NRG ONCOLOGY

NRG-GU005
(ClinicalTrials.gov NCT #* 03367702*)

PHASE III IGRT AND SBRT VS IGRT AND HYPOFRACTIONATED IMRT FOR LOCALIZED INTERMEDIATE RISK PROSTATE CANCER

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This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Group; and SWOG.

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☒ Canada
☒ Approved International Member Sites

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PHASE III IGRT AND SBRT VS IGRT AND HYPOFRACTIONATED IMRT FOR LOCALIZED INTERMEDIATE RISK PROSTATE CANCER

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Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)

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Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</td><td>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.</td><td>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</td></tr>
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<tr><td colspan="3"><u>For clinical questions,</u> <u>contact the Study PI of the Lead Protocol Organization.</u>
For questions concerning eligibility, please contact the Biostatistical/Data Management Center (via the contact list on the protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (via the contact list on the protocol cover page).</td></tr>
<tr><td colspan="3"><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
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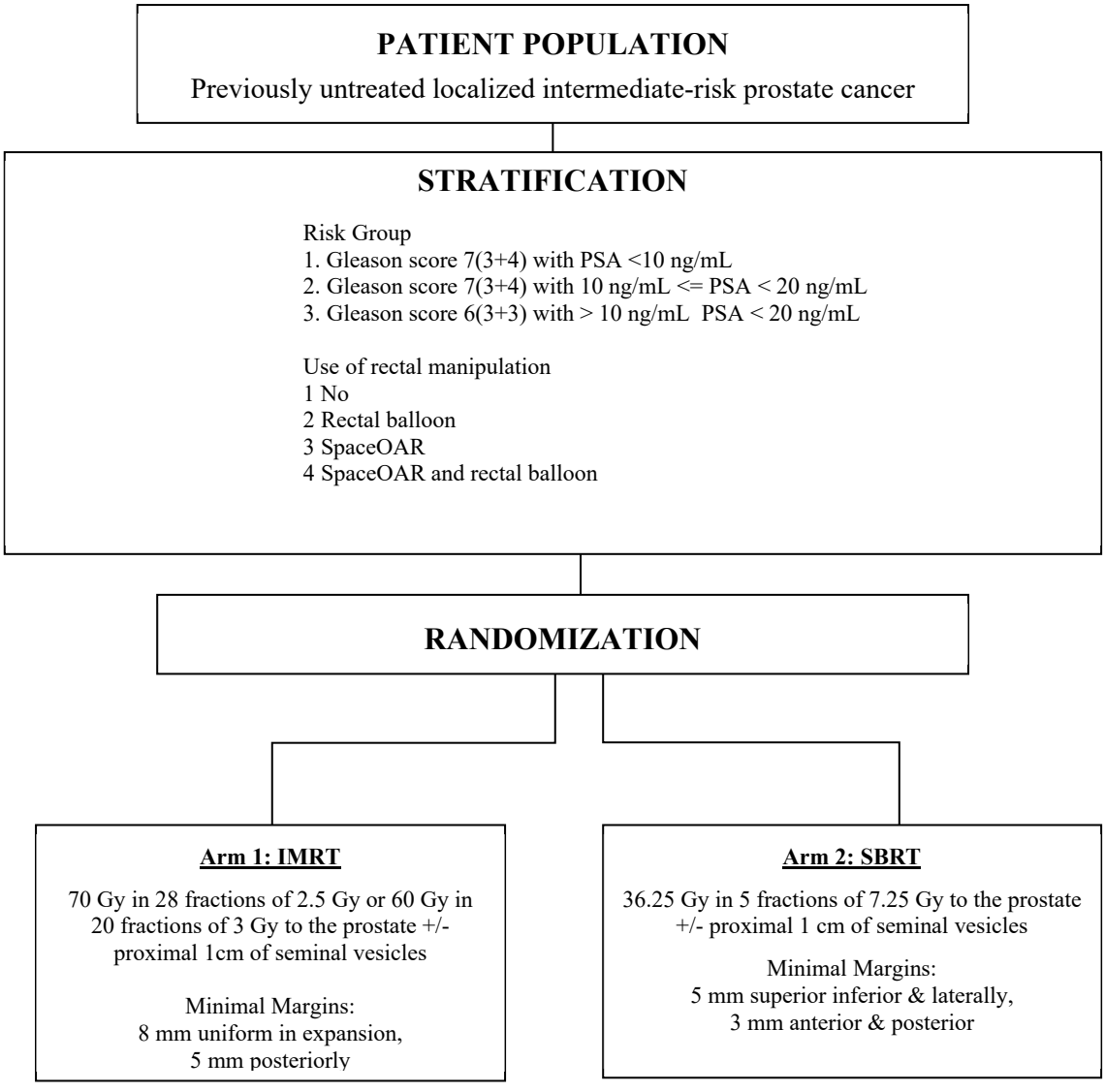
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GU005
SCHEMA (14-JAN-2022)



Prostate specific antigen (PSA); Gray (Gy)

1. OBJECTIVES

1.1 Primary Objectives (23-JAN-2020)

- To determine whether SBRT can be shown to be superior to hypofractionated IMRT in terms of GU and GI toxicity by having fewer patients that experience a minimal important decline (MID) in urinary irritation/obstructive and bowel HRQOL as measured by EPIC-26 at 24 months post completion of therapy.
- To determine if SBRT (5 fractions of 7.25 Gy) is superior to hypofractionated IMRT (28 fractions of 2.5 Gy or 20 fractions of 3 Gy) as measured by Disease Free Survival (DFS).

1.2 Secondary Objectives (23-JAN-2020)

- To determine whether SBRT can be shown to be superior to hypofractionated IMRT at 12 and 24 months post completion of therapy in terms of HRQOL by having fewer patients that experience a minimal important decline (MID) bowel (12 months only) sexual, hormonal, urinary irritation/obstructive (12 months only) and in urinary incontinence HRQOL as measured by EPIC-26
- To determine if SBRT (5 fractions of 7.25 Gy) is superior to hypofractionated IMRT (28 fractions of 2.5 Gy or 20 fractions of 3 Gy) as measured by biochemical failure, overall survival, local failure, prostate cancer specific survival, and distant metastases
- To determine the correspondence between the diagnostic MRI and biopsy
- To determine if PIRADSv2.1 = 4/5 disease is prognostic for biochemical failure at baseline and follow up

1.3 Exploratory Objectives (23-JAN-2020)

- To determine whether a potentially more expensive therapy, SBRT, would be cost-effective than standard hypofractionated IMRT as measured by the EQ-5D-5L
- To determine if disease characteristics captured on baseline and follow-up MRI can be used to predict which patients will respond to SBRT versus hypofractionated IMRT
- To validate autosegmentation tools for the prostate and tumors
- Collect specimens for future translational research analyses

2. BACKGROUND

2.1 Rationale for Selected Approach and Trial Design (23-JAN-2020)

Over-treatment in prostate cancer is a well-recognized issue. While most patients with low-risk prostate cancer may not need immediate treatment and can be followed with active surveillance (Chen 2016) when they show signs of tumor progression -- by PSA elevation or development of a higher Gleason score -- treatment is indicated. Thus, many initially active surveillance managed patients ultimately develop intermediate to high-intermediate risk factors at the time of treatment. While higher risk patients often need combined modality, such as surgery followed by radiation or hormonal therapy combined with radiation, many men who are intermediate risk may be offered either surgery or radiation as monotherapy. Through rigorous studies including randomized trials, radiation treatment for localized

prostate cancer has continued to shorten. Instead of 9 weeks of RT, RTOG 0415 has demonstrated that 70 Gy in 28 treatments (5.5 weeks) provides similar biochemical disease-free survival (bDFS) outcomes. This now forms the standard arm of this trial. The goal of this trial is to further shorten radiation treatment for prostate cancer; the experimental arm (36.25 Gy in 5 fractions) comes from the recently completed RTOG 0938 randomized Phase II trial. The central hypotheses of the current trial are that further reducing radiation treatments will 1) not worsen patient-reported quality of life, and 2) improve DFS. There will be an embedded cost-effectiveness analysis to quantify the magnitude of cost benefit from shortening localized prostate cancer RT to only 5 treatments.

RTOG 0415 provided level 1 evidence based on a bDFS endpoint using PSA that hypofractionated radiation of 70 Gy in 28 fractions is non-inferior to standard daily dose radiation of 73.8 Gy in 41 fractions for favorable patients and has only a slight increase in late grade 2 GI/GU toxicity. In 2016 the CHHiP study with 3216 men confirms what was previously reported from RTOG study 0415, hypofractionation does not result in any loss of efficacy and could make treatment less expensive and more convenient for patients in comparison with conventionally fractionated radiotherapy. Patients were randomly assigned (1:1:1) to receive conventional treatment (74 Gy delivered in 37 fractions over 7.4 weeks) or one of two hypofractionated schedules (60 Gy in 20 fractions over 4 weeks or 57 Gy in 19 fractions over 3.8 weeks) all delivered with intensity-modulated techniques. This study concluded that the 60 Gy was non-inferior to 74 Gy. However non-inferiority could not be claimed for 57 Gy compared with 74 Gy. The CHHiP study results indicate that the hypofractionated regimen used in their study should be considered the new standard of care for localized disease. More recently the PROFIT trial also confirmed that the hypofractionated treatment with 20 fractions was not inferior to standard IMRT to 79 Gy in nine weeks in intermediate risk men. These results allow us to be confident we are not losing efficacy when using hypofractionation. Furthermore, most recent updates note that while dose less than 5 Gy appear reasonable to offer as a standard treatment, much promise may lay in larger doses as used in RTOG 0938 to further reduce cost and perhaps improve efficacy of the treatment. RTOG 0938 provided compelling evidence that it is safe to further reduce hypofractionated radiotherapy to 5 fractions using SBRT to deliver 36.25 Gy in 7.25 Gy dose per fraction to utilize the very low α/β ratio for prostate cancer projected to be between 1 and 3, thus utilizing the fraction-sensitive biology for prostate cancer to allow further hypofractionation to shorten treatment lengths. Prior single institutional randomized trials performed by Pollack (2013) and Hoffman (2014) studied hypofractionation (versus IMRT) and failed to show that moderate hypofractionation was superior to conventionally fractionated RT. Additionally, the HYPRO study also fails to show treatment superiority with a moderately increased dose fractionation. Patients in the HYPRO study were randomized to either hypofractionated radiotherapy of 64.6 Gy (19 fractions of 3.4 Gy, three fractions per week) or conventionally fractionated radiotherapy of 78.0 Gy (39 fractions of 2.0 Gy, five fractions per week). Based on an estimated α/β ratio for prostate cancer of 1.5 Gy, the equivalent total dose in fractions of 2.0 Gy was 90.4 Gy for hypofractionation compared with 78.0 Gy for conventional fractionation. The conventional fractionation group experienced 22% treatment failure rate, and a 20% treatment failure rate in the hypofractionation group.

While this third study failed as well to prove superiority of moderate hypofractionation,

several single institutional studies as well as pooled data do show promise for improved bDFS as well as QOL with SBRT. It should be noted though that while SBRT has been reported to be more cost effective than standard IMRT, it is still unclear the treatment can be delivered at higher extremely hypofractionated SBRT doses without a risk of increased toxicity. Recent publications have confirmed that rectal toxicity and declines in QOL can be improved with the use of an FDA approved hydrogel devise inserted between the prostate and rectum, this use will be allowed in this trial and outcomes stratified in each arm based on the use of the product (SpaceOAR, Augmenix Inc Austin Tx). Finally, advanced image guidance with MRI-assisted treatment planning and fiducial marker use will be utilized to allow of reduced margins in the planning target volumes to hopefully reduce GU toxicity as well.

Our hypothesis is that SBRT can be proven **superior** to hypofractionated IMRT using a patient-reported toxicity and DFS co-primary endpoints. Although overall survival is a desirable endpoint to assess efficacy of a treatment for any cancer, the prolonged natural history for prostate cancer makes overall survival a challenging endpoint for intermediate risk prostate cancer. The more accessible endpoint of biochemical failure free survival (BFFS) may not be sufficiently persuasive to lead to widespread practice change. Therefore, the endpoint of DFS was chosen as the primary disease-related endpoint. BFS and OS remain important, and will be analyzed as secondary endpoints.

Amendment to Moderate Hypofractionation Arm (Arm 1)
Moderate hypofractionation using 60 Gy in 20 fractions of 300 cGy and 70 Gy in 28 fractions of 250 cGy is very likely equivalent and interchangeable in terms of efficacy and toxicity. This fractionation is considered the standard moderate hypofractionation scheme in the UK and Canada, as well as an alternative and equivalent moderate hypofractionation scheme in the US. Therefore, as of Amendment 2, we will allow 60 Gy in 20 fractions as an acceptable fractionation scheme within the moderate hypofractionation arm of this study (Arm 1).

For the additional moderate hypofractionation schema (60 Gy in 20 fractions), CHHiP (Dearnaley 2017) and PROFIT (Catton 2017) established 60 Gy in 20 fractions as equivalent to standard fractionation in large randomized controlled trials. As noted previously, RTOG 0415 established 70 Gy in 28 fractions as equivalent to standard fractionation as well (Lee 2016). Because of these results, moderately hypofractionated regimens involving 240-340 cGy per fraction are considered interchangeable and were grouped together in the most recent ASTRO-ASCO-AUA evidence-based guideline (Morgan 2018). Further, a study that informs the hypothesized difference between moderate hypofractionation and SBRT fractionation in the current study also grouped multiple fractionation schema together within the umbrella term “moderate hypofractionation” and was able to detect a difference between moderate hypofractionation and SBRT fractionation (Johnson 2016). The hypothesized effect size for the statistical power of this study is therefore derived from a group of potential schema for “moderate hypofractionation”, rather than a single accepted regimen. In addition to robust non-inferior efficacy data compared to standard fractionation, as the 70 Gy in 28 fractions of 2.5 Gy regimen, the 60 Gy in 20 fractions of 3 Gy regimen has shown equivalent quality of life to standard fractionation as measured by patient reported outcomes. The

PROFIT study collected EPIC survey data and found no difference in patient reported outcomes between moderate and standard fractionated arms [Personal communication, Charles Catton – PI PROFIT study]. It is likely that since there is no difference between moderate hypofractionation and standard fractionation in terms of patient reported outcomes for either regimen, it is highly unlikely that there is any difference between the two moderate hypofractionated arms given their relative similarity compared to standard fractionation. Therefore, the study protocol will include the commonly used 60 Gy in 20 fractions arm with the expectation that patients treated with this fractionation will be interchangeable with patients treated to 70 Gy in 28 fractions.

Quality of Life

Whether a patient's quality of life after treatment differs between the study arms is a critical question, and is meaningful even if there are no differences between the arms in terms of biochemical disease free control. For that reason, the quality of life endpoints are considered a co-primary endpoint. If it is shown that patients have superior quality of life with 5 fraction treatment compared to the 20 or 28 fraction treatment options for hypofractionation vs extreme hyporactionation as supported by RTOG 0938 showing no increase in toxicity in the phase II setting, the 5 fraction treatment will be preferred even with equivalent biochemical control. Furthermore, patients may be motivated to travel further to centers where 5 fraction treatment is offered given its relative convenience. Balancing the need for long term quality of life evaluation with an efficient and feasible study design, we are proposing comparison of patient reported outcomes at 24 months post treatment. Patient reported outcomes at 24 months is representative of long-term toxicity (Chang 2016) and there is evidence that though there may be changes in quality of life from 3 to 10 years post-treatment, these changes are modest (Punnen 2015). As the largest and most significant declines in HRQOL for radiotherapy are in the urinary irritative/obstructive and bowel domains of the EPIC-26 survey instrument (Sanda 2008), these two domains were chosen for comparison. Finally, we hypothesize that SBRT can be proven superior to hypofractionated IMRT in terms of the domains of urinary irritation/obstruction and bowel function of the EPIC-26 survey at 24 months based on data from Johnson et al. (2016) which found superiority of SBRT in these domains (compared to hypofractionated radiotherapy) in a multi-institutional retrospective analysis.

Additional enhancements for ECOG performance status and Charlson Modified Morbidity are utilized in this concept to select patients to justify a DFS endpoint by limiting patient selection to a cohort of men for whom survival post treatment is anticipated to be sufficiently long such that a biochemical failure is indeed likely to predict the actual risk for a disease-specific survival endpoint.

2.2 Why This Trial Is Important (23-JAN-2020)

The importance for this study is in evidence initially by the volume of patients that undergo treatment within the selected patient cohort. While some of the high-intermediate patients in this cohort may have elected to enroll in RTOG 0924, that study design is inherently more aggressive mandating some use of hormonal therapy and looking at pelvic nodal irradiation as the primary randomization point. The proposed concept would serve well to offer patients in the intermediate risk group a clinical study with highly important endpoints and lower anticipated treatment related morbidity.

The biologic principle that prostate cancer has an inherently low alpha/beta ratio would be corroborated in this trial if the superiority can be established for SBRT over less hypofractionated IMRT. Assuming that the five fraction arm is able to produce superior DFS, then in relatively healthy patients this should translate to an improvement in disease-specific survival as well as overall survival as no other competing risk factors such as concurrent use of potentially cardiotoxic hormonal manipulation is anticipated in the current study. Additionally if the primary endpoint analysis of EPIC-26 based quality of life is able to confirm the anticipated superiority of outcomes from SBRT, then SBRT would most likely become the preferred standard treatment modality due to its wide availability and reduced cost compared to surgery or IMRT.

2.3 Pertinent Data (23-JAN-2020)

Both RTOG 0938 and RTOG 0415 have recently been reported setting the background for this particular study design (Lukka 2016, Lee 2016). RTOG 0938 was a randomized phase II trial assessing EPIC-based quality of life as a primary endpoint and using the standard dose for Stereotactic Body Radiation Therapy (SBRT) initially developed and reported by King et al. (2012) from Stanford University using robotic SBRT. The SBRT arm in RTOG 0938 used 36.25 Gy delivered in 5 fractions of 7.25 Gy over two and one-half weeks (in 15-17 days) versus 51.6 Gy in 12 fractions of 4.3 Gy also over a two and one-half week period (in 16-18 days). As the use of SBRT has now been recommended by ASTRO for routine use as of the January 2014 public announcement, it was felt that using the 5 fraction arm of 0938 should be selected over the 12 fraction arm for comparison in this study of hypofractionated verses extreme hypofractionated radiotherapy. In 2015 at ASTRO and at ASCO Genitourinary Cancer Symposium in 2016 the results for RTOG 0415 were presented comparing hypofractionated IMRT to 70.2 Gy in 28 fractions of 2.5 Gy each compared to a standard dose of IMRT of 73.8 Gy in 41 fractions of 1.8 Gy in low risk prostate cancer patients. The endpoint for non-inferiority was achieved showing that mild to moderate hypofractionation could be safely used in low risk prostate cancer patients with only minimal increase in late grade 2 gastrointestinal and genitourinary toxicity

While both the Pollack (2013) and Hoffman (2014) studies using similar hypofractionated scheduled as used in RTOG 0415, both showed limited added toxicity with hypofractionation, but failed to be shown to be superior to standard IMRT. The current proposal relies on the developing evidence that the low alpha-beta ratio for prostate cancer will be more favorable for disease control in prostate cancer using even larger doses of extremely hypofractionated IMRT capable of being delivered only by SBRT. As RTOG 0415 showed hypofractionated IMRT to be non-inferior to conventional IMRT it has been chosen as the standard arm for this trial to compare with the SBRT arm from RTOG 0938 to test the hypothesis that further hypofractionation can achieve a superior outcome for biochemical disease free survival. However, more recently both PROFIT (Catton 2017) and CHHiP (Dearnaley 2012) trials have shown 60 Gy in 20 fractions to be adequate for standard treatment and thus these regimens have been added as a stratification option on the standard arm

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (via the contact list on the NRG web site). For radiation therapy-related eligibility questions, please contact RTQA (via the contact list on the NRG web site).

3.1 Patient Selection Guidelines (23-JAN-2020)

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Men who are sexually active should be willing and able to use medically acceptable forms of contraception during treatment and for 6 months afterward.

3.1.3 Submission of original biopsy material for testing is optional for all patients. Investigators should check with their site Pathology department regarding release of H&E slides and FFPE block biospecimens before approaching patients about participation in the trial. (See details of submissions in Section 10.1.) Prostate MRI scans will be submitted to IROC per Section 13.2.

3.2 Eligibility Criteria (14-JAN-2022)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.2.1 Previously untreated (no local therapy such as surgery, radiation cryotherapy, HIFU, etc.) localized adenocarcinoma of the prostate with the following clinical findings:

- Clinical stage by digital rectal exam of either T1c or T2a/b (limited to one side of the gland). (AJCC, version 7) or cT1a-c or 2a or 2b.
- Stages T1a-T1b are eligible if patient underwent TURP;
- The patient must meet one of the following 3 criteria: 1) Gleason score must be Gleason 7(3+4) with a PSA < 20 ng/mL, or 2) Gleason 6 (3+3) with a PSA > 10 ng/mL and < 20 ng/mL which is considered intermediate risk and eligible for the study. (AJCC, version 7), or 3) Group Grade 1 with a PSA > 10 ng/mL and < 20 ng/mL or 2 with a PSA < 20 ng/mL.
    - If patient is receiving a 5-alpha reductase inhibitor at the time of enrollment, the baseline PSA value may be double the initial value and the medication should be discontinued but a washout period is not required. To be eligible, a PSA drawn while still on the medicine must be:
        - <10ng/mL if Gleason 7(3+4) (note this patient would be on stratification level 1 if PSA < 5ng/mL and stratification level 2 if less than 10 ng/mL).

- >5ng/mL and less than 10 ng/mL for Gleason 6(3+3) (note this patient would be on stratification level 3.)
- The prostate volume must be < 70 cc as reported at time of biopsy or by separate measure with ultrasound or other imaging modalities including MRI or CT scan.
- Patients in active surveillance who elect to be treated are eligible if they meet protocol requirements

3.2.2 Age ≥ 18

3.2.3 History and physical including a digital rectal exam 60 days prior to registration

3.2.4 ECOG Performance Status 0-1 60 days prior to registration

3.2.5 MRI of the prostate and pelvis (per institutional SOC - should be compliant with PIRADSv2.1 guidelines) within 1 year prior to registration

3.2.6 Bone scan as clinically indicated within 120 days prior to registration

3.2.7 Charlson modified co-morbidity score ≤4 for patients under 60 and ≤5 for patients 60 and over (see Appendix I) 21 days prior to registration

3.2.8 International Prostate Symptom Score (IPSS) of <15 21 days prior to registration

3.2.9 The patient must provide study-specific informed consent prior to study entry.

3.2.10 Willingness and ability to complete the Expanded Prostate Cancer Index Composite (EPIC-26) questionnaire

3.2.11 Completion of all items of the EPIC-26 which will be data entered at registration 60 days prior to registration.

3.2.12 Only English, Spanish, and French-speaking patients are eligible to participate as these are the only languages EPIC-26 has been validated in.

3.3 Ineligibility Criteria (23-JAN-2020)

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Definitive clinical or radiologic evidence of metastatic disease. No nodal involvement or evidence of metastatic disease allowed as defined by screening of the pelvis.

3.3.2 Definitive T3 disease on MRI

3.3.3 Prior or current invasive malignancy with current evidence of active disease within the past 2 years.

- Exceptions: Non-melanomatous skin cancer, carcinoma *in situ* of the male breast, penis, oral cavity, or stage Ta of the bladder, or stage I completely resected melanoma.

3.3.4 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable; must be off treatment for at least 3 years.

3.3.5 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.3.6 The use of hormonal therapy is not allowed. If the patient in on a 5-alpha reductase inhibitor, then they should be stopped prior to treatment once enrolled onto the study. No washout period is required for this study to participate.

3.3.7 Severe, active co-morbidity defined as follows:

- HIV positive with CD4 count < 200 cells/microliter. Note that patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ 200 cells/microliter within 30 days prior to registration. Note also that HIV testing is not required for eligibility for this protocol. This exclusion criterion is necessary because the treatments

involved in this protocol may be significantly immunosuppressive.

- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol. (Patients on Coumadin or other blood thinning agents are eligible for this study.)

3.3.8 Contraindication to MRI

- Cardiac pacemaker or defibrillator
- Surgically implanted electrical devices such as spinal stimulation devices or intracranial stimulation devices, cochlear implants, the presence of metallic foreign bodies in the orbits, and incompatible old mechanical heart valves and aneurysm clips

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP (14-JAN-2022)

PRE- TREATMENTASSESSMENTS

Assessments	Prior to Registration (60 DAYS)	Prior to Registration	Prior to Treatment
History/Physical exam including digital rectal exam	X		
Performance Status	X		X
PSA	X		
Adverse Event Evaluation			Dysuria, hematuria, incontinence, rectal hemorrhage, fatigue
MRI of prostate and pelvis *See Section 5.3.1 for mandatory MRI imaging requirements* (report to be uploaded in RAVE and please redact PHI on every page on these reports)*		1 year	
Bone scan (only as clinically indicated) sodium fluoride acceptable if available and covered by insurance		120 days	
Concomitant Med Assessment *(Rx, OTC, herbal supplements)*			X
EPIC-26 Questionnaire, EQ5D-5L (See Time windows for more details)	X		
Charlson modified co-morbidity score (see Appendix I)	21		
Pathology report to be uploaded in RAVE and please redact PHI on every page on these reports*			X
International Prostate Symptom Score (IPSS)	21		
Tissue for banking (for consenting patients)			X
Blood for banking Plasma, Serum, Whole blood (for consenting patients)			X
Urine for banking (for consenting patients)			X

***Reports should be uploaded when RAVE access is given**

ASSESSMENTS DURING TREATMENT

Assessments	Weekly During RT
Adverse Event Evaluation	X
Blood for banking - Plasma and Serum (for consenting patients)	Last week of RT
Urine for banking (for consenting patients)	Last week of RT

This study uses Medidata Patient Cloud ePRO. Remember to register the patient to the Patient Cloud ePRO. For instructions on registering the patients, please refer to Appendix II.

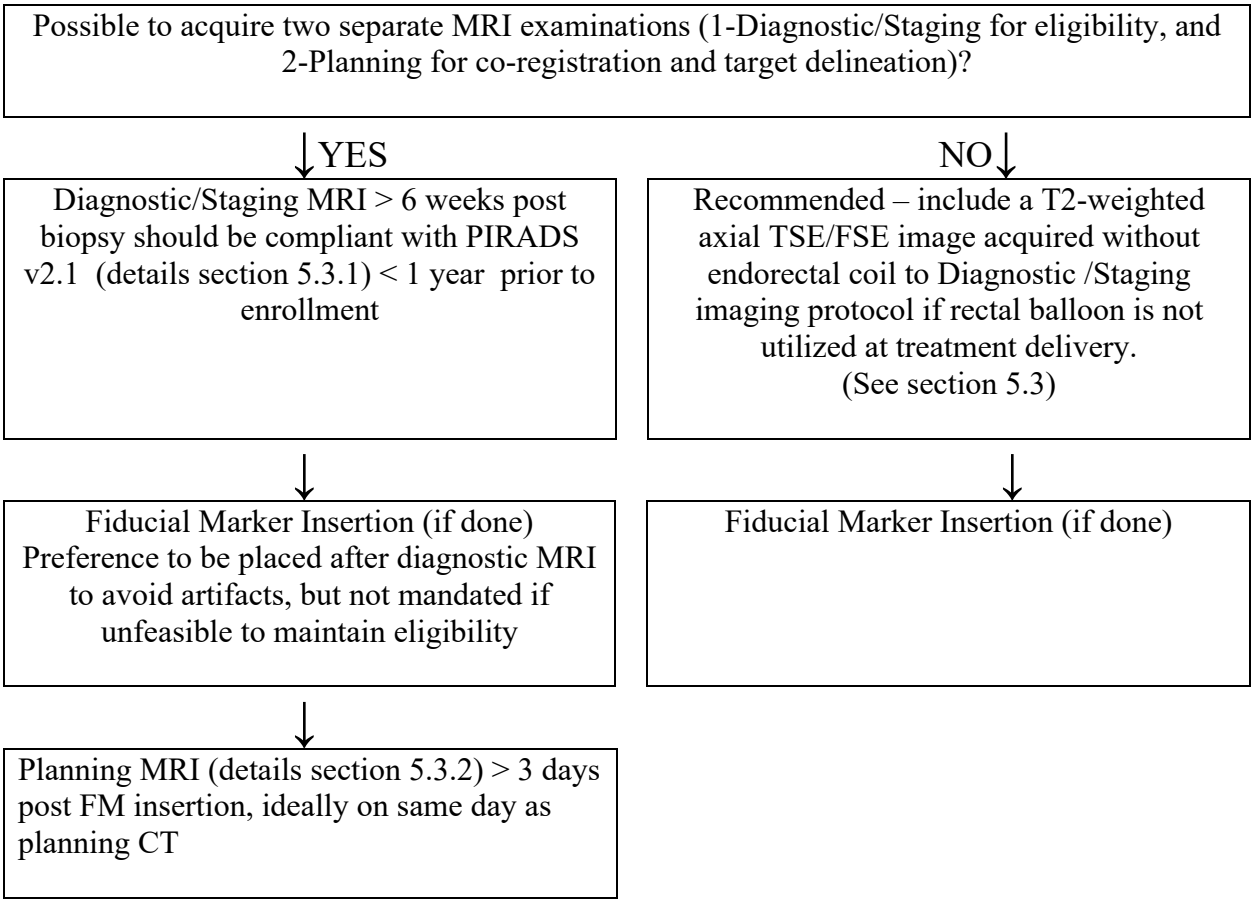
ASSESSMENTS IN FOLLOW UP

Assessments	
PSA	Every 6-12 months
DRE	Following a rise in PSA or as clinically indicated
Adverse Event Evaluation	With each follow up visit
Concomitant Med Assessment *(Rx, OTC, herbal supplements)*	With each follow up visit
EPIC-26 Questionnaire, EQ5D-5L	Year 1 and 2 post treatment completion
Bone scan, MRI of the prostate; consider Fluciclovine or C-11 PET if available	Only as clinically indicated by rise in PSA or based on physical exam such as change with digital rectal exam suspicious for local or distant recurrence at the discretion of the treating physician
Blood for banking- Plasma and Serum (for consenting patients)	At 12 months after completion of RT
MRI of the prostate	Patients with baseline MRI reporting a PIRADSv2.1=4 or 5 lesion who either have post-RT PSA nadir > 0.8ng/mL or had a post-RT PSA rise of > 0.2 ng/mL above nadir: • If PSA criteria is met before 24 months from end of RT, then MRI is to be done at 24 months • If PSA criteria is met after 24 months from end of RT, MRI is to be done within 12 months of meeting PSA criteria Examinations **to** be performed at 3T or 1.5T (3T strongly preferred) and compliant with PIRADSv2.1 guidelines, including DCE acquisition. *Note:Guided biopsy may be considered if suspicious findings are identified on MRI at the discretion of the treating physician.*

This study uses Medidata Patient Cloud ePRO. Remember to register the patient to the Patient Cloud ePRO. For instructions on registering the patients, please refer to Appendix II.

Time windows for patient completion of EPIC and EQ-5D-5L: Baseline assessments (EPIC and EQ-5D-5L) must be completed prior to start of treatment. However, per eligibility, EPIC must be completed prior to registration. The EQ-5D-5L data must be entered in Medidata Rave before treatment starts. The 1 year assessments must be completed within 6 weeks (1 year +/- 6 weeks) and the 2-year assessments must be completed within 8 weeks (2 years +/- 8 weeks). Please submit the data soon after the patient completes the assessments to allow for monitoring of patient compliance.

Prostate MRI for eligibility evaluation and treatment planning
A diagnostic/staging MRI within 1 year is mandatory for eligibility evaluation (to exclude patients with definitive T3 disease on MRI). A dedicated planning (simulation) MRI is also recommended to assist target delineation. The following workflow is meant as a guide to institutions in devising their prostate MRI plan:



5. TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 Chemotherapy/Hormonal Therapy/Other Agent-Based Therapy

Not applicable

5.2 Radiation Therapy (14-JAN-2022)

Protocol treatment must begin within 4 weeks after simulation.

NOTE: A Pre-Treatment Review is required for the first Arm 2 patient enrolled from each institution PRIOR TO DELIVERY of radiation treatment. The patient cannot start treatment until they have received approval from the Imaging and Radiation Oncology Core (IROC)-Philadelphia RT. The Pre-Treatment Review process requires 3 business days from the receipt of complete data to TRIAD. If an unacceptable deviation occurs the next case may require a Pre-Treatment review. See Section 8.3 for specifics on submission requirements.

After an institution has passed the Pre-Treatment review of the first Arm 2 patient enrolled, review of all other Arm 2 cases do not require Pre-Treatment review.

Note: For Arm 2 SBRT QA, see Section 8.3.

Radiation Therapy Schema

Schema at the beginning of the protocol should be followed.

5.2.1 Treatment Technology

This protocol requires photon treatment. IMRT techniques including Tomotherapy and VMAT are required. MRI linacs and CyberKnife are allowed. Proton therapy is excluded. All patients will have daily IGRT. SBRT is defined by 5 or fewer fractions with reduced margin and tighter penumbra versus IMRT for this trial.

This protocol requires the use of IMRT (DMLC or SMLC) or related techniques (Tomotherapy/VMAT/Cyberknife). Related techniques include robotic dose delivery that uses inverse treatment planning to determine weighting for a large number of fields sequentially irradiating sub-regions of a target. Allowed IMRT techniques include the VMAT moving gantry delivery. Three-dimensional coplanar or noncoplanar beam arrangements will be custom designed for each case to deliver highly conformal dose distributions. For fixed gantry angle IMRT delivery, a least 5 gantry positions should be used. The recommended photon energies for this protocol are 6-10 MV with the exception for ViewRay which may use ^{60}Co. The use of beams with higher energy is discouraged. These energies will result in an increased neutron dose reaching the patient's total body. However, it is recognized that increasing the energy has advantages in improving dose distributions for larger patients. For this reason, beams as high as 15 MV will be allowed only when improvement of the dose distribution is evident to the treatment planner. If an institution uses mixed beam energies as part of the IMRT optimization process, using a limited number of beams with energy higher than 10 MV is allowed for the longer path lengths encountered in a particular plan for larger patients. Such beams should be mixed with beams energies that do not result in neutrons (i.e., 6-10 MV).

5.2.2 Immobilization and Simulation-**Arm 1 and Arm 2**

Immobilization

Patients will be typically positioned supine in a comfortable posture. The minimum immobilization apparatus will be a pillow under the knees and the feet taped or rubber-banded together or equivalent. More complex immobilization devices are allowed, as per the discretion of the treating physician, as long as they do not interfere with the proper functioning of the image guidance. Prone position is discouraged but allowed if tracking is used. A full bladder daily for treatment is strongly recommended. The degree of bladder fullness should be made to duplicate what is anticipated for daily treatment, i.e., if the patient is instructed to maintain a full bladder for treatment, he should be simulated as such. Consistent bladder filling procedure should be used for an individual patient for simulation and for each treatment. The degree of bladder filling for each patient entered into this study will be documented for future analysis. The use of rectal balloons will be allowed but are not required in this protocol. The use of a rectal manipulation (rectal balloon and/or SpaceOAR) will be allowed per institutional standards. The use of rectal manipulation is allowed on either treatment arm at the discretion of the treating radiation oncologist, and use will be stratified per protocol.

Localization

The acceptable IGRT techniques will be utilized for initial localization, and tracking or periodic monitoring to guarantee that beam positioning is maintained throughout long treatments. The localization technique will be documented for each institution on the facility questionnaire. If an institution uses more than one treatment/localization technology, each must be described and appropriately credentialed. The initial localization and alignment is based on the center of mass of the transponders/fiducial markers. After initial localization is performed, all effort should be made to initiate the treatment delivery as quickly as possible. Significant rotations may be corrected at initial localization stage, and intra-fractional rotations may be corrected if detected if able to do so. Further adjustment during the treatment will be translational shift of the center of mass determined utilizing the IGRT technique and using remote couch motion. Periodic monitoring of prostate position – minimum every 8 minutes during radiation delivery will be strongly recommended for all techniques (except where tracking devices are utilized). If tracking devices are not employed repeat localization images will be taken at the end of each treatment. At the discretion of the radiation oncologist/physicist, monitoring of intrafraction motion may be required more frequently. If in an individual patient the end-of-treatment images identify significant prostate movement compared to pretreatment images, monitoring of intrafraction motion more frequently would be recommended.

5.2.3 Imaging for Structure Definition, Image Registration/Fusion and Follow-Up --- **Arm 1 and Arm 2**

Simulation Imaging

The treatment planning CT and/or MRI scan will be acquired with the patient set up in the same position as for daily treatments. Each patient will typically be positioned in the supine position. The CT and/or MRI scan of the pelvis should start at or above the iliac crest down to the perineum.

CT-based simulation imaging:

All tissues to be irradiated must be included in CT scan. CT scan thickness should be 3 mm (**2 mm for SBRT**) or less through the region that contains the target volumes (i.e., from the bottom of the sacroiliac joints down to the penile urethra). The regions above and below the target volume region may be scanned with slice thickness ≤ 1.0 cm. If 3 mm (2 mm for SBRT) or less slice thickness is not possible for the entire scan, the reconstructed axial slice thickness shall, in the vicinity of the target volumes, be sufficient to enable accurate dose calculation resolution.

It is advised that extreme bladder or rectal filling not be present at the time of the planning CT scan. A distended bladder or rectum can introduce a systematic patient positioning error that may increase the probability of missing the CTV. An enema before the planning CT scan and use of a hollow (robnel) catheter to evacuate flatus will empty the rectum and is highly recommended, thereby allowing a narrow posterior PTV margin (~5 mm) to account mainly for set up errors. The GTV, CTV, and PTV and normal tissues must be outlined on all CT slices in which the structures exist.

MRI is required for GTV, CTV and urethra definition and must be fused into the planning CT scan for CT based planning.
Other modality images used in assisting segmentation should be submitted along with DICOM registration files, when feasible. Internal peer review of registration quality is strongly recommended.

MR-based simulation imaging:

The primary volumetric image acquired for target delineation and dose calculation purposes may be MR imaging, provided that the voxel-by-voxel density-assignment techniques are accommodated. The FOV and superior-inferior extent of the primary planning image shall be large enough so as to encompass the target volume, the entirety of the OARs, and any regions through which treatment beams may propagate through the patient

The reconstructed axial slice thickness shall, in the vicinity of the target volumes, be sufficient to enable accurate dose calculation resolution. The protocol recommends a reconstructed slice thickness of 3 mm or less (2 mm for ultra-hypofractionation or SBRT). For regions of the patient either superior or inferior to the target-volume region, a greater slice thickness may be used (up to 5 mm), with the scan range extending superiorly and inferiorly from the boundaries of the target volume.

For MRI simulation the following imaging protocol is recommended (*refer to* ***Section 5.3.2***):
● Patient setup should represent treatment conditions (bowel prep, bladder prep, immobilization devices, etc.).
● Bladder filling should be comfortable to reduce image blurring.
● Buscopan or Glucagon can (optional) be administered just prior to the scan to limit peristalsis unless contraindicated.
● Field of view should generally be 12-20, to include prostate and SV and skin surface.
● Each imaging sequence should strive to minimize acquisition times (< 5 minutes if possible) to minimize image blurring due to motion.
● Utilize optimal MR sequences for prostate such as T2W, T2W TSE/FSE, DWI, DCE, 3DFFE, T2 cube etc.
● A synthetic CT may be generated for treatment planning.

Imaging for Structure Definition, Image Registration/Fusion and Follow-up --- **Arm 1 and Arm 2**

MRI may be used as part of staging and to assist in volume delineation in all eligible patients.

MRI registration to CT consists of a prostate-to-prostate registration. Bone-to-bone registration of the pelvis is prohibited. In the absence of FMs, manual or automated (mutual information algorithm) registration restricted to prostate and adjacent periprostatic soft tissues must be performed. In the presence of FM, a manual point-based registration using common points (superior and inferior aspect of each FM, if possible) is recommended. If a separate independent image was acquired to resolve FMs, inter-sequence motion must be evaluated and corrected by registering the T2w image to the FM image if motion is found. Finally, the ADC map or high b-value (calculated or acquired) image may be registered to assist in delineation in a manner that accounts for geometric distortion.

The quality of registration must be evaluated prior to treatment planning. Internal peer review of registration quality strongly recommended. DICOM registration files are to be submitted when feasible. Errors in registration translate to systematic errors through a course of treatment, and must be minimized.

5.2.4 Definition of Target Volumes and Margins

The definition of volumes will be in accordance with the ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.

Gross Tumor Volume (GTV) is defined by the physician as all known disease as defined by the planning CT, and clinical information. The GTV for the purposes of this protocol is the prostate only. Prostate dimensions should be defined as visualized on co-registered MRI and CT scan.

Clinical Target Volume (CTV) is the GTV plus areas considered to contain microscopic disease, delineated by the treating physician, and is defined as the GTV prostate gland +/- 1cm of SV. Planning CT fused to MRI mandated for planning and allows for up to 1 cm of proximal seminal vesicles to be included in the Clinical Target Volume (CTV) at the discretion of the treating Radiation Oncologist based on the MRI findings and the positive biopsy locations (i.e base of prostate biopsy positive).

Planning Target Volume (PTV) will provide a margin around the CTV to compensate for the variability of treatment set up and internal organ motion per the selected treatment in the schema. Superior and inferior margins (capping) should be minimized depending on the thickness and spacing of the planning CT scan. Careful consideration should be made when defining the margin in three dimensions to avoid undue expansion into either the rectum or bladder based on initial CT slice thickness to accommodate the 5-8 mm superior and inferior expansion on each treatment arm. Treatment will be given only to the PTV using IMRT fields shaped to exclude as much of the bladder and rectum as possible. Field arrangements will be determined by IMRT planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on an analysis of the volumetric dose including dose-

volume histogram (DVH) analyses of the PTV and critical normal structures.

Planning Volume Summary:
GTV = Prostate
CTV = Prostate +/- 1 cm proximal Seminal Vesicles
PTV = CTV + 8mm minimum superiorly, inferiorly, anteriorly, and laterally, with 5 mm minimal posteriorly for Arm 1 and 5mm superiorly, inferiorly, and laterally with 3mm both anteriorly and posteriorly for Arm 2.

NOTE: All structures must be named for digital RT data submission to TRIAD as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Arm 1		
Standard Name	**Description**	Validation
CTV_ xxxx, xxxx=7000 or 6000	Clinical Target Volume	Required
GTV_xxxx, xxxx=7000 or 6000	Gross Tumor Volume (Prostate)	Required
PTV_xxxx, xxxx=7000 or 6000	Planning Target Volume	Required

Arm 2		
Standard Name	**Description**	Validation
CTV_3625	Clinical Target Volume	Required
GTV_3625	Gross Tumor Volume	Required
PTV_3625	Planning Target Volume	Required

5.2.5 Definition of Critical Structures

* SemVes_Prox to be added if the treating Radiation Oncologist elects to add 1 cm of proximal Seminal Vesicles to the CTV

- The normal tissues will be contoured and considered as solid organs rather than contouring the bladder and rectal walls.
- **Bladder** should be contoured from its base to the dome.
- **Rectum** should be contoured from the anus (at the level of the ischial tuberosities) for a length of 15 cm or to the recto sigmoid flexure. This generally is below the bottom of the sacroiliac joints.
- Femoral_Head_L/R should be contoured from the acetabulum to the inferior aspect of the pubic symphysis.

- Spc_Bowel should be the 'bowel bag' contour defined as the volume where moveable bowel can reside within the peritoneal cavity
- E-PTV-OAR The tissue within the skin and outside all other critical normal structures and PTVs are designated as unspecified tissue.

NOTE: All structures are REQUIRED and must be named for digital RT data submission to TRIAD as listed in the table below. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Standard DICOM Name	**Description**	Validation
Bladder	Bladder	Required
Spc_Bowel	Space occupied by bowel	Required
Rectum	Rectum	Required
External	External Patient Contour	Required
E-PTV-OAR	External less all PTV and OAR	Required
Femur_Head_L	Left Femur Head	Required
Femur_Head_R	Right Femur Head	Required
Femurs	Both Femur Heads	Required
PenileBulb	Penile Bulb	Required
SeminalVes	Seminal Vesicles	Required
SemVes_Prox	1 cm Proximal Seminal Vesicles	Required when applicable
Urethra	Urethra	Required when applicable per physician

5.2.6 Dose Prescription

Prescription dose to the PTV shall be according to the following dose schemas. The prescription dose is the minimum dose to the PTV.

Arm 1 delivered in 2.5 Gy/28 fractions or 3.0Gy/20 fractions minimum dose per fraction. All fields treated once daily, 5 fractions per week in less than 32 business days.

Arm 2 delivered in 7.25 Gy minimum dose fractions. SBRT will be treated 2-3 fractions per week, at least every other day in less than 17 business days.

*****SBRT treatments should be delivered with a minimum of 40 hours interval and a maximum of 128 hours interval between all 5 fractions.***

Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**	**Frequency**	**Dose specification technique**
PTV_7000	70	2.5	28	Daily	Covering 98% of PTV

PTV_6000	60	3	20	Daily	Covering 98% of PTV
PTV_3625	36.25	7.25	5	***Two to three fractions per week. A minimum of 40 hours and a maximum of 128 hours should separate each treatment.***	Covering 98% of PTV

The maximum dose must not be within an "Organ at Risk" such as the Rectum, Bladder, or Penile Bulb.

5.2.7 Compliance criteria

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended

Target Volume Constraints and Compliance Criteria

Table 1. Target Volume Constraints

Name of Structure	Dosimetric parameter*	Per Protocol	Variation Acceptable	Notes
PTV_7000	D0.03cc[Gy]	<=77	<=80.5	**Arm 1- 70 Gy**
	D99% [Gy]	>=70	>=65.1	
	D98%[Gy]	>=70	>=66.5	
CTV_7000	D99%[Gy]	>=70	>=66.5	
PTV_6000	D0.03[Gy]	<=63	<=64.5	**Arm 1 – 60Gy**
	D99%[Gy]	>=60	>=55.80	
	D98%[Gy]	>=60	>=57	
CTV_6000	D99%[Gy]	>=60	>=59.4	
PTV_3625	D0.03cc[Gy]	<= 38.78	<=43.5	**Arm 2**

	D99% [Gy]	>=34.4	>=33.7	
	D98%[Gy]	>=36.25	>=34.4	

Normal Structure Constraints and Compliance Criteria
Critical Normal Structures IRIS or individual beam collimation for Cyberknife or multileaf collimation must be used in conjunction with conformal IMRT planning to restrict the dose to the normal structures. Dose-volume histograms (DVHs) must be generated for all critical normal structures and the unspecified tissues. Portions of the bladder and rectum will, by necessity, receive the full dose to the PTV; however, careful planning must be performed to ensure that the volume of the bladder and rectum receiving the full dose is kept to a minimum. Based upon a review of patient dosimetry on dose RTOG 0415 and 0938, the following normal tissue guidelines should be followed:

Table 2: Arm 1 **Normal Structure Constraints**

Name of Structure	Dosimetric parameter*	Per Protocol	Variation Acceptable
Rectum	D15%[Gy]	<=70	<75
	D25%[Gy]	<=65	<70
	D30%[Gy]	<=50	<60
	D50%[Gy]	<=38	<45
Bladder	D0.03cc[Gy]	<= 73.5	<75
	D30%[Gy]	<=50	<60
	D50%[Gy]	<=38	<45
	D90%[Gy]	<=15	<20
Spc_Bowel	D0.03[Gy]	<=45	<50

Table 3: Arm 1 Recommended dose acceptance criteria for other normal tissue, but not to be used for plan score.

Structure	Recommended dose acceptance criteria	
Penile Bulb	Mean[Gy]	<=52.5

Table 4: Arm 2 **Normal Structure Constraints**

Name of	Dosimetric parameter*	Per Protocol	Variation	Notes

Structure			Acceptable	
Rectum	D0.03cc[Gy]	<=38	< 40	
	D3cc[Gy]	< =35	< 36	
	D10%[Gy]	<= 32	< 34	
	D20%[Gy]	<= 25	< 30	
	D50%[Gy]	<=18	< 19	
Bladder	D0.03cc[Gy]	<=39	< 40	
	D50% [Gy]	<=15	< 20	
Spc_Bowel	D0.03cc[Gy]	<=20	<30	
Urethra	D0.03cc[Gy]	<=38.78	43.5	For patients where the maximum point dose to a point that is 0.03 cc exceeds 38.78 Gy, visualization of the urethra is required

Table 5: Arm 2 Recommended dose acceptance criteria for other normal tissue, but not to be used for plan score (% to Prescription Dose of 36.25 Gy).

Structure	Dosimetric Parameter	Acceptable
Penile Bulb	D0.03cc[%]	<= 100
	D3cc[%]	<= 55 (19.9Gy)
Femurs	D10cc[%]	<= 43 (15.6Gy)
	D1cc[%]	<= 55 (19.9Gy)
E-PTV-OAR***	D10cc[%]	<= 30 (10.9Gy)

	D1cc[%]	<= 43 (15.6Gy)

*In this table, each dose value represents a treatment planning guideline and not a clinical study constraint. Care should be taken not to shield the penile bulb at the expense of adequate coverage of the PTV in this study on either treatment arm.
**Urethra must be visualized by Foley or MRI if hot spot from plan is located along the central prostate volume, and central hot spot should be avoided in planning.
*** E-PTV-OAR: Unspecific tissue defined as: External minus PTVs and all listed OARs.

5.2.8 Treatment Planning Priorities and Instructions

- Critical Structure and Target priorities must be listed in order of decreasing importance (We may also use one importance factor for a group of structures).

1. Rectum
2. Bladder
3. PTV
4. Urethra
5. Small Bowel
6. Penile Bulb

- Required Algorithms

Acceptable choices of algorithms are listed at: http://irochouston.mdanderson.org

For Convolution/Superposition type algorithms, dose should be reported as computed inherently by the given algorithm. For Monte Carlo or Grid Based Boltzmann Solver algorithms, conversion of Dm (dose-to-medium) to Dw (dose-to-water) should be avoided. Dm, computed inherently by these algorithms, should be reported.

- Primary dataset for dose calculation

The primary dataset for dose calculation must be a free-breathing CT.

-Dose matrix resolution

If an MRI is used for treatment planning, appropriate and approved density conversion techniques shall be utilized. The TPS may assign electron densities or physical densities for each voxel in the volumetric planning image, to account for tissue density for beam attenuation and dose calculation. Depending upon the protocol, the following techniques may be used for density assignment:
• Voxel-by-voxel assignment using an appropriate image value to density table (IVDT)
• Uniform assignment of the entire patient volume, to the density of water or the density of tissue
• Assignment of specific ROIs to specific uniform density values appropriate to the ROI; examples include density overrides to correct for image artifacts (e.g. due to the presence of highly-attenuating materials), to remove from the image any contrast agent that was present during simulation, and the assignment of ROIs delineated in an MR planning image to an appropriate density (“synthetic CT”)

An accurate accounting of the variable tissue density within the planning image shall be done within the TPS. For CT-based planning, a CT-number-to-electron-density, CT-number-to-physical density, CT-number to relative stopping power, or CT-number-to-mass-density table shall be measured within the institution's imaging system, and reviewed and credentialed as appropriate. For MR-based planning, an atlas-based "synthetic CT" image with appropriate densities assigned to all regions of interest may be obtained from the planning MR image.

Dose grid size should be ≤ 3 mm in all directions.

5.2.9 Patient specific QA

Any patient-specific QA that needs to be acquired should follow institutional guidelines.

For photon IMRT plans, patient specific QA is highly recommended. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 3% dose difference and 3 mm distance to agreement. The pass rate should be at least 90% measured for the entire plan.

5.2.10 Treatment Localization/IGRT

This protocol will require treatments to be performed with an IGRT technique using a 3-D coordinate system defined by 3D volumetric data or orthogonal 2D images. 6DoF IGRT is allowed.

> IGRT and Electromagnetic Transponders Used for Target Localization and Field Adjustment. Allowed x-ray IGRT techniques with or without real-time tracking:
>
> The x-ray IGRT system that can be used for this study are:
> - 2D and 3D IGRT systems are allowed for this protocol
> - o These systems can use either kV or MV x-rays
> - o A computerized method for image registration is required for determination of the patient shift information
> - o The image registration can be either manual (drag and drop images) or automatic
> - Examples of 2D systems are the ExacTrac, on board imaging (OBI), electronic portal imaging device (EPID), CyberKnife real-time system, etc.
> - Examples of the 3D systems are the use of helical tomo CT imaging, cone-beam CT and CT-in-the-room
> - EPID imaging is allowed as long as the above conditions are met. The use of target tracking during treatment is encouraged when this technology is available and strongly encouraged when the treatment time from initial beam-on to the end of dose delivery is longer than 8 minutes.
>
> Repeat IGRT procedures can be used to detect and correct field positions when real-time tracking is not available. Treatments that take less than 8 minutes do not require an end-of-treatment IGRT procedure.

An end-of treatment IGRT procedure should be obtained when real-time tracking is not used, and the time period from the last IGRT procedure exceeds 8 minutes.

Use of fiducial markers: Fiducial markers placed within the prostate are required for this protocol if planned with CT scan, but may be omitted for MRI only based planning and delivery platforms. The size and material used for these markers must be determined based on each institution's CT-simulator and IGRT system. The markers must be visible and artifact-free on both systems. It is recommended that at least three markers are placed for each patient. If Calypso markers are used they must be placed after the diagnostic MRI for eligibility assessment is acquired.

Dose from x-ray IGRT: Estimates of patient doses per imaging study for various imaging systems vary considerably. The doses are in the range of 1 mGy for Cyberknife's and BrainLab's ExacTrac planar kV-systems. The doses from helical MV CT scan on a tomotherapy unit were estimated to be in the range of 1 to 3 cGy for head and neck studies, similar to doses reported for kV cone beam CT on the Elekta Synergy machine. The doses for MV cone beam CT are in the range of 10 cGy for a pelvis study to 6 cGy for a head and neck study. Thus, the doses for 3D imaging systems are in the range from 1 to 6 cGy for head and neck imaging and can contribute from 0.5 to 3% to the daily dose of 2.0 Gy. These dose estimates apply to a single imaging procedure and can be compared to the dose delivered for a single treatment fraction when IGRT imaging is performed once each day of treatment. The imaging dose typically exceeds the boundaries of the high-dose region(s) treated therapeutically, and it is sometimes necessary to repeat the procedure a number of times during, before, or after a single fraction. The imaging dose to nearby critical structures will increase when repeated IGRT procedures are performed for patients with severe set up problems (e.g., requiring frequent corrections of more than 5 mm).

It is recommended that patients expected to have severe set up problems not be enrolled in the study. Patients who are found to have severe set up problems after commencement of treatment may have their treatment modified in the best interest of the patient. An intention to treat analysis will be conducted. As a technique of controlling patient dose, it is recommended that a daily IGRT QA procedure be established at each institution to verify the accuracy of the imaging isocenter, coincidence of the imaging and radiation isocenter, image registration software, couch motion, etc. on a daily basis. This QA check should be performed by the therapists operating a particular treatment device and is aimed at reducing the use of repeat imaging to check that the registration software has functioned properly when a shift of patient position is carried out.

Additionally, it is not recommended that an institution use a daily imaging technique that delivers greater than 10 cGy/day imaging dose to the patient. This limit dictates that repeat imaging on a particular day is held to a minimum when systems that deliver up to 10 cGy per fraction are used. Adding the imaging dose to the patient's treatment dose distribution is not allowed for this protocol. This approach is taken because this dose has not traditionally been added, and many institutions using IGRT do not have a method for

accurately modeling imaging dose. The exception to this rule is the technique of adding "imaging beams" to the IMRT optimization process. In this case, one or more orthogonal sets of conformal beams, having the same energy as the treatment beams, are used as input to the optimization so that the imaging dose is automatically accounted for in the final dose distribution. This method of handling the imaging dose is allowed for this protocol.

5.2.11 Case Review

NOTE: Pre-treatment reviews are required for the first Arm 2 patient enrolled from each institution (See Section 5.2 and Section 12.1 for details and Section 8.3 for specifics on submission requirements). After an institution has passed the Pre-Treatment review of the first Arm 2 patient enrolled, review of all other Arm 2 cases will be ongoing and performed remotely. Review of Arm 1 cases will be ongoing and performed remotely.

5.3 MR Imaging (14-JAN-2022)

5.3.1 Diagnostic/Staging MRI (mandatory)

This examination is considered standard-care, and required for eligibility evaluation, and for correlative science study. Acquisition and reporting per institutional SOC -should comply with institutional guidelines. For this study, the following are timing and imaging guidelines:

- > 6 weeks post prostate biopsy
- Patient should evacuate the rectum, if possible, just prior to the MRI exam.
- 1.5T and 3T systems are both permitted, although 3T is preferred
- axial T2w image obtained with 2D RARE (rapid acquisition with relaxation enhancement) pulse sequence, more commonly known as fast-spin- echo (FSE) or turbo-spin-echo (TSE). In order to avoid blurring, excessive echo train lengths should be avoided. In plane dimension: ≤0.7mm (phase) x ≤0.4mm (frequency). Slice thickness: 3mm, no gap. FOV: generally 12-20 cm to encompass the entire prostate gland and seminal vesicles
- axial DWI: Free-breathing spin echo EPI sequence combined with spectral fat saturation. TE: ≤90 msec; TR: ≥3000 msec Slice thickness: ≤4mm, no gap. FOV: 16-22 cm. In plane dimension: ≤2.5mm phase and frequency; At a minimum, lowest b-value should be set at 0-100 sec/mm2 and one intermediate value at 800-1000 sec/mm2. A high b-value (≥1400 sec/mm2) image set is also mandatory and preferably should be obtained from a separate acquisition or calculated from the low and intermediate b-value images.
- Above should be repeated if motion-blurred.
- Radiology reporting should include: definitive T3 disease, and location of all PIRADs 4-5 lesions if reported.

5.3.2 Planning (simulation) MRI (optional, recommended)

The following imaging protocol is recommended, in compliance with the Consensus Statement from the MR in RT symposium:

- bladder filling state comfortable to reduce motion blurring
- patients should evacuate the rectum, if possible, just prior to the MRI exam

- no endorectal coil, if balloon not used at time of treatment
- Patient set-up should be performed in a manner that balances reproducing treatment conditions (bowel prep, bladder prep, +/- immobilization devices), without compromising SNR (i.e. surface coils should be applied as close as possible to the patient surface).
- FOV generally 12-20 cm to include prostate and SV
- Each imaging sequence must strive to minimize acquisition times (aim < 5 minutes when possible) in order to reduce motion blurring.
- Sequence A: axial T2w TSE/FSE. In plane dimension: ≤0.7mm (phase) x ≤0.4mm (frequency). Slice thickness: 2-3mm, no gap. This image may be acquired using a dual-echo technique (PD/T2) in order to highlight FM locations for registration.
- Sequence B (optional). 3D volumetric T2w acquisition (axial, isotropic voxels max 1x1x1mm), using a variable flip angle technique (for prostate boundary delineation)
- Sequence C (optional). If implanted FMs are not clearly resolved in above sequences, an additional axial acquisition using a balanced steady-state free precession (bSSFP) technique is recommended.
- Sequence D. DWI (per diagnostic protocol in 5.3.1). Distortion can be minimized by phase-encoding R-L, volume shimming, minimizing the effect of echo-spacing, and considering segmented or other non-EPI techniques.
- Above sequences to be repeated if motion blurred
- For above sequences, activation of vendor-provided gradient distortion correction, and optimization of bandwidth.

5.3.3 Follow-up MRI (mandatory when criteria are met)

This examination is not considered standard care, and **must** be performed **only** in patients with PIRADSv2.1=4/5 lesions reported at **baseline** (institutionally or after central review), only **at or after 24 months** of follow-up, and within 12 months of patients meeting the following criteria: 1) if PSA nadir is greater than 0.8 ng/mL, or 2) when there has been a PSA rise of greater than 0.2 ng/mL above nadir. If a patient meets the criteria prior to 2 years, the MRI should be conducted at 2 years. Examinations to be performed at 3T or 1.5T (3T strongly preferred) and compliant with PIRADSv2.1 guidelines, including DCE acquisition.

Note: Guided biopsy may be considered if suspicious findings are identified on MRI at the discretion of the treating physician.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Permitted Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

Diarrhea/rectal frequency/urgency may be managed with diphenoxylate or loperamide. Bladder irritation may be mitigated with phenazopyridine. Urinary frequency/urgency can be managed with anticholinergic agents or alpha-blockers such as tamsulosin. Erectile dysfunction can be managed with phosphodiesterase (PDE) inhibitors such as sildenafil.

5.4.2 Prohibited Therapies: concurrent hormonal therapy, including LHRH agonist and 5-alpha reductase inhibitors

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT

Not applicable.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Adverse Events and Serious Adverse Events (12-NOV-2018)

7.1.1 The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for all AE reporting, CTEP-AERS, and case report forms. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; all study case report forms will continue to use CTCAE version 4.0 through May 10, 2018, at which point adverse event reporting in case report forms will be collected in CTCAE version 5.0.

7.1.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device (i.e, fiducials, SpaceOAR, rectal balloon in this trial), and drug.

7.1.3 Solicited Adverse Events

The following AEs should be assessed and recorded at each protocol mandated data collection interval: dysuria, hematuria, incontinence, rectal hemorrhage, fatigue.

7.2 Expedited Reporting of Adverse Events

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-

AERS, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology by phone at 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.3 Expedited Reporting Methods (12-NOV-2018)

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS-24-hour notification must be followed by a complete report within 5 days.
- Supporting source documentation is requested by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page; contact NRG Oncology at 1-215-574-3191 for source documentation assistance.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.4 Expedited Reporting Requirements for Adverse Events

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 3 adverse events

7.5 Additional Protocol-Specific Instructions or Exceptions to Expedited Reporting Requirements (23-JAN-2020)

The following adverse events are exclusions to expedited reporting up to and including grade 3 severity: dysuria, hematuria, incontinence, rectal hemorrhage, fatigue.

7.5.1 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.5.2 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS . In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])

- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:
A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8. REGISTRATION AND STUDY ENTRY PROCEDURES (14-JAN-2022)

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and

In addition, all investigators act as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization. Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

8.2 CTSU Registration Procedures (14-JAN-2022)

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at

CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record to be completed:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements for Protocol NRG-GU005 Site Registration

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- IROC Credentialing Status Inquiry form; this form is submitted to IROC to begin the modality credentialing process.
- Compliance with all protocol-specific requirements (PSRs).

Protocol Specific Requirements for NRG-GU005 Site Registration

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. A primary role on any roster is required to update provider associations,

though all individuals at a site may view provider associations. To find who holds primary roles at your site, please view the Person Roster Browser under the RUMS link on the CTSU website.

IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in the protocol to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, IROC will automatically send the approval to the Regulatory Support System (RSS) to comply with the protocol-specific requirement. IROC will continue to copy the provider and/or enrolling site on modality approvals.

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *NRG Oncology* and protocol number *NRG-GU005;*
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the sites 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

8.3 RT-Specific Pre-Registration Requirements (14-JAN-2022)

SBRT QA
-All sites must be credentialed for IGRT
-When appropriate sites will be grandfathered for credentialing
-Sites with both Linac and Cyberknife units, the Cyberknife unit must be credentialed for SBRT (any anatomical site) due to possibility case randomized to SBRT
-New credentialing will be completed with an anthropomorphic end-to-end QA phantom.

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, the IROC Houston QA Center will notify your institution and NRG Headquarters when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study.

Credentialing Requirements	**Web Link for Procedures and Instructions: http://irochouston.mdanderson.org**	
	Treatment Modality	**Key Information**
	Photons	

Facility Questionnaire	✓	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email **irochouston@mdanderson.org** to receive your FQ link.
Credentialing Status Inquiry Form	✓	Complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (**http://irochouston.mdanderson.org**).
Phantom Irradiation	✓	An IMRT Head and neck phantom irradiation provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org). Note that an institution, depending on its treatment delivery modalities, may be required to irradiate a phantom on different delivery machines such as TomoTherapy and CyberKnife
IGRT Verification Study	✓	Institutions must be credentialed for soft tissue IGRT by IROC Houston. Find details on the IROC Houston QA Center website (http://irochouston.mdanderson.org) Institutions that have previously been approved for IGRT may not need to repeat credentialing.
Credentialing Issued to:		
Institution		IROC Houston QA Center will notify the site that all desired credentialing requirements have been met. The site will need to upload a PDF of approval email from IROC Houston to the CTSU Regulatory Portal for RSS to be updated.

8.3.1 Digital RT Data Submission to NRG Using TRIAD

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid CTEP-IAM account.
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installations:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.
This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

8.4 Patient Enrollment (14-JAN-2022)

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.4.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.5 Medidata Patient Cloud ePRO Registration (14-JAN-2022)

This study includes the use of Medidata Patient Cloud ePRO (electronic patient-reported outcomes). After the patient is registered to the trial via OPEN, and if the patient is willing to participate in electronic data collection, the site staff will then complete a registration for the patient to the Patient Cloud ePRO through iMedidata. Note: Site staff must have already completed required eLearning for the Patient Cloud ePRO application to register a patient and information about the training is in the ePRO Appendix. The

registration to the Patient Cloud ePRO will create a unique patient registration code that the site staff will provide to the patient. The patient (with assistance from the site staff) should be instructed to download the Patient Cloud ePRO app onto his/her own device (IOS, Android, phone or tablet) and use the unique patient registration code to create an account. Once the patient's account is set up, the patient will be able to complete the submission of patient reported outcomes electronically for the trial. There are multiple versions of the app available. The **Patient Cloud** App (the version with the cloud logo) will be used on this study. Ensure that the patient downloads the correct version of the ePRO app. Note only 1 version of the app is active per protocol.

For sites providing a shared institutional device for use by multiple patients on site:

- The site staff should assist the patient with access and registration to the Patient Cloud ePRO app, and the patient can then complete the electronic data submission independently. Site staff may need to assist patients with logging on to the device at each visit.

8.5.1 CRA Patient Registration Instructions for ePRO

Please visit the Medidata Learning Tool for reference information on Patient Cloud ePRO for CRAs.

i. The subject registration process starts in iMedidata. Begin by selecting the Patient Cloud ePRO Registration link for your study

ii. The patient management app will display, select your STUDY and SITE from the drop downs and click Launch.

iii. Now you can register your first patient. Create a subject ID and select a Country / Language from the drop down, (these are the only required data fields). The subject initials are optional, but are helpful in identifying which subject ID maps with which activation code. When finished, click Add.

iv. The subject added and will include the date the patient was added, the subject ID, subject initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which indicates if the patient has registered. When the patient has registered the status will change from "invited" to "registered".

Reminder- site staff must have already completed the Medidata Patient Cloud training in order to register study participants .Please visit the Medidata Learning Tool for reference information on Patient Cloud ePRO for CRAs. https://learn.mdsol.com/patient-cloud/en/video-library-for-providers-102101952.html

9. DRUG INFORMATION

Not applicable

10. PATHOLOGY/BIOSPECIMEN

10.1 Optional Specimen Submissions (23-JAN-2020)

(Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.)

See detailed specimen collection/processing/shipping instructions on the protocol-specific pages at www.ctsu.org.

Optional Study Description #1

1) Tissue, urine, and blood (including serum and plasma) samples will be collected and banked for future research studies. These exploratory studies will include identifying genes or proteins, expressed in the tissue, urine, or blood, that may be associated with toxicity following hypofractionated or conventionally fractionated radiation. These studies will include assessment of both baseline and follow-up samples (urine and blood), to determine if early post-treatment changes in genes or proteins can predict subsequent toxicity or response.
2) Specimen collection kits and instructions are available for frozen specimens from NRGBB@ucsf.edu. Please allow 5-10 business days for receipt.
3) Forms- Submit with NRG label on them with Study#, Case#, patient initials, submitting site name and NCI number.
   -ST forms are to be included with all submissions.
   -FFPE submissions must also include pathology reports with all PHI redacted except the pathology accession number and date of procedure.
4) Shipping days for Frozen biospecimens: Monday-Wednesday (US Sites). Monday-Tuesday (Canada and overseas). Check NRG Oncology broadcasts for holiday shipping information.
5) Shipping costs- One prepaid label for each case in provided with kits to be used for batch shipment of frozen specimen shipments.
6) Returns: Formalin fixed tissues will be banked for an indefinite time for all patients who consented to banking. Sites should only submit FFPE tissue if the bank can keep it.
7) Processing instructions can be found in the Pathology and Correlatives Instructions document on the www.ctsu.org protocol specific pages.

For kit requests and questions, contact:
NRG-GU005
NRG Oncology Biospecimen Bank—San Francisco
2340 Sutter Street, Room S341
University of California San Francisco
San Francisco, CA 94115
415-476-7864; NRGBB@ucsf.edu

Specimen Type	Collection Time Points	Collection Information and Requirements/Instructions for Site	Shipping
Representative H&E stained slides of the highest grade area from the primary tumor from biopsy	Pre-radiation treatment	H&E stained slides Slides can be duplicate cut H&Es, they do not have to be the diagnostic slides. H&E slides cannot be returned to sites.	Slide shipped ambient to NRGBB-SF
A paraffin-embedded	Pre-radiation treatment	Paraffin-embedded block. Must be	Block shipped ambient or

tissue block of the primary tumor from biopsy		same block as H&E being submitted. NOTE: unstained slides are not accepted for this trial.	with a cold pack in warmer weather to NRGBB-SF
Plasma- EDTA tube 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	Pre-radiation treatment During treatment: Last week of RT Post- treatment: At 12 months after completion of RT	Frozen plasma samples containing minimum **0.5 mL per aliquot** in 1 mL cryovials (five). Store frozen at -70 to -80°C until ready to ship.	Plasma sent frozen in batch shipments on dry ice via overnight carrier to NRGBB-SF
Serum- Red top tube 5-10 mL of whole blood in 1 red-top tube and centrifuge	Pre-radiation treatment During treatment: Last week of RT Post-treatment: At 12 months after completion of RT	Frozen serum samples containing minimum of **0.5 mL per aliquot** in 1 mL cryovials (five). Store frozen at -70 to -80°C until ready to ship.	Serum sent frozen in batch shipments on dry ice via overnight carrier to NRG BB-SF
Whole Blood-EDTA tube Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Pre-radiation treatment Note: if site misses this collection they may collect it at any of the other noted timepoints instead.	Frozen whole blood samples containing **1-2 ml per aliquot** in 2ml cryovials (three). Store frozen at -70 to -80°C until ready to ship.	Whole blood sent frozen in batch shipments on dry ice via overnight carrier to NRG BB-SF
10-20 mL clean-catch urine	Pre-radiation treatment Last week of RT	10 mL urine aliquots in 1 sterile 15 ml polypropylene centrifuge tube. Store frozen at -20° or 70 to -90° C. (-20°C storage is only advisable for short term storage)	Urine sent frozen in batch shipments on dry ice via overnight carrier to NRG BB-SF

11. SPECIAL STUDIES (NON-TISSUE)

11.1 Patient reported outcome – Quality of life Analysis

Patient reported health related quality of life (HRQoL) is the primary endpoint given the importance of post-treatment quality of life after prostate cancer treatment. The widely used and validated Expanded Prostate Cancer Index Composite (EPIC) -26 survey instrument will be used to record and track patient reported quality of life in 5 domains: Urinary incontinence, urinary irritation/obstruction, bowel, sexual, and hormonal function. Two domains have been chosen for the primary endpoint: urinary irritation/obstruction and bowel function based on clinical relevance and as well as likelihood of difference based on prior published study [Johnson SJ et al.]. The other measurable domains (urinary incontinence, sexual, and hormonal function) will be reserved for secondary analysis.

NRG Oncology has obtained permission to use the EQ-5D and EPIC-26 in English, French and Spanish. The forms are available on the CTSU website.

The study will be designed and powered to detect statistically significant differences in the incidence of pre-specified Minimally Clinically Important Declines (MCID) in quality of life. Clinically insignificant differences in scores (i.e., differences that are less than what has been defined as "clinically important") will not contribute to the endpoint. We expect this analysis to be complementary to the secondary endpoint of disease free survival.

In addition to the EPIC-26 HRQoL survey instrument, the general health survey instrument EQ-5D will be recorded simultaneously for the purpose of assessing general quality of life and calculating health utility. The calculated health utility will then be used to produce a quality adjusted life year (QALY) survival estimate post-treatment. This estimate, in combination with cost of treatment data and other cost estimates, will be used to analyze the cost effectiveness of the two treatment arms.

11.2 MR Imaging Correlative Science Study (14-JAN-2022)

An additional MRI will be performed on eligible patients after 24 months of follow up. The purpose of the MRI is to determine if PIRADSv2.1 = 4/5 disease is prognostic for biochemical failure at baseline and follow up.

These examinations are not considered standard care, and must be performed only in patients with PIRADSv2.1=4/5 lesions reported at baseline and only after 24 months of follow-up. The MRIs must be performed within 12 months of patients meeting a certain criteria. The criteria are as followed; the MRI must be performed if PSA nadir is greater than 0.8 ng/mL or when there has been a PSA rise of greater than 0.2 ng/mL above nadir. Examinations will be performed at 3T or 1.5T (3T strongly preferred) and in compliance with PIRADSv2.1 guidelines, including DCE acquisition.
All MRIs will be centrally stored and reviewed for the purpose of correlative research. See Section 8.3.1 for TRIAD account access and installation instructions. Dedicated planning MRI images and the planning CT images will be stored for correlative science comparing the accuracy of registration techniques and image quality.

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews

The Radiation Oncology Principal Investigator, Dr. Rodney Ellis, M.D. and his designees will perform RT Quality Assurance Reviews.

A pre-treatment review is required for the first Arm 2 patient registered from each institution PRIOR TO DELIVERY of radiation treatment. The patient cannot start treatment until they have received approval from the Imaging and Radiation Oncology Core (IROC)-Philadelphia RT. The Pre-Treatment Review process requires 3 business days from the receipt of **complete data** to TRIAD. If an unacceptable deviation occurs the next case may require a Pre Treatment review.

After an institution has passed the Pre-Treatment review of the first Arm 2 patient enrolled, review of all other Arm 2 cases will be ongoing and performed remotely for

all patients. Review of Arm 1 cases will be ongoing and performed remotely. The Study PI, Dr. Rodney Ellis, M.D. and his designees will perform the RT Quality Assurance Reviews after IROC-Philadelphia RT has received complete data in TRIAD. These reviews will be on-going and performed remotely. The final cases will be reviewed within 6 months after this study has reached the target accrual or as soon as IROC-Philadelphia RT has received complete data for all cases enrolled, whichever occurs first. The scoring mechanism is: **Per Protocol, Variation Acceptable, and Unacceptable Deviation**.

12.2 Standard of Care (SOC) MRI Imaging Quality Assurance Reviews

All SOC MRI imaging along with treatment planning CT and dicom structures should be submitted to the IROC PHL Core Laboratory via TRIAD for Image Quality Assurance (IQA) review. Imaging should be submitted within (3) business days to ensure rapid review and prompt feedback on quality and acceptability from the Core Lab.

Upon image receipt, an Imaging Technologist will perform an IQA review to ensure that all imaging has been submitted in its entirety, the recommended protocol parameters were followed, and the exam is of adequate image quality. In the event that an exam is deemed non-compliant, a Core Lab Imaging Technologist will issue a query within the Medidata Rave data management system. Sites are expected to resolve data queries within **(7)** business days.

13. DATA AND RECORDS

13.1 Data Management/Collection (14-JAN-2022)

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study

invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2 Summary of Data Submission (14-JAN-2022)

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7.2 for information about expedited and routine reporting.

Summary of Data Submission: Refer to the NRG/CTSU website.

See Section 8.3.1 for TRIAD account access and installation instructions.

<table>
<tr><td>DICOM DIGITAL DATA</td><td>DICOM Staging MR
DICOM CT Data Set
(CT-based treatment planning)
DICOM MR Data Set (MR-based treatment planning)
DICOM Planning MR, when applicable for CT-based treatment planning
MP-RAGE, TSE, axial T2/FLAIR sequences, and gadolinium contrast-enhanced three-dimensional SPGR
DICOM Registration, when applicable
DICOM RT Structure
DICOM RT Dose
DICOM RT Plan</td><td rowspan="3">Due within 1 week of the start of RT

TRIAD submission time point = RT DIGITAL PLAN

<u>ARM 2 Cases Only</u>:
First case enrolled from each Institution requires a Pre-Treatment Review

TRIAD submission time point= BASELINE and 24 month if applicable</td></tr>
<tr><td colspan="2">All required structures MUST be labeled per the tables in Sections 5.2.4 and 5.2.5</td></tr>
<tr><td colspan="2">Entire MRI fused with Planning CT must be submitted with RT data.</td></tr>
<tr><td colspan="3">Digital Data Submission Information Form (DDSI)
Upon submission of the digital data via TRIAD, complete an online Digital Data Submission form
https://www.irocqa.org/Resources/TRIAD</td></tr>
</table>

<table>
<tr><td>Diagnostic Imaging Data Submission:
MRI Prostate:

MRI Prostate in its entirety, all series must be submitted
• Baseline MRI of the Prostate (per institutional SOC - should be compliant with PIRADSv2.1 guidelines)
• 2 Year Follow-up MRI (mandatory when criteria are met). See section 5.3.3 for more details
Note: 2 Year Follow-up MRI prostate examinations to be performed at 3T or 1.5T (3T strongly preferred) and must be compliant with PIRADSv2.1 guidelines, including DCE acquisition.

See Appendix IV for the Imaging Guidelines for the 2 year MRI Prostate exam</td><td>Diagnostic Imaging TRIAD Imaging Time Points:
Baseline

2 year Follow-up</td></tr>
<tr><td colspan="2"><u>NOTE:</u> Please refrain from anonymizing the DICOM header of any imaging exam prior to</td></tr>
</table>

uploading into the TRIAD application. Custom DICOM editing can exclude an exam from the final analysis, due to the omission of technical data elements. These elements include, but are not limited to, the study date (0008,0020), acquisition date (0008,0022) scanner station name (0008,1010), scanner serial number (0018,1000), patient weight (0010,1030), patient height (0010,1020) and any scan acquisition parameter. TRIAD has been uniquely configured to locate and scrub all PHI from the exam's DICOM header during the image transfer to ensure the anonymity of our trial patients.

ATTENTION: Imaging PACS systems store all files associated with patient imaging (ex: dose reports, patient questionnaires, etc). TRIAD cannot anonymize the PHI embedded within these files; however, TRIAD does de-identify all PHI within the image metadata. To screen for and remove any potential PHI, outside of the metadata, during the image submission process, please expand all series within the TRIAD Preview Window and deselect any file which may contain PHI before the files are moved to the submission queue. TRIAD Clean Pixel Tool should be utilized for the removal of PHI that has been "burned into" images as part of their acquisition.

Summary of MRI Digital Data Submission

All MRI exams must be submitted to IROC DI - Philadelphia using ACR TRIAD v4x or higher software. For questions regarding the MRI contact IROCPHILA-DI@acr.org. In the subject line enter: "IROC-NRG GU005 MRI"

TRIAD will be the sole means of image transfer to the IROC Core Laboratory. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging. Information and instructions for download and installation of TRIAD software is available at http://triadhelp.acr.org/ under "Clinical Trials".

Staff submitting imaging must first be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members' web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

13.3 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design

This is a prospective randomized phase III superiority trial comparing SBRT (36.25 Gy in 5 fractions of 7.25 Gy) to hypofractionated IMRT (70 Gy in 28 fractions of 2.5Gy). Patients will be stratified according to use of rectal manipulation (SpaceOAR vs. rectal balloon vs. SpaceOAR and rectal balloon vs. no manipulation), and the following risk groups, Gleason score 7 (3+4) with PSA < 10 ng/mL vs. Gleason score 7 (3+4) with PSA ≥10 ng/mL vs. Gleason score 6 (3+3) with PSA > 10 ng/mL, then randomized 1:1 to receive SBRT or hypofractionated IMRT according to the permuted block design by

Zelen (1974). This is an intent-to-treat analysis and all randomized at-risk patients will be included in the primary analysis.

14.2 Study Endpoints (14-JAN-2022)

Primary endpoints:

- Patient-reported GI and GU toxicity, as measured by EPIC-26 bowel and urinary irritation domains
- Disease free survival, defined as time to biochemical failure (Phoenix definition), local failure, regional failure, distant metastasis, or death from any cause.

Secondary endpoints:

- HRQOL, as measured by EPIC-26 urinary incontinence, sexual, and hormonal domains
- Biochemical failure (Phoenix definition)
- Local failure and regional failure
- Distant metastasis
- Prostate Cancer Specific Survival
- Overall Survival
- Adverse events, as measured by the CTCAE v.5
- MRI-pathology correspondence
- Prognostic value of PIRADSv2.1=4/5 for biochemical failure at baseline and follow up.

Exploratory endpoints:

- Cost-effectiveness
- PIRADSv2.1 grade

14.3 Primary Objectives Study Design (14-JAN-2022)

14.3.1 Primary Endpoint and Hypotheses

- Patient-reported GI and GU toxicity, as measured by EPIC-26 bowel and urinary irritation domains at 24 months post completion of therapy
  Hypothesis: SBRT is superior to hypofractionated IMRT in terms of GU and GI toxicity by having fewer patients that experience a minimal important decline (MID) in urinary irritation/obstructive and bowel HRQOL as measured by EPIC-26 at 24 months post completion of therapy.
- Disease free survival, defined as time to biochemical failure (Phoenix definition), local failure, regional failure, distant metastasis, or death from any cause
  Hypothesis: SBRT is superior to hypofractionated IMRT as measured by DFS.

14.3.2 How Primary Endpoints Will Be Analyzed

For the short-term toxicity primary endpoint: The proportion of patients experiencing a MID for the bowel and urinary irritation domains of EPIC 26 at 2 years will be compared between treatment arms using a test of proportions with two-sided significance level of 0.05. The MIDs are 4 for bowel and 5 for urinary irritation. All patients with EPIC bowel and urinary irritation domain scores will be included in this co-primary endpoint analysis. The EPIC scoring manual will be followed, which

requires ≥ 80% of items in a domain to be completed in order to obtain a score for that domain. Missing data for both the primary and secondary QOL endpoints will be analyzed as described below (14.6.2). This endpoint will be reported once all patients have at least 2 years on study.

For the long-term disease-related primary endpoint: DFS will be measured from the date of randomization to the date of biochemical failure, local progression, regional progression distant metastasis, or death, whichever occurs first, or last known follow-up date. Event-free patients are censored at their last known follow-up date. DFS will be estimated using the Kaplan-Meier method and treatment arms compared using the stratified log-rank test. Cox proportional hazards models will be used to determine hazard ratios and to assess the effects of stratification factors and other covariates of interest, such as age, race, ethnicity, T stage, and ECOG performance status on outcomes (Cox 1972). This endpoint will be reported once 178 DFS events have been reported.

Since two different fractionation schedules are permitted on the control arm, a comparison of pretreatment patient and clinical characteristics between each fractionation schedule will be tested. The proportion of patients experiencing a MID for the bowel and urinary irritation domains of EPIC 26 at 2 years will be compared between both control arm fractionation schedules. A separate Cox proportional hazards model will be run with a three level treatment arm variable, with the SBRT arm as the reference level. These analyses will occur only if a sufficient number of patients receive 60 Gy in 20 fractions.

14.3.3 Sample Size and Power Calculations:

Short-term toxicity primary endpoint: RTOG 0415, a randomized phase III trial of hypofractionated vs. conventionally fractionated RT in the same patient population and employed the EPIC instrument, is used as a basis for targeting further improvement in PRO endpoints. From the RTOG 0415 trial, the subset of questions that make up the bowel and urinary irritation domains in the EPIC 26 were scored. Skolarus et al (2015) found the minimally important difference (MID) for these domains to be a 4-6 point change for the bowel domain and a 5-7 point change for the urinary irritation domain. Johnson et al (2016) used a ½ standard deviation change as a basis to determine a clinically relevant improvement, resulting in MIDs of 4.3-5.8 points for the bowel domain and 6.3-7.6 points for the urinary irritation domain, depending on the institution. They furthermore found that SBRT resulted in statistically significant reductions in both the bowel and urinary irritation domains as compared to hypofractionated RT (32.3% and 57.3%, respectively). Thus, the MIDs that will be used in this study are 4 for bowel and 5 for urinary irritation (Skolarus 2015). In the hypofractionated arm in RTOG 0415, the percent of patients experiencing a MID at 2 years in EPIC bowel and urinary irritation scores were 22.9% and 13.6%, respectively. Using absolute reductions of 10% and 8% for the bowel and urinary irritation domains, the SBRT arm is projected to have 12.9% and 5.6% of patients experiencing a MID at 2 years. Using a 2-sided type I error=0.05 and 1 interim look, 466 evaluable patients are required for 80.1% and 83.3%

statistical power for the bowel and urinary irritation domains, respectively. Inflation of 25% due to EPIC 26 non-compliance makes **the target accrual 622 patients**.

Due to death prior to 2 years and consent withdrawal immediately after randomization, the sample size will further be inflated by 10%, bringing **the target accrual to 692 patients**.

Long-term disease-related primary endpoint: Biochemical failure is expected to constitute the majority of the events in the DFS endpoint. King et al. (2013) have previously reported on pooled analysis for SBRT showing a 16% biochemical failure rate in intermediate risk men at a median follow-up of 5 years and 7% in a sub-cohort of men with intermediate risk disease with a minimum follow up of 5 years. Among men treated on RTOG 9910 with intermediate risk factors of Gleason 7 (3+4) disease and PSA < 20 ng/mL the 5-year biochemical failure rate of 16% by Phoenix criteria when treated with hormonal therapy and radiation was shown. However, men with similar intermediate risk factors on RTOG 0126 treated to the higher dose arm of 79.2 Gy without hormonal therapy had an overall failure rate of 17%. This cohort included failure rates of 16% for Gleason 6(3+3) and PSA between 10-20 ng/mL, 13% for Gleason 7(3+4) with PSA < 10 ng/mL, and 34% for Gleason 7(3+4) with PSA between 10-15 ng/mL. Although data is not available for the anticipated failure rate for IMRT alone for Gleason 7 (3+4) with PSA levels between 15-20 ng/mL from RTOG 0126 as the protocol had a maximal PSA level of 15, the biochemical failure rate in these patients is expected to be higher. A study by Zelefsky et al (2011) found a failure rate at 48 months ranging between 37% and 23% for doses of <81 Gy and >81Gy in patients with Gleason 7 or greater and PSA greater than 10. Based on these data, a biochemical failure rate of 23% for IMRT alone using 70 Gy in 28 fractions is estimated for the proposed study cohort. A hypothesized relative reduction of 40% is deemed clinically meaningful. The hazard ratio (HR; experimental/control) for the difference in biochemical failure is 0.57. For both the rate of DFS events in the IMRT arm and the hazard ratio, it is assumed that 5% of patients will experience a local or distant failure without a biochemical failure at 5 years (assuming the HR is the same as for biochemical failure) and 10% will die prior to experiencing a biochemical or local/distant failure (under the conservative assumption that the HR=1.05). Therefore, the failure rate at 5 years is expected to be 38% in the IMRT arm corresponding to a 62% of patients being disease free at 5 years on the IMRT arm. The HR for DFS = 85%*0.57 + 5%*.57 + .10*1.05 = 0.62. Therefore, it is hypothesized that 74.3% of patients will be disease-free at 5 years on the SBRT arm. The power for an increase from 62% to 74.3% (survival exponential parameters of 0.0956 and 0.0594, respectively) with 15 patients/month using a two-sided type I error of 0.05 and 590 evaluable patients (178 events) is 89.0%. This allows for 5% loss to follow-up from the target accrual of 622 patients. This endpoint will be reported once 178 events have occurred. With the inflated sample size of 692, this now allow for 13% lost to follow-up and consent withdrawal.

14.4 Study Monitoring of Primary Objectives

Monitoring of EPIC Compliance

Completion rates of the bowel and urinary irritation domains of EPIC will be monitored monthly. Since not all patients will have 2 year EPIC data by the time the study closes to accrual, both 1 and 2 year time points will be used to monitor compliance. If the EPIC non-compliance rate is ≥ 20% at either of these time points, the study PI and QOL co-chair will work in collaboration with the NRG Oncology Statistics and Data Management Center to contact sites and RAs with delinquent data, assessments completed too early or too late, and assessments not completed due to institution errors. If the EPIC non-compliance rate is > 30% at either time point, the study will be presented to the DMC for reassessment of feasibility or change in study design.

Interim Study Progress, Safety, and Endpoint Monitoring

The NRG Oncology Data Monitoring Committee (DMC) will provide external oversight of the trial. As all or most patients will have been enrolled and treated before substantial information on both primary endpoints, a conservative interim endpoint monitoring plan will be implemented.

An interim futility analysis will occur for the DFS endpoint once 50% of events for definitive analysis (89) have occurred. At that point, a test to reject the alternative hypothesis at one-sided $\alpha = 0.001$ will be performed (Fleming, Harrington, O'Brien). If the hypothesis is rejected (consistent with an observed HR = 1.13 in favor of the hypofractionation arm), then the study statistician and DMC will consider early release of these findings, with the conclusion that SBRT may not provide acceptable disease control. For the toxicity endpoint, the O'Brien & Fleming boundary will be used to assess futility for both the GI and GU endpoints. It will be performed once 50% of evaluable patients (233 patients) have 2 years on study. Table 1 below specifies the boundary.

Table 1

GI/GU Toxicity Futility Bound					
Endpoint	**Analysis**	**Sample size**	**Cumulative β spent**	**Futility Boundary ($\|z\ scale\|$)**	**Futility Boundary ($\|\delta\|$)**
Bowel	Interim	233	0.040	0.353	0.018
	Final	466	0.199	1.96	0.069
Urinary	Interim	233	0.029	0.305	0.012
	Final	466	0.167	1.96	0.053

δ=difference in proportions

Given the accrual rate of 15 patients/month, the DFS analysis is projected to occur approximately 6.5 months after study closure and the toxicity analysis is projected to occur approximately 3 months after study closure.

The NRG Oncology DMC will review the study twice a year with respect to patient accrual, general data quality, study conduct, and morbidity/adverse events. The DMC also will review the study on an "as needed" basis.

14.5 Accrual/Study Duration Considerations (14-JAN-2022)

NRG/RTOG 0126 accrued 19.8 patients/month, RTOG 0415 accrued 36 patients/month, and NRG/RTOG 0938 accrued 9 patients/month. Therefore, this study is expected to accrue 15 patients/month so accrual would be completed in 46 months (just over 3 years), after a 6 month ramp up period of negligible accrual. The primary endpoint of GU and GI toxicity will be ready to report approximately 2 years from study closure. Full information for the DFS secondary is expected to be mature for analysis approximately 6.5 years from study activation.

14.6 Secondary or Exploratory Endpoints (including correlative science aims) (23-JAN-2020)

14.6.1 Secondary Hypotheses and Endpoints:

- Secondary HRQOL endpoints (distinct from primary), as measured by EPIC-26 (12 month bowel and urinary irritation/obstructive domains, 12 and 24 month sexual, hormonal, and urinary incontinence domains).
  Hypothesis: SBRT will have a lower rate of MID compared to hypofractionated IMRT for urinary and bowel domains at all time points. There will be no difference in urinary incontinence, sexual, and hormonal HRQOL.
- Biochemical failure
  Hypothesis: SBRT will have a lower rate of biochemical failure as compared to hypofractionated IMRT
- Local and regional failure
  Hypothesis: SBRT will have a lower rate of local failure as compared to hypofractionated IMRT
- Distant metastasis
  Hypothesis: SBRT will have a lower rate of distant failure as compared to hypofractionated IMRT
- Prostate cancer specific survival
- Local failure
  Hypothesis: SBRT will have a lower rate of local failure as compared to hypofractionated IMRT
- Regional failure
  Hypothesis: SBRT will have a lower rate of regional failure as compared to hypofractionated IMRT
- Overall Survival
- Adverse events, as measured by the CTCAE v.5
- MRI pathology correspondence
  Hypothesis: Higher PIRADS lesions will correlation with higher percent core positive biopsy.
- Prognostic value of PIRADSv2.1=4/5 disease for biochemical failure at baseline and follow up.
  Hypothesis: PIRADSv2.1=4/5 disease will be prognostic of biochemical failure using both baseline and follow-up MRIs.

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Health-Related Quality of Life (HRQOL)

The proportion of patients experiencing a MID for the additional 3 domains of EPIC 26 not included as the primary endpoint (urinary incontinence, sexual, and hormonal) will be compared between treatment arms using a test of proportions at 1 and 2 years. Additionally, bowel and urinary irritation outcomes will be compared at 1 year. A significance level of 0.02 (due to the correlated nature of these scores) will be used. The MIDs for the domains are 4 for bowel and hormonal, 5 for urinary irritation, 10 for sexual, and 6 for urinary incontinence (Skolarus 2015). While both modalities are anticipated to worsen QOL acutely, in order to simplify the primary and secondary QOL analysis, only endpoints at 12 and 24 months are being suggested to improve patient compliance and decrease workload for the enrolling sites compared to more rigorous attempts to repeat the EPIC-26 and multiple time points. Furthermore, long term-outcomes are arguably more important for patients undergoing therapy with good prognosis and long-term survival as in this trial.

An exploratory longitudinal analysis incorporating the 1 and 2 year follow-up time points will be conducted separately for each domain score using longitudinal linear modeling methods, adjusting for baseline domain score, treatment arm, stratification factors (risk group utilizing Gleason score and PSA, rectal manipulation including the use of rectal balloons and/or SpaceOAR), T-stage, age, and race.

Prior to performing analyses, an evaluation of the amount, reasons and patterns of missing data will be performed, using the well-known categories of missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) (Fairclough 2010, Verbeke 2000). If ≥15% of the data is missing at any time point for the EPIC bowel and urinary irritation domain scores, patient characteristics will be compared between patients with completed assessments and those with missing assessments. If any are found to differ significantly, they will be included in the mixed effects model, which assumes that the data is MAR. If the missingness is determined to be non-ignorable, other methods may be applied. Specifically, a joint model that allows a shared parameter between the repeated measurements and time to death or drop out can be used if considered MNAR due to the high number of patient deaths or dropouts (Rizopoulos 2012). Other options for MNAR data are pattern mixture and selection models (Fairclough 2010, Little 1995). Sensitivity analyses will be performed to compare the results of different analytic strategies (Fairclough 1998).

Efficacy Endpoints

Overall survival (OS) will be measured from the date of randomization to the date of death or last known follow-up date, with patients alive at the last known follow-up time treated as censored. OS will be estimated using the Kaplan-Meier method and treatment arms compared using the stratified log-rank test.

All other secondary time to event endpoints have precluding events that act as competing risks. Time to biochemical failure will be measured from the date of randomization and use the Phoenix definition (Roach 2006). Death prior to a biochemical failure, distant metastasis, or local failure will be treated as a competing risk and those who are alive without a biochemical failure, distant metastasis, or local failure will be censored at the

last known follow-up time. Time to local and regional failure will be measured from the time of randomization to the date of local failure, date of precluding death, or last known follow-up date. Time to distant metastasis will similarly be measured from the time of randomization to the date of distant metastasis, date of precluding death, or last known follow-up date. For cause-specific mortality, death from the complementary cause (prostate cancer vs. non-prostate cancer) acts as a competing risk.

The cumulative incidence estimator will be used to estimate time to event distributions for endpoints with competing risks (biochemical failure, local and regional failure, distant metastasis, and cause-specific mortality)

For all efficacy endpoints, Cox proportional hazards models will be used to determine hazard ratios (cause-specific hazard ratios in the case of endpoints with competing risks) and to assess the effects of stratification factors and other covariates of interest, such as age, race, ethnicity, T stage, and ECOG performance status (Cox 1972) on outcomes. Gray's test may also be used to compare cumulative incidence between arms (Gray 1988), and similarly, the Fine-Gray subdistribution hazards model may be applied to further explore outcomes by treatment arm and other covariates (Fine and Gray 1993).

All efficacy endpoints will be reported once 178 DFS events have occurred, as described in Section 14.3.3. A significance level of 0.05 will be used to determine significance.

Adverse events
Adverse events (AEs) will be graded using CTCAE v5. Counts of all AEs by grade will be provided by treatment arm. Counts and frequencies will be provided for the worst grade AE experienced by the patient by treatment arm. The number of patients with at least 1 grade 3 or higher AE will be compared between the treatment arms. A comparison between treatment arms of grade 3 and higher GU and GI events related to treatment (separately) will also be tested. There are 5 pre-specified AEs, dysuria, hematuria, incontinence, rectal bleeding, and fatigue. A comparison of any event and grade and higher events will be compared between treatment arms. All comparisons will be tested using a Chi-Square test with a significance level of 0.05.

MRI-pathology correspondence
A frequency table showing the frequencies of biopsy and MRI (both determined from site report) to identify dense disease (percent core-length involvement > 40%) will be provided and the methods compared using McNemar's test. Location of the MRI-identified lesion and the positive core biopsy will be compared to determine if they match. If the lesion is identified on the same side of the urethra in adjacent sextants, they will be considered a match due to the variability of biopsy site and the fact that MRI location usually describes the center of the tumor rather than its full extent (Anderson 2014). A kappa statistic will be used to assess the inter-rater correlation between MRI and biopsy to identify dense disease. The frequency of dense disease identified by biopsy and not MRI will also be provided.

PIRADSv2.1 = 4/5

Analyses will be conducted using baseline (diagnostic) MRIs as well as 2 year MRIs. Diagnostic MRI reports will be collected and centrally reviewed. Frequencies of the presence of PIRADSv2.1 = 4/5 score on the report as well as the scores reported will be provided. Spearman correlation coefficients will be used to assess the association of PIRADS score with percent core positive biopsy.
The prognostic value of the binary variable, whether the patient has PIRADSv2.1 = 4/5 disease, for biochemical failure will be determine using a Cox proportional hazard model (Cox 1972). Treatment arm stratification factors and other covariates of interest, such as race, ethnicity, T stage, and ECOG performance status, will be included in the model to determine if PIRADSv2.1 = 4/5 disease is independently associated with biochemical failure. If the study shows a treatment effect in favor of SBRT, then treatment arm will be incorporated into the model along with an interaction between PIRADSv2.1=4/5 and treatment to determine if PIRADSv2.1=4/5 still has a significant effect and if that effect varies by treatment arm.

Enrolled patients will be eligible for follow-up MRI acquisition if PIRADSv2=4/5 disease was reported at baseline via central review and either PSA nadir ≥ 0.8 or PSA rise > 0.2 above nadir. Most patients who meet this criteria are expected to meet it prior to 2 years from end of treatment meaning that the MRI will be conducted at 2 years. The prognostic and/or predictive value of the binary variable, whether the patient has PIRADSv2.1 = 5 disease in follow-up, for local control and biochemical failure will be determined using a Cox proportional hazard model (Cox 1972). The distribution of the time from end of treatment to MRI will be assessed. Although the MRI will be performed prior to an event (biochemical or local failure), the timing of the MRI may vary between patients and thus may need to be treated as a time-dependent covariate in the model. Treatment arm, stratification factors and other covariates of interest, such as race, ethnicity, T stage, and ECOG performance status, will be included in the model to determine if PIRADSv2.1 = 5 disease is independently associated with local control.

Primary central analysis will consist of independent PIRADSv2.1 scoring (as an ordered categorical variable) at a per-patient level coordinated by an expert radiologist. If more than one lesion is identified on MRI, the one with the highest PIRADS score will be recorded and used for analysis at a per-patient level. If central analysis differs from institutional reports, a third expert radiologist will score, and if needed adjudicate by consensus. Disagreements between two experienced central readers will be adjudicated by a third tie-breaking vote of a separate expert radiologist.

14.6.3 Power Calculations

In this study cohort of patients with low-intermediate risk disease, we estimate 60-70% of patients enrolled will harbor PIRADSv2.1 = 4/5 disease. This threshold was selected as PIRADSv2.1 score of 4 represents the presence of a focal lesion on MRI, whereas PIRADSv2.1 scores ≤3 indicate either the absence of definite lesions or indeterminate findings. We expect to demonstrate a 30-50% increase in the rate biochemical failure in patients with PIRADSv2.1 = 4/5 disease vs. without.

It is anticipated that 140-150 biochemical failure and local failure events will be observed

among all trial participants. At the expected range of PIRADSv2.1 5 disease prevalence of PIRADSv2.1 = 4/5 disease, effects representing 1.6-2.0 fold greater relative failure risk for the 4/5 group can be detected with statistical power exceeding 80% (at one-sided alpha 0.05). There is a lack of data on the strength of the association between PIRADS score and other covariates such as PSA and number of positive biopsy cores. There is conflicting data on the association between PIRADS score and Gleason score in general with the distinction between 6 (3+3) and 7 (3+4) being even less clear (An 2018, Slaoui 2017). Thus, these power calculations assume that the strength of association between PIRADS scores with these other covariates is zero.

	Prevalence of PIRADSv2.1 4/5		
Hazard Ratio	**0.50**	**0.60**	**0.70**
2.00	0.99	0.99	0.98
1.85	0.98	0.97	0.95
1.70	0.93	0.92	0.89
1.55	0.83	0.81	0.77
	Table entries: statistical power to detect HR at left.		

A subsample of 200 participants will enroll in the GU005 imaging sub-study based on meeting pre-specified criteria (baseline PIRADSv2.1=4/5 disease and either PSA nadir ≥ 0.8 or PSA rise > 0.2 above nadir). Given this population which expected to have a higher rate of failure (approximately 60%) than the general study population, it is anticipated that 103 biochemical failure and local failure events will be observed among these trial participants. At the expected range of PIRADSv2.1=4/5 disease prevalence of 25-40%, effects representing 1.7-2.0 fold greater relative failure risk for the 4/5 group can be detected with statistical power exceeding 80% (at one-sided alpha 0.05). As noted above, these power calculations assume that the strength of association between PIRADS scores with relevant covariates is zero.

	Prevalence of PIRADSv2.1 4/5			
Hazard Ratio	**0.25**	**0.30**	**0.35**	**0.40**
2.00	0.92	0.94	0.96	0.96
1.90	0.88	0.91	0.93	0.94
1.80	0.83	0.86	0.89	0.90
1.70	0.75	0.79	0.82	0.84
	Table entries: statistical power to detect HR at left.			

14.7 Exploratory Hypothesis and Endpoints (12-NOV-2018)

14.7.1 Exploratory Hypotheses and Endpoints

- Cost-effectiveness
- Imaging endpoints:
  - Central manual user segmentation of tumors
  - Performance of supervised automated tumor detection toolset
  - Performance of supervised automated tumor segmentation toolset
  - Image registration performance

- Predictive utility of radiomic analysis

14.7.2 Definitions of Exploratory Endpoints and How These Will Be Analyzed

Cost effectiveness

If SBRT is shown to be superior to IMRT for either DFS or GU and GI toxicity, then this analysis will be conducted. The VAS and index scores from the EQ-5D-5L will be calculated at each time point (baseline, 12 and 24 months) and compared between treatment arms using a t-test with a 2-sided significance level of 0.05. If there are significant differences, then a cost analysis will be conducted.

Quality-adjusted life years (QALY) is defined by the weighted sum of different time episodes added up to a total quality-adjusted survival time. A Markov model will be used to model cost for this analysis. The Medicare reimbursement in dollars/QALY will be calculated as a function of the monetary cost per relative value of each health state and its duration. The EQ-5D-5L index score at 12 and 24 months will be used for the cost-utility analysis. The z-test will be used to test the hypothesis that the cost-utility in the two treatment arms is the same with significance level of 0.05. The cost-utility using the Medicare reimbursement in dollars/QALY will be compared between the two treatment arms after adjusting for the baseline and stratification variables.

Central manual user segmentation of tumors

User reproducibility in tumor segmentation between two radiation oncologists and two radiologists will be reported using joint DICE similarity coefficient, and standard deviation of the contour distances. It is expected to show poor inter-user reproducibility in manual tumor segmentation.

Performance of supervised automated tumor detection toolset

The performance of a computer-aided diagnostic (CAD) system utilizing T2-weighted and high-b-value diffusion-weighted imaging (DWI) and associated texture features based on local binary patterns will be compared to the gold standard central PIRADSv2.1 scoring using area under the curve (AUC) analysis. The current model, trained and validated at NIH (single institution) against MRI-guided biopsy achieves an AUC 0.89 (CI: 0.84-0.93) (Kwak 2015).

Performance of supervised automated tumor segmentation toolset

Voxel classification performance of a radical prostatectomy histopathology-trained features-based model has achieved an AUC of 0.775 +/- 0.13 in two cohorts in Leuven and Amsterdam. This trained model will be independently validated by first generating an individual tumor probability map for each of the patients. The tumor probability map will then converted into tumor segmentation by applying a threshold at the inflection of the ROC curve (Dinh 2017). A median central observer contour (derived in the central manual user segmentation of tumors exploratory endpoint) will serve as gold-standard.

Image registration performance

Clinical registration performance between MRI and planning CT will be evaluated by

identifying common landmarks applied to target registration error analysis. Common landmarks will consist of implanted fiducial markers when present, or calcifications visible in both image sets. Large standard deviations are hypothesized across the study cohort and institutions. The range of error introduced in the treatment planning process will be quantified using vector distance of common points between two image sets.

Predictive utility of radiomic analysis
A machine learning technique to predict response to radiotherapy will be investigated. A feature-based morphometry (FBM) technique, a general statistical analysis technique that operates on data in the form of local features (generic, salient image patches that are automatically extracted from medical image data), will be applied and adapted (Toews 2015). Local features can be organized into highly efficient data structures for computing robust image-to-image correspondences, and machine learning algorithms based on local feature-based thus scale gracefully to arbitrarily large sets of image data. The FBM approach has been validated in a range of clinical contexts including predicting Alzheimer`s disease (AD) from neurological MRI data and chronic obstructive pulmonary disorder (COPD) from lung CT data.

14.8 Gender/Ethnicity/Race Distribution (14-JAN-2022)

No differences in treatment response across the patient subsets below are anticipated.

Racial Categories	**DOMESTIC PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	6	0	0	6
Asian	0	18	0	0	18
Native Hawaiian or Other Pacific Islander	0	3	0	0	3
Black or African American	0	124	0	3	127
White	0	335	0	26	361
More Than One Race	0	5	0	0	5
Total	0	491	0	29	520

Racial Categories	**INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	

American Indian/Alaska Native	0	3	0	0	3
Asian	0	3	0	1	4
Native Hawaiian or Other Pacific Islander	0	2	0	0	2
Black or African American	0	5	0	1	6
White	0	148	0	7	155
More Than One Race	0	2	0	0	2
Total	0	163	0	9	172

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APPENDIX I

Modified Charlson Comorbidity Index

1. Scoring: Comorbidity Component
    1. Myocardial Infarction (1 point)c
    2. Congestive Heart Failure (1 point)
    3. Peripheral Vascular Disease (1 point)
    4. Cerebrovascular Disease (1 point)
    5. Dementia (1 point)
    6. COPD (chronic obstructive pulmonary disease) (1 point)
    7. Connective Tissue Disease (1 point)
    8. Peptic Ulcer Disease (1 point)
    9. Diabetes Mellitus (1 point uncomplicated, 2 points if end-organ damage)
    10. Moderate to Severe Chronic Kidney Disease (2 points)
    11. Hemiplegia (2 points)
    12. Leukemia (2 points)
    13. Malignant Lymphoma (2 points)
    14. Solid Tumor, excluding prostate cancer (2 points, 6 points if metastatic)
    15. Liver Disease (1 point mild, 3 points if moderate to severe)
    16. AIDS (not just HIV positive) (6 points)

2. Scoring: Age
    1. Age <50 years: 0 points
    2. Age 50-59 years: 1 point
    3. Age 60-69 years: 2 points
    4. Age 70-79 years: 3 points
    5. Age >80 years: 4 points

APPENDIX II (14-JAN-2022)
Medidata Patient Cloud ePRO Operational Instructions

Introduction
Electronic collection of patient-reported outcomes (ePRO) through Medidata Patient Cloud ePRO is preferred but not mandatory. Traditional paper submission is the other option. Patients who will be submitting PRO data via Patient Cloud ePRO must be registered to Patient Cloud ePRO by an authorized site user after the patient has been registered to the study. Patients may use their own device or one provisioned by the site.

Sites can use a site-specific tablet for multiple study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log in to Patient Cloud ePRO with their passwords or their PIN codes on the same device.

CRA Site Users
Site users of Patient Cloud ePRO require the same access as Rave. Access to the trial in the Patient Cloud ePRO is granted through the iMedidata. Site users will receive an invitation to Patient Cloud ePRO and the site user must accept the invitation to begin patient registration. Users who have not previously activated their iMedidata/Rave account at the time of initial approval of site registration will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Please note, site users will not be able to access the study in the Patient Cloud ePRO until all required Rave and study specific trainings are completed.

Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

CRA Instructions for Setting the Patient Cloud ePRO App to Multi-User Mode
Sites conducting studies entirely on-premise, where participants travel to the sites to fill out questionnaires, can use multi-user mode. Multi-user mode lets multiple study participants log in to Patient Cloud with their passwords or their PIN codes on the same device. . If patients will be using devices supplied by the institution, site staff will need to help the patient to access the device if the device is locked.

The study provider will download the Patient Cloud ePRO app to the device and set the Patient Cloud ePRO App to multi-user mode if applicable.
To switch from personal mode (default setting) to multi-user mode:

1. Tap **About** at the bottom of the log in screen.
2. Scroll to the bottom and tap **Advanced User**.
3. Tap **Mode**, then select **Multi-User**.
4. Tap **Yes** to confirm.
5. Tap the back arrows to return to the log in screen.

Note: If enabling multi-user mode on a device, it is highly recommended that completion reminders are turned off on that device.

For a video demonstration, see Show Me How to Switch to Multi-User Mode.

ePRO Application Download
Note that there are multiple versions of the Medidata Patient Cloud ePRO Application. Patients should be instructed to download the version chosen by the study team for the protocol. The patient will receive an error if the wrong version is downloaded.


Patient Cloud ePRO


Patient Cloud

Patient Users
To use the Patient Cloud ePRO, patients will need to use their own device (IOS, Android phone or tablet). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and will no longer be visible on the patient's device.

Sites can provide a site-specific tablet for multiple study participant use on site. If a site-specific tablet is used, study staff need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log into Patient Cloud ePRO with their passwords or their PIN codes on the same device.

Patient Instructions for Accessing the Patient Cloud Using Your Personal Device
Downloading the Patient Cloud ePRO App
If you are using your personal device, and you do not have the Patient Cloud ePRO app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the Patient Cloud ePRO app is already on the device, or if you are using a provider's device, you can skip this section.

You will need an email address that you agree to use for this purpose. The e-mail address is needed to identify you on the Patient Cloud Application and for you to receive notifications to let you know when forms are due. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e-mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS:

1. An Apple ID is required for downloading the Patient Cloud ePRO app.
2. Tap the *App Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Note: Patient Cloud ePRO is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:

1. A Google account is required for downloading the Patient Cloud ePRO app
2. Tap the *Play Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud ePRO app.

Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud ePRO app.

1. If registering from the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.

7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud ePRO app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud ePRO app. You can then proceed to log in with the credentials you created.

Logging in to the App

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap **Forgot Password**, and follow the instructions provided.

Setting a PIN Code

The first time you log in to the Patient Cloud ePRO app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud ePRO app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap **Forgot PIN** and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms

Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. Review your responses by scrolling down the list.
4. If you need to change an answer, tap the question to go back and change the answer.
5. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

Patient Compliance
The patient data imports directly from a device into the Rave database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.

Security
All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.

The data will only reside on the device for a short period of time. Once the user clicks “Submit,” the data is securely transferred over HTTPS between the device and internal relay to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The email address is stored for what purpose? The patient’s email links the device (used) and (ePRO) account to where the data is stored. The patient’s email is not visible to anyone in the system.

The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and LPOs.

The Patient Cloud ePRO application is 21 CFR Part 11 compliant and acts as a gateway between the device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud ePRO are encrypted and therefore this information cannot be read if intercepted while in transit.

Site checklist for activities prior to consenting a patient

- ☐ Site staff must have already completed required eLearning for the Patient Cloud ePRO application. See last bullet with hyperlink to training video library. Contact the LPO to request appropriate Rave access to register patients in Patient Cloud ePRO
- ☐ Accept study invitation at iMedidata.com
    - Note: you must be rostered in RSS and have received an invitation to Patient Cloud ePRO
- ☐ Verify the IOS or Android operating system is using the most current version
- ☐ Verify Patient Cloud ePRO app is using the most current version
- ☐ If using institutional shared devices, first patient only: Verify Patient Cloud ePRO app is in Multi-User mode
- ☐ Refer to Review Quick Reference Guides for videos and other procedural information

Patient withdraws study consent or withdraws consent from participating on ePRO

CRA must instruct the patients that are participating on ePRO who decide to withdraw consent to delete the App from their smart phones. This will prevent QOL reminders from being sent to the patient.

APPENDIX III: MRI SUB-STUDY (14-JAN-2022)

1 Objectives

1.1 Secondary Objectives:

- To determine if PIRADSv2.1 = 4/5 disease is prognostic for biochemical failure at baseline and follow up.

1.2 Exploratory Objectives:

- To determine if disease characteristics captured on baseline and follow-up MRI can be used to predict which patients will respond to SBRT versus hypofractionated IMRT.
- To validate autosegmentation tools for the prostate and tumors

2 Assessments in Follow Up

Assessments	
MRI of the prostate	Patients with baseline MRI reporting a PIRADSv2.1=4 or 5 lesion who either have post-RT PSA nadir > 0.8ng/mL or had a post-RT PSA rise of > 0.2 ng/mL above nadir: • If PSA criteria is met before 24 months from end of RT, then MRI is to be done at 24 months • If PSA criteria is met after 24 months from end of RT, MRI is to be done within 12 months of meeting PSA criteria Examinations **to** be performed at 3T or 1.5T (3T strongly preferred) and compliant with PIRADSv2.1 guidelines, including DCE acquisition. *Note:Guided biopsy may be considered if suspicious findings are identified on MRI at the discretion of the treating physician.*

3 MRI Imaging

3.1 Follow-up MRI (mandatory when criteria are met)

This examination is not considered standard care, and **must** be performed **only** in patients with PIRADSv2.1=4/5 lesions reported at **baseline** (institutionally or after central review), only **at or after 24 months** of follow-up, and within 12 months of patients meeting the following criteria: 1) if PSA nadir is greater than 0.8 ng/mL, or 2) when there has been a PSA rise of greater than 0.2 ng/mL above nadir. If a patient meets the criteria prior to 2 years, the MRI should be conducted at 2 years. Examinations to be performed at 3T or 1.5T (3T strongly preferred) and compliant with PIRADSv2.1 guidelines, including DCE acquisition.

4 MR Imaging Correlative Science Study

An additional MRI will be performed on eligible patients after 24 months of follow up. The purpose of the MRI is to determine if PIRADSv2.1 = 4/5 disease is prognostic for biochemical failure at baseline and follow up.

These examinations are not considered standard care, and must be performed only in patients with PIRADSv2.1=4/5 lesions reported at baseline and only after 24 months of follow-up. The MRIs must be performed within 12 months of patients meeting a certain criteria. The criteria are as followed; the MRI must be performed if PSA nadir is greater than 0.8 ng/mL or when there has been a PSA rise of greater than 0.2 ng/mL above nadir. Examinations will be performed at 3T or 1.5T (3T strongly preferred) and in compliance with PIRADSv2.1 guidelines, including DCE acquisition.
All MRIs will be centrally stored and reviewed for the purpose of correlative research. See Section 8.3.1 for TRIAD account access and installation instructions. Dedicated planning MRI images and the planning CT images will be stored for correlative science comparing the accuracy of registration techniques and image quality.

5. STATISTICAL CONSIDERATIONS

5.1 Secondary endpoints:

- Prognostic value of PIRADSv2.1=4/5 for biochemical failure at baseline and follow up.

5.1.1 Secondary Hypotheses and Endpoints:

- Prognostic value of PIRADSv2.1=4/5 disease for biochemical failure at baseline and follow up.
  Hypothesis: PIRADSv2.1=4/5 disease will be prognostic of biochemical failure using both baseline and follow-up MRIs.

5.1.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

PIRADSv2.1 = 4/5

Analyses will be conducted using baseline (diagnostic) MRIs as well as 2 year MRIs. Diagnostic MRI reports will be collected and centrally reviewed.

The prognostic value of the binary variable, whether the patient has PIRADSv2.1 = 4/5 disease, for biochemical failure will be determine using a Cox proportional hazard model (Cox 1972). Treatment arm stratification factors and other covariates of interest, such as race, ethnicity, T stage, and ECOG performance status, will be included in the model to determine if PIRADSv2.1 = 4/5 disease is independently associated with biochemical failure. If the study shows a treatment effect in favor of SBRT, then treatment arm will be incorporated into the model along with an interaction between PIRADSv2.1=4/5 and treatment to determine if PIRADSv2.1=4/5 still has a significant effect and if that effect varies by treatment arm.

Enrolled patients will be eligible for follow-up MRI acquisition if PIRADSv2=4/5 disease was reported at baseline via central review and either PSA nadir $\geq$ 0.8 or PSA rise $>$ 0.2 above nadir. Most patients who meet this criteria are expected to meet it prior to 2 years from end of treatment meaning that the MRI will be conducted at 2 years. The prognostic and/or predictive value of the binary variable, whether the patient has

PIRADSv2.1 = 5 disease in follow-up, for local control and biochemical failure will be determined using a Cox proportional hazard model (Cox 1972). The distribution of the time from end of treatment to MRI will be assessed. Although the MRI will be performed prior to an event (biochemical or local failure), the timing of the MRI may vary between patients and thus may need to be treated as a time-dependent covariate in the model. Treatment arm, stratification factors and other covariates of interest, such as race, ethnicity, T stage, and ECOG performance status, will be included in the model to determine if PIRADSv2.1 = 5 disease is independently associated with local control.

Primary central analysis will consist of independent PIRADSv2.1 scoring (as an ordered categorical variable) at a per-patient level coordinated by an expert radiologist. If more than one lesion is identified on MRI, the one with the highest PIRADS score will be recorded and used for analysis at a per-patient level. If central analysis differs from institutional reports, a third expert radiologist will score, and if needed adjudicate by consensus. Disagreements between two experienced central readers will be adjudicated by a third tie-breaking vote of a separate expert radiologist.

5.2 Power Calculations

In this study cohort of patients with low-intermediate risk disease, we estimate 60-70% of patients enrolled will harbor PIRADSv2.1 = 4/5 disease. This threshold was selected as PIRADSv2.1 score of 4 represents the presence of a focal lesion on MRI, whereas PIRADSv2.1 scores ≤3 indicate either the absence of definite lesions or indeterminate findings. We expect to demonstrate a 30-50% increase in the rate biochemical failure in patients with PIRADSv2.1 = 4/5 disease vs. without.

It is anticipated that 140-150 biochemical failure and local failure events will be observed among all trial participants. At the expected range of PIRADSv2.1 5 disease prevalence of PIRADSv2.1 = 4/5 disease, effects representing 1.6-2.0 fold greater relative failure risk for the 4/5 group can be detected with statistical power exceeding 80% (at one-sided alpha 0.05). There is a lack of data on the strength of the association between PIRADS score and other covariates such as PSA and number of positive biopsy cores. There is conflicting data on the association between PIRADS score and Gleason score in general with the distinction between 6 (3+3) and 7 (3+4) being even less clear (An 2018, Slaoui 2017). Thus, these power calculations assume that the strength of association between PIRADS scores with these other covariates is zero.

	Prevalence of PIRADSv2.1 4/5		
Hazard Ratio	0.50	0.60	0.70
2.00	0.99	0.99	0.98
1.85	0.98	0.97	0.95
1.70	0.93	0.92	0.89
1.55	0.83	0.81	0.77
	Table entries: statistical power to detect HR at left.		

A subsample of 200 participants will enroll in the GU005 imaging sub-study based on

meeting pre-specified criteria (baseline PIRADSv2.1=4/5 disease and either PSA nadir ≥ 0.8 or PSA rise > 0.2 above nadir). Given this population which expected to have a higher rate of failure (approximately 60%) than the general study population, it is anticipated that 103 biochemical failure and local failure events will be observed among these trial participants. At the expected range of PIRADSv2.1=4/5 disease prevalence of 25-40%, effects representing 1.7-2.0 fold greater relative failure risk for the 4/5 group can be detected with statistical power exceeding 80% (at one-sided alpha 0.05). As noted above, these power calculations assume that the strength of association between PIRADS scores with relevant covariates is zero.

	Prevalence of PIRADSv2.1 4/5			
Hazard Ratio	**0.25**	**0.30**	**0.35**	**0.40**
2.00	0.92	0.94	0.96	0.96
1.90	0.88	0.91	0.93	0.94
1.80	0.83	0.86	0.89	0.90
1.70	0.75	0.79	0.82	0.84
	Table entries: statistical power to detect HR at left.			

5.3 Exploratory Hypothesis and Endpoints

- Imaging endpoints:
  - Central manual user segmentation of tumors
  - Performance of supervised automated tumor detection toolset
  - Performance of supervised automated tumor segmentation toolset
  - Image registration performance
  - Predictive utility of radiomic analysis

5.4 Definitions of Exploratory Endpoints and How These Will Be Analyzed

Central manual user segmentation of tumors

User reproducibility in tumor segmentation between two radiation oncologists and two radiologists will be reported using joint DICE similarity coefficient, and standard deviation of the contour distances. It is expected to show poor inter-user reproducibility in manual tumor segmentation.

Performance of supervised automated tumor detection toolset

The performance of a computer-aided diagnostic (CAD) system utilizing T2-weighted and high-b-value diffusion-weighted imaging (DWI) and associated texture features based on local binary patterns will be compared to the gold standard central PIRADSv2.1 scoring using area under the curve (AUC) analysis. The current model, trained and validated at NIH (single institution) against MRI-guided biopsy achieves an AUC 0.89 (CI: 0.84-0.93) (Kwak 2015).

Performance of supervised automated tumor segmentation toolset

Voxel classification performance of a radical prostatectomy histopathology-trained features-based model has achieved an AUC of 0.775 +/- 0.13 in two cohorts in Leuven and Amsterdam. This trained model will be independently validated by first generating

an individual tumor probability map for each of the patients. The tumor probability map will then converted into tumor segmentation by applying a threshold at the inflection of the ROC curve (Dinh 2017). A median central observer contour (derived in the central manual user segmentation of tumors exploratory endpoint) will serve as gold-standard.

Image registration performance
Clinical registration performance between MRI and planning CT will be evaluated by identifying common landmarks applied to target registration error analysis. Common landmarks will consist of implanted fiducial markers when present, or calcifications visible in both image sets. Large standard deviations are hypothesized across the study cohort and institutions. The range of error introduced in the treatment planning process will be quantified using vector distance of common points between two image sets.

Predictive utility of radiomic analysis
A machine learning technique to predict response to radiotherapy will be investigated. A feature-based morphometry (FBM) technique, a general statistical analysis technique that operates on data in the form of local features (generic, salient image patches that are automatically extracted from medical image data), will be applied and adapted (Toews 2015). Local features can be organized into highly efficient data structures for computing robust image-to-image correspondences, and machine learning algorithms based on local feature-based thus scale gracefully to arbitrarily large sets of image data. The FBM approach has been validated in a range of clinical contexts including predicting Alzheimer`s disease (AD) from neurological MRI data and chronic obstructive pulmonary disorder (COPD) from lung CT data.

APPENDIX IV: MRI: PROSTATE, PI-RADS V2.1 (14-JAN-2022)

Image quality in the multicenter setting can be greatly influenced by variances in acquisition protocols. These variances may be related not only to equipment manufacturer and model, but also technique.

The study may permit imaging per institutional standard-of-care. However, aligning image acquisition to established standards is essential for robust quality data.

Prostate MRI exams should be acquired on a 1.5T or 3.0T MRI scanner. *3T imaging is preferred*.

With some 1.5T MRI systems, especially older ones, use of an endorectal coil (ERC) is considered indispensable for achieving the high-resolution diagnostic quality imaging needed to stage prostate cancer.

The patient should evacuate the rectum, if possible, just prior to the MRI exam.

Prostate MRI acquisition protocols should always be tailored to specific patients, clinical questions, management options, and MRI equipment.

The tables below are provided as a guideline and overview for MRI Prostate exams. Please refer to your site's specific MRI manufacturer's imaging protocols for the optimal scanning protocol.
The Prostate MRI examination should be acquired according to the PIRADSv2.1 standard. The exam should contain, at a minimum, the following series:

Pre-Contrast

1. 3-plane localization scan
2. T1-weighted sequence
3. T2-weighted sequence
4. Diffusion weighted sequence
5. Generated ADC map from DWIs

Post-Contrast

6. Dynamic Contrast-enhanced T1-weighted sequence

Exam and Patient Preparation		
Magnet Strength	1.5T or 3T	Low-field magnets are not acceptable
Coil	Phased Array Coil Endorectal Coil (ERC) as necessary	ERC as needed, particularly at 1.5T
FOV	Smallest FOV that encompasses the prostate gland and seminal vesicles	For all sequences
Patient Position	Supine	
Contrast Injection	Dual-chamber power injector recommended Contrast Bolus = 0.1 mmol/kg Bolus Rate = 2–3 mL/s Saline Flush = 20 mL	Insertion of intravenous catheter in upper extremity prior to the start of contrast imaging.
Slice Plane	Axial [Plus orthogonal plane(s) for T2w]	May be oblique to match long axis of prostate.

Additional Considerations	Antispasmodic agent may be administered to reduce motion artifacts. Patient should evacuate rectum just prior to the MRI exam	Diminishes bowel peristalsis and improves quality of imaging. Reduces DWI artifact, can facilitate use of ERC.

Image Acquisition and Map Generation

Localization Scan	3-plane localization scan	
T1-Weighted (T1w) Sequence	Per site's standard acquisition parameters	Performed prior to contrast
Pre-Contrast T2-Weighted (T2w) Sequence	Slice thickness = 3.0 mm FOV = 120–200 mm Resolution ≤ 0.7 mm (phase) ≤ 0.4 mm (frequency) Gap = 0 mm	Typical pulse sequences are 2D RARE, e.g., FSE or TSE. To avoid blurring, excessive echo train lengths should be avoided. T2w images should always be obtained in the axial plane (either straight axial to the patient or in an oblique axial plane matching the long axis of the prostate) and a minimum of one additional orthogonal plane (i.e., sagittal and/or coronal).
Pre-Contrast Diffusion-Weighted Imaging (DWI) with ADC mapping	Slice thickness ≤ 4.0 mm Gap = 0 mm TR ≥ 3000 ms TE ≤ 90 ms Resolution ≤ 2.5 mm phase and frequency *b*-values minimum 2 **see ADC Maps**	DWI image set must include a *b*-value ≥1400 s/mm^2. This can be calculated from other *b*-values (and resultant ADC map) or physically acquired.
ADC Maps	<u>Generated from DWIs at multiple *b*-values</u> For only 2 *b*-values: Low *b* = 0–100 s/mm^2 (Preferred low *b* = 0–50 s/mm^2) Intermediate *b* = 800–1000 s/mm^2 For all ADC maps: Max *b* ≥ 1000 s/mm^2	For ADC maps, if only two *b*-values can be acquired due to time or scanner constraints, use one low *b*=0–100 s/mm^2 (preferably 50–100 s/mm^2) and one intermediate *b*=800–1000 s/mm^2. A high *b*-value (≥1400 s/mm^2) image set is also mandatory and preferably should be obtained from a separate acquisition or calculated from the low and intermediate *b*-value images. To calculate ADC, use *b*≤1000 s/mm^2 to avoid diffusion kurtosis effect that have been described at higher *b*-values. An acquired *b*≥1400 s/mm^2 should **not** be used to generate ADC maps.

Dynamic Contrast Enhanced (DCE) T1-Weighted (2D or 3D technique)	Slice thickness = 3.0 mm FOV = 120–200 mm Resolution ≤ 2.0 mm phase and frequency Gap = 0 mm TR < 100 ms TE < 5 ms Temporal Resolution ≤ 15 s Observation Time ≥ 120 s	FOV should encompass the entire prostate gland and seminal vesicles. While both 2D or 3D T1w gradient echo (GRE) sequences have been described in the literature, 3D T1w GRE is generally available using modern systems and is preferred. Scan should be carried out for several minutes and temporal resolution should be ≤15 seconds per acquisition to depict focal early enhancement.

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