higher score indicating more or worse dysfunction. Minimal clinically important differences for PCSI domains have not been defined. Parallel to each of the 4 domains are additional questions that ask patients about the magnitude of bother related to urinary obstruction and irritation, urinary incontinence, sexual, and bowel symptoms. In addition to numerical scoring for each domain described above, the PCSI has established functional levels (normal, intermediate, and poor) that incorporate the symptom as well as bother questions. These function levels complement the score reporting because QOL score changes are well recognized to be difficult for patients and physicians to interpret. Normal function describes a patient with essentially no dysfunction or distress in a domain (eg, normal function in the urinary incontinence domain describes a man who has full urinary control without incontinence). Intermediate function describes a patient with at least 1 distressful symptom but none very distressful (e.g., intermediate urinary incontinence represents leaking only at certain times, and no more than a few drops). Poor function describes patients with at least 1 very distressful symptom (eg, poor sexual function represents no erections capable of intercourse or a lot of difficulty getting and keeping an erection). This classification adds clinical meaning to numerical scores, and also allowed analysis of QOL outcomes stratified by each participant's baseline level. Effect sizes between functional levels of the PCSI are large.

8.0 EVALUATIONS AND ASSESSMENTS

8.1 Time and Events Table

Study Assessments	Pre-radiation[1]	Radiation Therapy	1, 3, 6, 9, 12 months post-radiation[1,3]	2-5 years post-radiation[1, 3]
Assessment, consultation	X			
Informed Consent	X			
History and PE[1]	X			X
Performance Status	X			X
Quality of Life[2]	X		X	X
Toxicity Evaluations[3]	X		X	X[3]
PSA Measurements	X		X	X
PSMA-PET/MRI+CT[4]	X			
CBC, coagulations[5], CMP	X			
Fiducials[6]		X		
Radiation planning[7]		X		
Androgen deprivation therapy[8]	X			
Radiation Therapy[9]		X		
Biopsy[10]		X		

Footnotes to Time and Events Table

1. History and physical exam may be performed within 8 weeks prior to day 1 of study treatment. Other evaluations must be performed within 8 weeks priors to Day 1 (D1) of study treatment. Screening labs performed within 8 weeks prior to D1 of study treatment do not need to be repeated on D1. A window of +/- 30 days applies to all study visits unless otherwise specified.
2. EPIC-26 (A.4 Quality of Life according to EPIC-26) and PCSI (A.5 The local Quality of Life questionnaire)
3. Subject will be regularly followed and seen by the treating physician every 6 months for up to 5 years after treatment. Patients who have an ongoing ≥grade 2 or serious AE (SAE) will continue to be followed until the event is resolved or deemed irreversible by the investigator.
4. PSMA-PET/MRI+CT should be no later than the day of starting ADT.
5. INR or PT and PTT
6. During CK-SBRT, the subject will have MRI-compatible fiducials (e.g. gold) placed into the prostate by the radiation oncologist. These will be used for image guided radiation therapy.
7. The irradiation technique will be a combination of EBRT and BT. The highest planning priority will be to satisfy the restrictions of the bowel, rectum and bladder. Refer to Section 6.1.1.3 for additional details including dose on target volumes and planning priorities.
8. Androgen deprivation therapy will start no earlier than the same day of the PSMA-PET/CT scan. Duration per standard of care.
9. Radiation therapy will consist of:
    a. 5 weeks of external beam radiation (EBRT). Typically 8 weeks after initiation of ADT.
        i. Prostate +/- pelvic LNs (determined by radiographic findings): 1.8 Gy/fx x 25fx
        ii. Regional radiographically pos LNs: 2.25 Gy/fx x 25 fx
    b. SBRT with CyberKnife
        i. DIL: 8.0 Gy/fx x 3fx.
10. At time of fiducial markers placement, prostate GTVs (i.e. DILs) will be biopsied. Refer to Section 7.2.3 for additional details.

8.2 Pre-Study Assessments

Patients will undergo the standard UNC work up for patients diagnosed with unfavorable intermediate/high-risk prostate cancer. They will undergo the standard pre-treatment evaluations for external beam radiotherapy and SBRT and androgen deprivation therapy. Their care will not deviate from any other patient that comes through the multi-disciplinary clinic.

8.3 Treatment Assessments

Patients will undergo the standard UNC treatment assessment for patients with unfavorable intermediate/high-risk prostate cancer under treatment. They will undergo the treatment assessments for external beam radiotherapy and SBRT and androgen deprivation therapy. Their care will not deviate from any other patient that comes through the radiation oncology clinic.

8.4 Post-Treatment/Follow-up Assessments

Subjects will be followed for five years after radiation therapy, with a final study follow-up visit at 5 years after the end of treatment. Subjects who have an ongoing ≥grade 2 or serious AE (SAE) will continue to be followed until the event is resolved or deemed irreversible by the investigator.

8.5 Early Termination Visit

Subjects may withdraw voluntarily from participation in the study at any time. Subjects may also withdraw voluntarily from receiving the study intervention for any reason. No specific evaluations will be required in the setting of early termination.

8.6 Assessment of Safety

All patients who received treatment (i.e. radiation) will be evaluated for toxicity at specified time points throughout the study; toxicity will be measured according to CTCAE version 5.0.

8.7 Assessment of Efficacy

Patients will be followed with routine PSA tests at follow up visits, as is standard practice.

8.7.1 Other Efficacy Parameters

Biochemical control after radiation is measured by PSA and defined by the Phoenix criteria.[33]

9.0 ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event (AE)

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

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

9.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

9.1.3 Unexpected AE or SAR

An AE or SAR is considered <u>unexpected if</u> the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure

(IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

9.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

9.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment (i.e. radiation) and continue through the 5-year follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

9.3 SAEs or Serious SARs

9.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout.

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment (i.e. radiation) and continue through the 5 year follow-up period after treatment is discontinued.

9.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence. Additionally, the UNC Study Coordinator must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

9.4 Adverse Event Reporting

9.4.1 IRB Reporting Requirements:

The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system within 7 days of the Investigator becoming aware of the problem. Please note, these events must be reported to the sponsor within 24 hours of learning of the occurrence.

9.4.2 FDA Expedited Reporting requirements for studies conducted under an IND:

A sponsor must report any suspected adverse reaction that is both serious and unexpected to the FDA. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. SARs are defined in Section 9.1.2.

The sponsor must submit each IND safety report on FDA Form 3500A. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division that has the responsibility for review of the IND. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

Timing

FDA must be notified of potential serious risks within 15 calendar days after the sponsor determines the event requires reporting. FDA must be notified of

unexpected fatal or life-threatening suspected adverse reactions as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. The sponsor must be notified of the SAE by the investigator within 24 hours of the event. If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable is reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

Follow-up
The sponsor must promptly investigate all safety information it receives. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report." Additionally, upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

Notification of Investigators
The sponsor must notify all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Process
If the sponsor deems that an event is both a serious adverse reaction (SAR) AND unexpected, it must also (in addition to Oncore) be recorded on the MedWatch Form 3500A as per 21 CFR 312.32. Unexpected adverse events or adverse reaction refers to an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed; or if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigation plan or elsewhere in the current IND application.

The MedWatch 3500a form can be accessed at:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

(Please be sure and access form 3500a, and not form 3500).

The MedWatch form should also be sent to the IND Specialist within 48 hours of the sponsor being aware of the event. The IND Specialist will submit the IND Safety Report via IND serial submission to the FDA review division.

All IND safety reports must be submitted on Form 3500A and be accompanied by Form 1571. The FDA must be notified or any unexpected or life-threatening suspected adverse reactions as soon as possible, but no later than 7 calendar days of learning of the event.
Additional Reporting Requirements

The following additional items must be reported via IND safety report:

- *Findings from other studies.* The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk to humans exposed to the drug.
- *Findings from animal or in vitro testing.* The sponsor must report any findings from animal or *in vitro* testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity t or near the expected human exposure.
- *Increased rate of occurrence of serious suspected adverse reactions.*

Additional Guidance
Please refer to 21CFR312.32 and "Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies" for additional information and reporting requirements. All IND Safety Reports will be submitted in accordance with these regulations/guidances.

9.5 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as study coordinators, data coordinator, regulatory associates, clinical data management associates, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4)

summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This will be a prospective, single-arm, non-randomized, phase II study to examine the feasibility and acute and late toxicities of standard radiation treatment for unfavorable intermediate and high risk prostate cancer - this involves a combination of external beam radiation therapy and SBRT-CK and androgen deprivation therapy – while using advanced imaging modalities (PSMA/PET-mpMRI) to intelligently adapt the radiation fields. The radiation therapy usually takes 2 months and the follow up is 60 months, while the duration of the evaluation of the final results will be about 12 months after the end of treatment.

There is one primary endpoint:

(1) Late genitourinary toxicity and gastrointestinal toxicity at 12 months (these will be recorded at 1, 3, 6, 9, 12, 24, 36, 48 and 60 months after radiotherapy, according to CTCAE v5).

Table *1* shows an overview of late toxicities in randomized studies of conventionally fractionated schemes in primary prostate carcinoma. On average, the rate of late GI / GU toxicities of grade 2 or higher averaged a rate of approximately 16%.

Table 1 Summary of results from recent clinical trials with external beam radiotherapy.

Study	**1**[38]	**2**[39]	**3**[40]	**4**[41]	**5**[42]	**6**[43]
Patient #	296	151	101	478	372	1065
Total dose (Gy)	76	76	75.6	86.4	76	74
Fractions #	38	38	42	39	38	37
Dose/fraction (Gy)	2	2	1.8	2	2	2
Late Reactions – RTOG G2+						
GI (%)	9	22.5	5.1	3.7	8	13.7
GU (%)	19	13.4	16.5	15.5	24	9.2

Table 2 shows an overview of late toxicities in randomized studies of combination external beam radiotherapy and SBRT in primary prostate carcinoma. On average, the rate of late Grade 2 or higher GU toxicities is ~11.4% and for GI toxicities ~6%.

Table 2 Summary of results from randomized clinical trials treating with combination external beam radiation therapy and SBRT.

Study	**1**[44]	**2**[45]	**3**[46]	**4**[47]	**5**[48]	**6**[49]	**7**[50]	**8**[51]
Patient #	121	26	76	39	108	48	41	45
EBRT dose (Gy)	45	44	46	45	45-50.4	45	45	45
EBRT Fractions #	25	20	23	25	25-28	25	25	25
CK dose (Gy)	21	18 or 21	18	21	19.5	19 or 21	21	18-21
CK Fractions #	3	3	3	3	3	2	3	3
Late Toxicity – Grade 2+								
GI (%)	3.4	4.0	9.3	12.8	5.0	0.0	0.0	13.3
GU (%)	20.6	4.0	1.4	10.3	13.7	27.0	11.0	2.9

We denote p the probability that a patient experiences a late grade 2+ GU/GI toxicity. We want p to be small enough to claim the new imaging strategy (PSMA/PET-mpMRI) as feasible with no greater late toxicity. Specifically, the null and alternative hypotheses are:

$$H_0: p \geq 0.30 \; vs \; H_1: p \leq 0.15$$

That is, we accept the claim that the new strategy is safe if the observed toxicity rate is not too high, and hope to reject the claim (H0) with sufficient power when the true toxicity rate is about 20%. With a sample size of 38, we reach 80% power to reject (if we observe ≤ 7 cases with late toxicity) the null hypothesis (H0) at alpha = 0.1. To account for 10% loss follow-up, we will enroll 42 patients to ensure 38 evaluable patients.

10.2 Sample Size and Accrual

Accrual will take place at UNC. The design as proposed in the above section leads to 80% power at an alpha level of 10%. Taking into account that the dominant intra-prostatic lesion (DIL, image-identified tumor in the prostate) can be safely defined in around 75% of the patients, and assuming a 10% patient drop-out (non-evaluable) rate, we will plan to enroll 42 patients in order to achieve the primary objective of this study. Based on a previous study conducted with a similar population, we anticipate averaged accrual of 2 patients per month, corresponding to 21 months to enroll 42 patients out of which we can accrue the 38 evaluable patients for this study.

Sequential boundaries will be used to suspend the trial if excessive grade 4 toxicity of any type, attributed to the treatment under study, is seen. If the study reaches a stopping boundary, it may be terminated by the PI, or submitted to the Data and Safety Monitoring Committee with a description of the failures to date and a rationale for why the study should be continued.

The accrual will be halted if the number of grade 4 toxicities is equal to or exceeds b_n out of n patients with full toxicity follow-up (see table below). This is a Pocock-type stopping boundary that assumes that a grade 4 toxicity rate of 0.05 is acceptable. If the true grade 4 toxicity rate is equal to 0.05, the probability of crossing the boundary is 0.20.

Number of Patients, n	1	2	3	4	5	6	7	8	9	10
Boundary, b_n	1	2	2	2	2	2	2	2	2	2
Number of Patients, n	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	3	3	3	3	3	3	3	3	3	3
Number of Patients, n	21	22	23	24	25	26	27	28	29	30
Boundary, b_n	3	3	4	4	4	4	4	4	4	4
Number of Patients, n	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	4	4	4	4	4	5	5	5		

In addition, grade 3+ toxicity (DLT) will also be monitored. The accrual will be halted if the number of grade 3+ DLTs is equal to or exceeds b_n out of n patients with full toxicity follow-up (see table below). This is a Pocock type stopping boundary that assumes that a DLT rate of 0.30 is acceptable. If the true DLT rate is equal to 0.30, the probability of crossing the boundary is 0.20.

Number of Patients, n	1	2	3	4	5	6	7	8	9	10
Boundary, b_n	-	-	3	4	4	4	5	5	6	6
Number of Patients, n	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	7	7	7	8	8	9	9	9	10	10
Number of Patients, n	21	22	23	24	25	26	27	28	29	30
Boundary, b_n	10	11	11	11	12	12	13	13	13	14
Number of Patients, n	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	14	14	15	15	15	15	16	17		

10.3 Data Analysis Plans

Analysis of primary endpoint, late toxicity rates, to decide whether to reject the null hypothesis, will be conducted as described above. In addition, the estimated acute and late toxicity rates will be reported with 95% confidence intervals in the final analysis.

As per the analyses of secondary outcomes, binary outcomes like (1) 2 and 5 years biochemical control according to the Phoenix criteria; (2) local recurrence rate after 2 and 5 years (defined by biopsy); and (3) rate of screened to truly included patients and compliance with dose restrictions, will be summarized by estimated proportions and associated 95% confidence intervals. Numerical outcomes like (4) quality of life (according to EPIC-26 and PCSI) will be summarized using descriptive (mean and standard deviation, median and range) statistics. Exploratory

correlation analyses will be conducted to identify biomarkers correlated with the diagnosis and the course of the disease, as well as gastrointestinal and urogenital toxicity.

In the event of an early termination of this study, the same analysis plan as described above will be followed, but based on the data available at the time of study termination.

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the LCCC Study Coordinator.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- CAP and CLIA Laboratory certification numbers and institution lab normal values

11.3 Registration Procedures

All subjects must be registered with the Lineberger Comprehensive Cancer Center via OnCore®.

11.4 Data Management and Monitoring/Auditing

The Department of Radiation Oncology will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®.

The sponsor will provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection. As an investigator initiated study, this trial will also be audited by the LCCC compliance committee every six or twelve months. It will also be monitored according to LCCC SOPs, within 8 weeks of the first patient enrolled, and subsequently every 4 months while there are subjects in the treatment period. Monitoring will occur annually once the study is closed to accrual and all subjects are in the follow-up period.

11.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.5.1 Emergency Modifications

UNC investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

11.5.2 Single Patient/Subject Exceptions

Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

11.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

Protocol Deviations: UNC personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

Unanticipated Problems:
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the study personnel using the IRB's web-based reporting system.

11.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

11.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor correspondence to Investigators, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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13.0 APPENDICES

A.1 NCCN Risk Stratification

Unfavorable intermediate risk disease:

- T2b-T2c OR
- Gleason score 3+4=7/grade group 2 or Gleason score 4+3=7/grade group 3 OR
- PSA 10-20 ng/mL

High risk disease:

- T3a OR
- Gleason score 8/grade group 4 or Gleason score 4+5=9/grade group 5 OR
- PSA>20 ng/mL

A.2. ECOG Performance Status

ECOG Performance Status
Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.*Am J Clin Oncol.* 1982;5:649-655.

A.3 Toxicity according to CTCAE

Common Terminology Criteria for Adverse Events (CTCAE v5)
Source: https://evs.nci.nih.gov/ftp1/CTCAE/About.html

MedDRA Code	MedDRA SOC	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
10002153	Gastrointestinal disorders	Anal fissure	Asymptomatic	Symptomatic	Invasive intervention indicated	-	-
10002156	Gastrointestinal disorders	Anal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
10055226	Gastrointestinal disorders	Anal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
10065721	Gastrointestinal disorders	Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
10065722	Gastrointestinal disorders	Anal necrosis	-	-	TPN or hospitalization indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
10002167	Gastrointestinal disorders	Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
10002176	Gastrointestinal disorders	Anal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; non-emergent operative intervention indicated; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
10002180	Gastrointestinal disorders	Anal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
10009995	Gastrointestinal disorders	Colonic fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
10009998	Gastrointestinal disorders	Colonic hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
10010000	Gastrointestinal disorders	Colonic obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
10010001	Gastrointestinal disorders	Colonic perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
10010004	Gastrointestinal disorders	Colonic stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
10010006	Gastrointestinal disorders	Colonic ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
10010774	Gastrointestinal disorders	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
10012727	Gastrointestinal disorders	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
10036774	Gastrointestinal disorders	Proctitis	Rectal discomfort, intervention not indicated	Symptomatic (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
10064993	Gastrointestinal disorders	Rectal fissure	Asymptomatic	Symptomatic	Invasive intervention indicated	-	-
10038062	Gastrointestinal disorders	Rectal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
10038064	Gastrointestinal disorders	Rectal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
10063190	Gastrointestinal disorders	Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
10065709	Gastrointestinal disorders	Rectal necrosis	-	-	Tube feeding or TPN indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
10065707	Gastrointestinal disorders	Rectal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
10038072	Gastrointestinal disorders	Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
10038073	Gastrointestinal disorders	Rectal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
10038079	Gastrointestinal disorders	Rectal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
10038080	Gastrointestinal disorders	Rectal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
10063575	Renal and urinary disorders	Bladder perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
10048994	Renal and urinary disorders	Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
10063057	Renal and urinary disorders	Cystitis noninfective	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated	Life-threatening consequences; urgent invasive intervention indicated	Death
10013990	Renal and urinary disorders	Dysuria	Present	-	-	-	-
10068405	Renal and urinary disorders	Glucosuria	Present	-	-	-	-
10019450	Renal and urinary disorders	Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent invasive intervention indicated	Death
10065368	Renal and urinary disorders	Urinary fistula	-	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent invasive intervention indicated	Death
10046539	Renal and urinary disorders	Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
10046543	Renal and urinary disorders	Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-	-
10046555	Renal and urinary disorders	Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective invasive intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
10061574	Renal and urinary disorders	Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but no hydronephrosis, sepsis, or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Altered organ function (e.g., hydronephrosis or renal dysfunction); invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
10062225	Renal and urinary disorders	Urinary tract pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
10046593	Renal and urinary disorders	Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
10046628	Renal and urinary disorders	Urine discoloration	Present	-	-	-	-

A.4 Quality of Life according to EPIC-26

The Expanded Prostate Cancer Index Composite (EPIC-26) scoring protocol was designed to measure Quality of Life issues in patients with Prostate cancer.

1. Over the **past 4 weeks**, how often have you leaked urine?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number)
   About once a week..... 4
   Rarely or never..... 5

2. Which of the following best describes your urinary control **during the last 4 weeks**?

   No urinary control whatsoever..... 1
   Frequent dribbling..... 2 (Circle one number)
   Occasional dribbling..... 3
   Total control..... 4

3. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks**?

   None 0
   1 pad per day..... 1
   2 pads per day..... 2 (Circle one number)
   3 or more pads per day..... 3

4. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?

   (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Dripping or leaking urine …….	0	1	2	3	4
b. Pain or burning on urination.....	0	1	2	3	4
c. Bleeding with urination.....	0	1	2	3	4
d. Weak urine stream or incomplete emptying.....	0	1	2	3	4
e. Need to urinate frequently during the day.....	0	1	2	3	4

5. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

   No problem..... 1
   Very small problem..... 2
   Small problem..... 3 (Circle one number)
   Moderate problem..... 4
   Big problem..... 5

6. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Urgency to have a bowel movement	0	1	2	3	4
b. Increased frequency of bowel movements.....	0	1	2	3	4
c. Losing control of your stools.....	0	1	2	3	4
d. Bloody stools	0	1	2	3	4
e. Abdominal/ Pelvic/Rectal pain...	0	1	2	3	4

7. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem..... 1
Very small problem..... 2
Small problem..... 3 (Circle one number)
Moderate problem..... 4
Big problem..... 5

8. How would you rate each of the following **during the last 4 weeks**? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good
a. Your ability to have an erection?.....	1	2	3	4	5
b. Your ability to reach orgasm (climax)?.....	1	2	3	4	5

9. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?

None at all..... 1
Not firm enough for any sexual activity..... 2
Firm enough for masturbation and foreplay only..... 3 (Circle one number)
Firm enough for intercourse..... 4

10. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?

I NEVER had an erection when I wanted one..... 1
I had an erection LESS THAN HALF the time I wanted one..... 2
I had an erection ABOUT HALF the time I wanted one ..... 3 (Circle one number)
I had an erection MORE THAN HALF the time I wanted one..... 4
I had an erection WHENEVER I wanted one..... 5

11. Overall, how would you rate your ability to function sexually **during the last 4 weeks?**

Very poor	1	
Poor	2	
Fair	3	(Circle one number)
Good	4	
Very good	5	

12. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks?**

No problem	1	
Very small problem	2	
Small problem	3	(Circle one number)
Moderate problem	4	
Big problem	5	

13. How big a problem **during the last 4 weeks**, if any, has each of the following been for you?
(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Hot flashes	0	1	2	3	4
b. Breast tenderness/enlargement	0	1	2	3	4
c. Feeling depressed	0	1	2	3	4
d. Lack of energy	0	1	2	3	4
e. Change in body weight	0	1	2	3	4

A.5 The local Quality of Life questionnaire

Prostate Cancer Symptom Indices (PCSI): The Quality of Life (QoL) questionnaire that is given to the patients before the beginning of their radiation therapy.

Prostate Symptoms Sheet

Date:_____

Current Dose: (Baseline) (In Treatment _____cGy)

(Follow up)

NAME:

Rectal Symptoms: In the past week have you...

1. Had diarrhea or loose watery stools?	Not at all 1	Occasionally (Once or twice) 2	Fairly Frequently (several times) 3	Frequently (at least once a day) 4	Very Frequently (Several times a day) 5
2. Had a sense of urgency that you move your bowels?	Not at all 1	Occasionally (Once or twice) 2	Fairly Frequently (several times) 3	Frequently (at least once a day) 4	Very Frequently (Several times a day) 5
3. Had any tenderness or pain when you move your bowels?	Not at all 1	Occasionally (Once or twice) 2	Fairly Frequently (several times) 3	Frequently (at least once a day) 4	Very Frequently (Several times a day) 5
4. Had bleeding with your bowel movements?	Not at all 1	Occasionally (Once or twice) 2	Fairly Frequently (several times) 3	Frequently (at least once a day) 4	Very Frequently (Several times a day) 5
5. Had abdominal cramping or pain?	Not at all 1	Occasionally (Once or twice) 2	Fairly Frequently (several times) 3	Frequently (at least once a day) 4	Very Frequently (Several times a day) 5
6. Passed mucus from your rectum?	Not at all 1	Occasionally (Once or twice) 2	Fairly Frequently (several times) 3	Frequently (at least once a day) 4	Very Frequently (Several times a day) 5
7. Had the urge to move your bowels, but had nothing to	Not at all 1	Occasionally (Once or twice) 2	Fairly Frequently (several times) 3	Frequently (at least once a day) 4	Very Frequently (Several times a day) 5

Urinary Symptoms: In the past week...

1. How easy has your urine flow been?	Very Easy 1	Fairly Easy 2	Slow, but I don't have to strain or bear down 3	Very slow, and I do have to strain or bear down 4	Very slow, and I have to strain or bear down hard 5
2. How often did you urinate at night?	Seldom or Never 1	Once a Night 2	2 to 3 times a night 3	More than 3 times a night 4	
3. How often did you urinate?	4 or fewer times a day 1	5 to 8 times a day 2	9 to 12 times a day 3	More than 12 times a day 4	
4. How often have you felt pain or burning during urination?	Not at all 1	Occasionally (once or twice) 2	Fairly frequently (several times) 3	Frequently (at least once a day) 4	Very frequently (several times a day) 5
5. How often did you have the feeling that it is urgent that you pass your urine?	Not at all 1	Occasionally (once or twice) 2	Fairly frequently (several times) 3	Little or no control 4	Very frequently 5
6. How much control did you have over your urine?	Had complete control (no leaking) 1	Leaked urine, but only at certain times 2	Leaked urine most of the time 3	Little or no control 4	
7. How often did you leak urine?	Not at all 1	Occasionally (once or twice) 2	Fairly frequently (several times) 3	Frequently (at least once a day) 4	Very frequently (several times a day) 5

A.6 Sequences of the mpMRI protocol

Sequence	***Plane***	***TR****	***TE****	***Flip Angle***	***Thickness/Gap***	***FOV*****	***Matrix***
Localizer	3-plane						
SS-ETSE[#]	Coronal	1500[Ψ]	85	170	6 mm/20%	350–400	192 × 256
SS-ETSE	Axial	1500[Ψ]	85	170	6 mm/20%	350–400	192 × 256
SS-ETSE	Sagittal	1500[Ψ]	85	170	6 mm/20%	350	192 × 256
SS-ETSE fat-suppressed	Axial	1500[Ψ]	85	170	8–10 mm/20%	350–400	192 × 256
T1 TSE	Axial	647	11	140	3 mm	180	256x256
T2 TSE (0.7 x 0.7 x 3.0 mm)[+]	Axial	8500	94	120	3 mm	230	320x240
T2 TSE (0.4 x 0.4 x 3.0 mm)[+]	Coronal	8500	115	120	3 mm	230	320x240
T2 TSE (0.7 x 0.7 x 3.0 mm)[+]	Sagittal	8500	115	120	3 mm	230	320x240
Diffusion Weighted Imaging (1 x 1 x 4 mm)[+] **(b50 800 1500)**[@]	Axial	3400	71	90	4 mm	260	128 x 128
Post-Gadolinium Sequences							
T1 3D GE DCE (80 measurements)	Axial	3.05	1.06	12	3 mm	250	128x128
T1 3D GE fat-suppressed*	Axial / Coronal / Sagittal	3.8	1.7	10	3 mm	350–400	160 × 256

*TR: Repetition time.
**TE: Echo time
***FOV: Field of view.
[#]SS-ETSE: Single shot echo train spin echo

[Ψ]TR between slice acquisitions.
[&]SGE: Spoiled gradient echo
[$]3D GE: Three dimensional gradient echo
*****Optional: T1 TSE fat-suppressed images could also be acquired in two planes including axial and sagittal planes.
[+]Voxel size
[@]b values