Proton Collaborative Group

PCG - GU002-10
A Phase III Prospective Randomized Trial of Standard-fractionation vs. Hypo-fractionation with Proton Radiation Therapy for Low Risk Adenocarcinoma of the Prostate

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PROTOCOL SIGNATURE PAGE

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Protocol Version 27May2016

I certify that I have read the protocol. I agree to conduct the protocol according to ethical principles stated in the Declaration of Helsinki, the applicable guidelines for good clinical practice, or the applicable laws and regulations, whichever provides the greatest protection of the individual. I will accept the monitor's overseeing of the study.

_____ _____
Signature of the Principal Investigator **Date**

_____
Principal Investigator's Printed Name

_____
Name of Facility

_____
Location of Facility (City, State)

PLEASE COMPLETE AND SEND VIA EMAIL (HQ@PCGRESEARCH.ORG) TO THE PROTON COLLABORATIVE GROUP OFFICE

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SCHEMA

STRATIFY

T stage
T1a, T1b, T1c
T2a

PSA
< 4
≥ 4 to < 10

Cores positive
1 to 4
≥ 5

RANDOMIZE

Conformal Proton Radiation

Arm I: Dose: 79.2 Gy (RBE); 1.8 Gy (RBE) five days a week in 44 treatments over 8.5-9 weeks

Arm II: Dose: 38 Gy (RBE); 7.6 Gy (RBE) five days a week in 5 treatments over 1-2 weeks

Patient Population: Adenocarcinoma of the prostate with low or intermediate risk features including ≤ T2a, Gleason score ≤ 6 and a PSA < 10 ng/ml.

Eligibility Criteria: ***(Note: The list below is for screening only. See Section 3.0 for complete eligibility)***

- Histologically confirmed prostate adenocarcinoma within 365 days prior to randomization
- Clinical stages T1-T2a N0 M0 (AJCC Criteria 7th Ed.)
- Prostate Specific Antigen (PSA) values < 10 ng/ml within 90 days prior to randomization. Done either prior to biopsy or at least 21 days after prostate biopsy.
- Gleason score 2 to 6
- No invasive cancer within 5 yrs (see section 3.2.9)- basal cell or squamous skin malignancies are permitted
- ECOG performance status of 0-1
- No previous prostate cancer surgery such as prostatectomy, hyperthermia, or cryosurgery
- No previous pelvic radiation or systemic chemotherapy for prostate cancer
- Androgen deprivation therapy prior to radiation is allowed. However, it may not be continued during radiation or as adjuvant therapy.
- Must be able to start treatment within 56 days of registration
- Signed study specific, IRB approved, Informed Consent
- IPSS score ≤ 16
- Use of a tissue spacer between the rectum and the prostate or a rectal balloon/rectal water

Required Sample Size: 150

1.0 Introduction

1.1 Treatment

Prostate cancer is the most common malignancy in the United States with an estimated incidence of 186,320 cases in 2008 [(1)]. An estimated 28,660 prostate cancer deaths will occur in 2008 [(1)].

Different approaches and modalities have been used for the treatment of low risk prostate cancer patients. Among these options, proton therapy is a novel radiation modality that employs particles to deliver high doses with high accuracy to the tumor and low doses to the surrounding normal tissue. However, with standard doses for image guided proton radiation, long treatment times consisting of between 8 and 9 weeks are necessary. Patients that are ideal candidates for this modality may elect alternative modalities due to the extended treatment time period. As a result we propose in this protocol to combine a hypo-fractionated approach that benefits from the low alpha/beta of low risk prostate cancer and the conformality achieved with proton therapy to deliver a hypo-fractionated course of therapy for low risk prostate cancer [(2-6)].

1.2 Rationale for Using Proton Radiation Therapy

Proton radiation therapy will be employed to deliver proton therapy either with standard fractionation or with hypo-fractionation. Using the dosimetric advantages of proton therapy, we will be able to reduce doses to the normal surrounding structures and decrease toxicity. Loma Linda University has found low toxicity rates with the use of proton radiation due to lower doses to normal structures [(12-15)]. Vargas et al., have published lower doses to the rectum and bladder with the use of proton therapy when compared to optimal IMRT techniques [(7)]. Zietman et al., has published high biochemical control rates with proton therapy for low risk prostate cancer patients even without the use of modern image guidance techniques [(8)]. Slater et al., has published the results of the largest series in proton therapy for prostate cancer. Gastrointestinal and urinary grade ≥ 3 toxicities were seen in 1.3% of patients. Urinary toxicity grade ≥ 3 was the most common of the two presenting in 1.1% [(9)].

1.3 Rationale for Image Guidance

The prostate is a mobile organ in the pelvis. It is subject to movement with respect to pelvic bones due to changes in rectal distention, bladder filling, and abdominal pressure. Multiple studies have shown movements larger than 5mm in more than 15% of cases, especially with a full rectum [(10, 11)] . The use of prostate fiducial markers will improve prostate positioning decreasing necessary margins for treatment [(12, 13)]. Image guidance approaches have been proven to be useful to limit toxicity [(14, 15)]. Thus, image guidance will improve accurate prostate targeting improving both cancer control rates and decreasing toxicity. Vargas et al., have published the rationale of his image guidance approach for proton therapy [(16-19)]. They provide the framework for the margins employed in this protocol.

1.4 Rationale for High Dose Proton Radiation

Multiple randomized trials and phase II studies have shown an advantage for higher doses for the treatment of prostate cancer [20-26]. This study proposes to employ high dose proton radiation for the treatment of prostate cancer patients. The standard fractionation arm dose of 79.2 Gy (RBE) is based on the 93% 10-year biochemical control found in a dose escalation proton phase III trial [8]. The hypo-fractionated dose of 38 Gy (RBE) is based on the clinical experience with 33.5 Gy by Madsen et al., King et al., and the clinical experience of high dose rate brachytherapy [3, 27-29].

1.5 Rationale for Hypo-fractionated Radiation Therapy

Prostate cancer has been found to have a low α/β [2, 5, 6]. As a result, a higher dose per fraction will have an increased effect on cancer cells than in normal tissue. Vargas et al., published improved biochemical control, clinical control, cancer specific survival and overall survival when employing a hypo-fractionated high dose rate scheme [30]. Hypo-fractionated approaches have been used and when accounting for PSA bounce good 4-year biochemical control rates have been found in 90% using nadir +2ng/ml definition [3]. This study proposes to employ a hypo-fractionated strategy with our image guided treatment to further improve cancer control and decrease toxicity.

Dose selection for the hypo-fractionated arm was based on both clinical and radio-biologic information. Clinical information include the publication of 5-year biochemical control and long term toxicity for patients treated to 38 Gy with high dose rate (HDR) at William Beaumont Hospital. High biochemical control rates as well as low rates of chronic toxicity were seen with this approach. Overall toxicity profile favored HDR compared to a more protracted dose delivery with low dose rate. Madsen et al., have also published high biochemical control rates with hypo-fractionated radiation 33.5 Gy [3]. In his publication no grade 3 or higher toxicity events were seen. Similarly to previous publications, Fowler et al., have extensively published on the ideal doses for fractionated radiation [2]. Based on an equivalent dose to the rectum he proposed 36 Gy in 5 fractions. King et al., published the results for 36 Gy in 5 fractions [29]. Grade 3 or higher toxicity was seen in two cases related to GU symptoms both of which resolved (Personal communication of the author). No grade 3 or higher GI toxicity was seen.

Similarly based on an equipoise assumption for an equivalence trial we will compare 38 Gy (RBE) in 7.6 Gy (RBE) fractions with 79.2 Gy (RBE) in 1.8 Gy (RBE) fractions. Based on a linear quadratic model as proposed by Fowler et al [2] both doses will be an equivalent to 76 Gy (RBE) in 2 Gy (RBE) fractions with a conservative α/β of 3.5 for the rectum. This should also translate to a dose of 76 Gy (RBE) in 2 Gy (RBE) fractions to the prostate based on an α/β of 3.5. The α/β being on the conservative side will deter an unrealistic hypo-fractionated approach based on a presumed too low α/β. With this approach we account for both equivalent doses to rectum avoiding unnecessary doses to normal structures, as well as delivering high enough doses to the prostate that will limit the risk of under-treatment.

The dose for the standard fractionated arm (79.2 Gy (RBE)) is based on the positive phase III trial published by Zietman et al. As published, with this dose we expect a 5-year biochemical control of 90-95%[8].

Biological Equivalent Dose

Treatment Arms	Rectum 2Gy α/β=3.5	Tumor dose 2Gy α/β=3.5
79.2 in 1.8Gy	76Gy	76Gy
38 in 7.6Gy	76Gy	76Gy

2.0 Objectives

2.1 Primary Objective

To assess if hypo-fractionation will result in 2-year freedom from failure (FFF) that is non-inferior to 2-year FFF following standard fractionation.

Freedom from failure (FFF): The events for FFF will be the first occurrence of clinical failure (local recurrence, regional recurrence, or distant metastasis), biochemical failure by the Phoenix definition (PSA $\geq$ 2 ng/ml over the current nadir PSA),[31] or the start of salvage therapy including androgen deprivation.

2.2 Secondary Objective

To estimate the incidence of grade 2 or greater GU and GI toxicity in each of the regimens at 6 months and 2 years post randomization.

2.3 Exploratory Objectives

2.3.1 To assess quality of life and sexual functioning issues at 6 months and at 2 years post randomization.

2.3.2 To estimate the freedom from biochemical failure (BF) rate at 5 years post randomization.

2.3.3 To estimate the clinical failure rate: local and/or distant at 5 years post randomization.

2.3.4 To estimate salvage androgen deprivation (SAD) use at 5 years post randomization.

2.3.5 To estimate progression-free survival: using clinical, biochemical and SAD as events at 5 years post randomization.

2.3.6 To estimate overall survival at 5 years post randomization.

2.3.7 To estimate disease-specific survival at 5 years post randomization.

2.3.8 To estimate prostate and normal structures movement during RT with the use of scans.

2.3.9 To assess the associations of pathologic and radiologic findings with outcomes at 5 years post randomization.

2.3.10 To assess the association of PSA, free PSA, and testosterone levels with outcomes at 5 years post randomization.

2.4 Planned Future Objectives

2.4.1 To develop a quality assurance process for proton prostate therapy.
2.4.2 To prospectively collect information that will help to define dose-volume relationships of normal structures with acute and chronic toxicity at 2 years.
2.4.3 To allow for future research of pathologic risk factors that may influence prognosis- this information will help us to attempt to characterize their presence in low and intermediate risk prostate cancer and their potential effect on outcomes.
2.4.4 To compare an IMRT plan with the proton therapy radiation plan.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Histologically confirmed prostate adenocarcinoma within 365 days prior to randomization.
3.1.2 History/physical examination with digital rectal examination of the prostate and baseline toxicity assessment within 90 days prior to randomization.
3.1.3 Histological evaluation of prostate biopsy with assignment of a Gleason score to the biopsy material; Gleason score must be in the range of 2-6. *> 6 cores are strongly recommended.*
3.1.4 PSA values < 10 ng/ml within 90 days prior to randomization. Either done prior to biopsy or at least 21 days after prostate biopsy.
3.1.5 Clinical stages T1-T2a N0 M0 (AJCC Criteria 7th Ed.). *Staging must be done by treating investigator.*
3.1.6 No pelvic lymph nodes > 1.5 cm in greatest dimension unless the enlarged lymph node is biopsied and negative.
3.1.7 Patients must be at least 18 years old.
3.1.8 ECOG performance status 0-1 (appendix I) documented within 90 days prior to randomization.
3.1.9 IPSS score $\leq$ 16.
3.1.10 *Removed wording - amendment #2 5-4-2011*
3.1.11 *Removed wording - amendment #2 5-4-2011*
3.1.12 Patients must give IRB approved, study specific, informed consent.
3.1.13 Patients must complete all mandatory tests listed in section 4.0 within the specified time frames.
3.1.14 Patients must be able to start treatment within 56 days of randomization.

3.2 Conditions for Patient Ineligibility

3.2.1 Previous prostate cancer surgery including: prostatectomy, hyperthermia and cryosurgery.
3.2.2 Previous pelvic radiation for prostate cancer.
3.2.3 Androgen deprivation therapy prior to radiation is allowed. However, it is not acceptable if continued during radiation or as adjuvant therapy.
3.2.4 Active rectal diverticulitis, Crohn's disease affecting the rectum, or ulcerative colitis.
3.2.5 Prior systemic chemotherapy for prostate cancer.
3.2.6 History of proximal urethral stricture requiring dilatation.

3.2.7 Current and continuing anticoagulation with warfarin sodium (Coumadin), heparin, low-molecular weight heparin, Clopidogrel bisulfate (Plavix), or equivalent (unless it can be stopped to manage treatment related toxicity, to have a biopsy if needed, or for marker placement).

3.2.8 Any major medical, addictive or psychiatric illnesses which would affect the consent process, completion of treatment and/or interfere with follow-up. Consent by legal authorized representative is not permitted in this study.

3.2.9 Evidence of any other cancer within the past 5 years and < 50% probability of a 5 year survival. Prior or concurrent diagnosis of basal cell or non-invasive squamous cell cancer of the skin is allowed.

3.3 Inclusion of Minorities

Members of all races and ethnic groups are eligible for this trial.

3.4 Inclusion of International Subjects

Patients from outside of the United States may participate in the study. Enrollment and treatment must be completed at PCG member institutions in the United States.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations that need to be completed prior to randomization. Also refer to section 11.0 for chart reference of these evaluations.

4.1 Each patient must have completed the following studies within 90 days prior to randomization unless otherwise indicated.

4.1.1 *Removed wording- amendment #2 5-4-2011*

4.1.2 CT scan or MRI of pelvis (diagnostic) for lymph node evaluation. **Results must be available pre-treatment but can be done after randomization.**

4.1.3 *Removed wording - amendment #1, 01-14-2011*

4.1.4 Trans-rectal ultrasound with core biopsies is required within 365 days prior to randomization (12 core biopsy preferred*). If less than 6 cores, re-biopsy is strongly recommended*. **A secondary pathology review is strongly recommended for patients whose reports come from another institution.**

4.1.5 Prostate fiducial markers are mandatory. Different types of markers can be employed including but not limited to transponders (Calypso), carbon markers, or Gold Seed (Visicoils).

4.1.6 The Expanded Prostate Cancer Index Composite (EPIC) quality of life questionnaire

4.1.7 The American Urologic Association IPSS score

4.1.8 CT scan or MRI of prostate (for planning and/or movement) may be completed pre or post randomization.

4.1.9 Pacemakers/Defibrillators: The guidelines of the American College of Radiology (ACR) and American Association of Physicists in Medicine (AAPM) will be strictly followed including the specific recommendations of the device manufacturer. A special physics consultation will be requested and all guidelines strictly followed if needed.

4.2 The following studies are not mandatory, although highly recommended.

4.2.1 Bone scan within 180 days prior to study randomization. *Mandatory if alkaline phosphatase elevated > 2 x the upper limit of institutional normal (ULN).*

4.2.2 Bone x-ray or CT if bone scan is equivocal

4.2.3 Urethrogram recommended at time of CT simulation if no MRI is available

4.2.4 PET or CT-PET as clinically indicated

4.2.5 Prostate MRI spectroscopy as clinically indicated

4.2.6 Chest x-ray

4.2.7 CBC, Alkaline phosphatase, testosterone level and free PSA

4.3 Ancillary Evaluations (not mandatory, although highly recommended)

Process optimization**:** To evaluate administrative and technical factors that influence the efficiency, convenience, precision and accuracy of proton therapy in this setting.

Ancillary studies will not be used for treatment planning unless approved by the study chair. Studies can be done prior to treatment, during treatment, after completion, or at the time of failure.

4.3.1 Kilovoltage images, x-rays, fluoroscopy, 4D CT-scan, additional planning CT/MRI scan, cine-MRI, ultrasound, or different imaging modalities that may aid to improve therapy or define outcome

4.3.2 CT-PET or Positron emission tomography (PET) scans, MRI spectroscopy, MRI diffusion, or different biologic imaging modalities that may aid to improve therapy or define outcome or therapy

5.0 REGISTRATION

5.1 PCG headquarters must have documentation of each institution's IRB approval of the protocol on file prior to registering patients.

5.2 Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

5.3 Verify the patient meets the eligibility criteria prior to randomizing the patient. The protocol-specific eligibility checklist provided in the Study Procedures Manual (SPM) should be used to document eligibility and placed in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

5.4 Patients must be registered through the PCG Electronic Data Capture (EDC) system. Patients can be registered only after eligibility criteria are met.

5.5 At minimum, the initial 5 treatment plans per institution will be centrally reviewed by a Proton Collaborative Group physicist and the Study Chair or designee prior to start of treatment. Refer to the Study Procedures Manual for additional information.

6.0 RADIATION THERAPY

NOTE: Protocol treatment must begin within 56 days after registration

6.1 Radiation Dose

6.1.1 Doses throughout will be prescribed in Gy for the IMRT (if used) and in Gy (RBE) for the proton treatment. The total dose will be the addition of the

treatment received with IMRT (if used) and proton therapy. One Gy will be the equivalent of one Gy (RBE). Total dose will be 79.2 Gy (RBE) or 38 Gy (RBE). The prescription dose is the minimum dose to 95% of the planning target volume and a minimum dose of 75.24 Gy (RBE) or 36.1 Gy (RBE) to 99.5% of the planning target volume. The maximum dose should not exceed the prescription dose by more than 7% (inhomogeneity less than or equal to 7% in a volume of 1cc of the PTV). The dose to the rectum or bladder even within the PTV cannot exceed 103% of the prescribed dose (i.e. 81.6 Gy (RBE) or 39.1 Gy (RBE)).

6.1.2 Prescription dose to the PTV shall be according to the following schema delivered in 1.8 Gy (RBE) per fraction or 7.6 Gy (RBE) per fraction. One-two fields are recommended to be treated once daily, for 5 fractions per week.

6.1.3 Volumes are as follows for low risk patients with a rectal balloon:

6.1.3.1 Fields:

CTV 1= Prostate
PTV 1= CTV + 2mm posterior and 3mm elsewhere
PTV eval (OTV) = PTV 1 + 5mm left and right (or follow the beam direction)

6.1.3.2 Dose:

Patients will be treated with 1.8 Gy (RBE) per fraction in 5 fractions per week for a total dose of 79.2 Gy (RBE) or in 7.6 Gy (RBE) per fraction in 5 fractions per week for a total dose of 38 Gy (RBE).

Volumes are as follows for low risk patients with a tissue spacer:

6.1.3.3 Fields:

CTV 1= Prostate
PTV 1= CTV + 4mm posterior and 6mm elsewhere
PTV eval (OTV) = PTV 1 + 2mm left and right (or follow the beam direction)

6.1.3.4 Dose:

Patients will be treated with 1.8 Gy (RBE) per fraction in 5 fractions per week for a total dose of 79.2 Gy (RBE) or in 7.6 Gy (RBE) per fraction in 5 fractions per week for a total dose of 38 Gy (RBE).

6.2 Equipment and Physical Factors

Radiation will be delivered using the available proton equipment. If it is necessary to use IMRT, non-opposed 5-7 field IMRT arrangement is recommended, with lateral obliques or lateral fields. Oblique fields are recommended for the proton component. However, different field arrangements or number of fields can be used as required for optimal PTV coverage.

6.3 Localization and Imaging Requirements

6.3.1 Localization: Proper localization of the appropriate target volumes requires reproducible immobilization and correlation of imaging studies. Planning CT scans will be performed using a high-resolution scanner with $\leq$ 2 mm cuts through the region of interest (prostate), and at least 5mm elsewhere in the pelvis. MRI will also be considered appropriate for structures' definition.

MRI of the pelvis and prostate will be used for treatment planning volume delineation. T2 sequence 3D with ≤ 2mm spacing is recommended.

6.3.2 Fiducial Markers: Will be placed within the prostate under ultrasound guidance. Different types of markers can be employed including but not limited to transponders (Calypso), carbon markers, or Gold Seed (Visicoils).

6.3.3 Immobilization: Patients will be immobilized for the treatment in a supine or prone position, using an appropriately customized immobilization device. An inflatable rectal probe may be inserted to displace the posterior rectal wall from the radiation beam and thus immobilizing the prostate. One hundred (100) cc of water is recommended to be used on a daily basis if a balloon is to be used. Water alone may also be used. A total of 100-200cc are recommended. Balloon inflations or placement techniques may vary, as well as water use or volume. A Foley catheter may be used for prostate immobilization or to improve bladder inflation. Seven (7) cc of saline with contrast are recommended to be used to inflate the Foley balloon. The catheter should be closed 20-30 minutes before treatment to assure bladder filling.

6.3.4 Tissue spacer: Tissue spacer can be used to increase the distance between the prostate and the rectum.

6.3.5 Treatment: Patients will be encouraged to undergo treatment with a full bladder and an empty bowel. Close fitting devices as used for simulation will be used for daily treatments.

Daily position verification: Patients will be setup with lasers in a custom fitting device. Patient orientation will be verified based on skin marks. Daily prostate position will then be verified based on prostate markers/beacon transponders employing the techniques described below.

6.4 On-line Daily Correction

We do realize that for an individual patient prostate movement and set up error may be non-parametric and a large random component may be present. Thus, several different image guidance modalities may be used.

Orthogonal x-rays: Orthogonal images (kV images) are recommended for inter-setup error (bony alignment) and prostate-position correction. X-rays in the beam orientation are recommended. Portal images (kV images) in other orientations such as AP-PA or oblique projections may be used as needed. Error will be measured and appropriate actions and corrections will be taken. In general, the goal is an inter-setup error or residual error < 2.5 mm based on fiducial markers or other type of prostate marker. An error of < 2.5 mm for the prostate, either with fiducials, rectal balloon, or soft tissue registration, is also the goal. If an error < 2.5mm is found, treatment can be delivered. Corrections will be done for errors ≥ 2.5mm.

Medcom system: If possible rotational vectors will be first corrected based on bony anatomy. After initial rotational corrections are completed, translational corrections will be done based on fiducial marker position until a position < 2.5mm in a vector is achieved.

6.5 Error Verification

In the 44 fx arm, post-treatment x-rays will be done for the first 10 treatments and then every week. If an error of ≥ 5mm is observed, the physician should be notified. Rectal balloons are recommended for persistent ≥ 5mm intra-fraction errors. If two movements larger than 5mm are found in the hypo-fractionated arm, a rectal balloon will be recommended.

6.5.1 MRI cine: MRI cine can be done to determine intra-fraction motion. Margins can be increased up to 5mm axial and 7mm superior to inferior.

6.5.2 3D volumetric guidance: cone beam CT, CT on rails, MRI, ultrasound or other means of 3D guidance can be employed. For image guidance, fiducial markers are required to participate in the study. Corrections will be done for any error ≥ 2.5mm. No re-imaging is recommended after correction. For cone-beam CT no re-imaging between beams is recommended.

6.6 Dose Calculations

6.6.1 Tumor doses will be 1.8 Gy (RBE) or 7.6 Gy (RBE) given usually once a day five times a week. Gy (RBE) equivalence will be based on the most recent proton biologic equivalent dosimetric calculations and review of the most current literature.

6.6.2 Dose volume histograms (DVH) for the prostate and important critical normal structures will be calculated. The different dose constraints will be reported. DVHs should be kept in the patient's records and at minimum the first 5 patients at each treatment site will be reviewed prior to the start of treatment for quality assurance. Electronic charts and remote dosimetric review are allowed.

6.7 Critical Normal Structures

6.7.1 Clinical Target Volume. CTV is the prostate alone as defined by MRI or CT. The external rectal wall will be contoured as outlined. After the rectal wall is contoured, prostate volume may be defined.

For CT definition:

- *Inferior:* Urethrogram is recommended. The prostate will be contoured starting on average 0.9 cm above the urethral beak if a urethrogram is used. Sagittal view will be used and 0.9 cm should be measured from the tip of the beak to the most inferior prostate slice on average.
- *Anterior:* The dorsal venous complex of santorini should not be included. It is located anterior to the prostate behind the symphysis pubis. It may also extend laterally to the prostate.
- *Posterior:* The seminal vesicles should not be included in the CTV. If in doubt, the most proximal portion of the seminal vesicles can be included where they exit the superior posterior aspect of the prostate. For the remainder of the posterior aspect, no overlap is allowed between the prostate and the rectal wall. Sagittal MRI or CT will be used to verify volumes.
- *Lateral:* The elevator ani muscles that form the urogenital diaphragm should not be included where they support the prostate

inferiorly. Coronal CT views will be used to determine appropriate prostate contouring.

- *Superior:* Contrast in the bladder is recommended. The prostate will extend superiorly but not include the contrast. A sagittal view will be used to determine appropriate superior coverage.

For MRI definition:

- *Inferior:* The prostate will be contoured starting on average 0.9 cm above the superior aspect of the penile bulb (corpus spongiosum). Sagittal MRI or CT view will be used and 0.9 cm should be measured from the penile bulb to the most inferior prostate slice on average. However, for individual patients the distance may be more or less based on MRI information
- *Anterior:* The dorsal venous complex of santorini should not be included. It is located anterior to the prostate behind the symphysis pubis. It may also extend laterally to the prostate.
- *Posterior:* The seminal vesicles should not be included in the CTV. If in doubt, the most proximal portion of the seminal vesicles can be included where they exit the superior posterior aspect of the prostate. For the remainder of the posterior aspect, no overlap is allowed between the prostate and the rectal wall. Sagittal MRI or CT will be used to verify volumes.
- *Lateral:* The elevator ani muscles that form the urogenital diaphragm should not be included where they support the prostate inferiorly. Coronal MRI or CT views will be used to determine appropriate prostate contouring.
- *Superior:* Contrast in the bladder is recommended. The prostate will extend superiorly but not include the contrast. A sagittal CT or MRI view will be used to determine appropriate superior coverage.

6.7.2 Planning Target Volume. CTV with a margin of 2mm posterior and 3mm elsewhere.

6.7.3 Preplan. The number of slices will be recorded. Slice spacing will be ≤ 2mm at the prostate, and 5mm elsewhere. The planimetric volume of the prostate will be the CTV.

6.7.4 Rectal wall is defined from the ischial tuberosities to the sigmoid flexure. The wall will be defined using an average thickness of 3mm. Sagittal MRI or CT view should be used to verify volume definition.

6.7.5 The bladder should be contoured in its entirety. The wall is defined using a 3 mm contraction on the external bladder contour.

6.7.6 Bladder wall high dose/Bladder neck. It encompasses the bladder wall included in the PTV.

6.7.7 Small bowel. It should be contoured including 2 cm above the treatment field.

6.7.8 Rectal wall high dose. The rectal wall is included in the PTV.

6.8 Normal Tissue Constraints (NTC)

6.8.1 Normal tissue constraints (NTC) to define dose.

Table 2a. For the standard-fractionation arm –Arm I

Structure	**Constraint**	**Minor deviation**	**Major deviation**
Rectum	V50 <35%	V50 <40%	V50 ≥ 40%
	V70 <10%	V70 <20%	V70 ≥ 20%
Bladder	V80 <8cc	V80 <12cc	V79.2 ≥ 12cc
Femoral heads	V45 <1 cc	V45 <2 cc	V45 ≥ 2cc
PTV	Min dose PTV	99.5% >75.24Gy	
PTV eval	PTV Coverage	95% to 79.2Gy	

Table 2b. For the hypo-fractionation arm- Arm II

Structure	**Constraint**	**Minor deviation**	**Major deviation**
Rectum	V24<35%	V24 <40%	V24 ≥ 40%
	V33.6 <10%	V33.6 <15%	V33.6 ≥ 20%
Bladder	V39 <8cc	V39 <12cc	V39 ≥ 12cc
Femoral heads	V23 <1 cc	V23 <2 cc	V23 ≥ 2cc
PTV	Min dose PTV	99.5% > 36.1Gy	
PTV eval	PTV Coverage	95% to 38Gy	

If the small bowel is found within the radiation fields, doses received will be recorded. Small bowel location and DVH may be used for treatment planning purposes. However, they will not be used as a NTC to define dose. Small bowel recommendation is a V40 <125cc and a V60 <10cc.

6.8.2 Doses will be adjusted employing normal tissue constraints and a minimum of 73.8 Gy (RBE) at 1.8 Gy (RBE) per fraction or 35 Gy (RBE) at 7.6 Gy (RBE) per fraction can be used for treatment. The maximum dose without a major deviation will be used for treatment.

6.8.3 In cases of major normal tissue constraint deviation, patients will be notified. No major NTC deviation is allowed in the protocol. Patients may elect to receive proton therapy outside the treatment protocol if clinically indicated. Alternative treatment will be offered on a case-by-case basis including, but not limited to: prostatectomy, brachytherapy, and standard photon radiation.

6.9 Proton planning

6.9.1 MRI fusion: Initial automatic fusion will be done. Soft tissue registration will then be done in the sagittal plane at midplane. Contours will be done of the prostate bladder interface and of the rectal prostate interface for fusion.

6.9.2 For proton planning, two un-opposed lateral oblique fields are recommended. Anterior orientation of 5 degrees or less is recommended. However, angles >5 degrees can be used upon physics approval. More fields can be used as necessary. The minimum number of beams necessary to meet the required treatment parameters should be used. Parallel opposed beams are acceptable for proton planning.

6.9.3 Uniform scanned radiation will be used. However, uniform dose distribution by means of pencil beam, spot scanning, double scatter or other delivery methods is acceptable.

6.9.4 For aperture definition a block edge margin of 7mm is recommended posteriorly and superiorly and 9mm inferiorly and anteriorly. However, larger block edge

margins can be used to have a minimum coverage to the PTV of the 95% IDL. For uniform dose distribution without apertures coverage of the PTV with 95% IDL is required.

6.9.5 Distal and proximal margin: PTV evaluation will be created based on the initial PTV + 5mm R and L expansions. Distal and proximal margins will be adjusted for coverage of the PTV Eval with the 98% IDL. For small areas a minimum coverage with the 95% IDL is required.

6.9.6 Smearing: PTV will be smeared 1.2cm.

6.10 Quality Assurance (Physics check)

6.10.1 Daily portal films or daily online radiographic imaging will be performed during radiation therapy. The position of the bony landmarks, and/or contrast/air-filled rectal balloons (used if clinically indicated) will be compared with DRRs (digitally reconstructed radiographs).

6.10.2 Coronal, transverse, and sagittal CT slices with overlaid doses representing the total dose to be delivered should be available.

6.10.3 Digitally reconstructed radiographs representing the treatment plan should be available.

6.10.4 Dose volume histograms (DVH) including, but not limited to, prostate, bladder wall, femoral heads, and rectal wall will be available.

6.10.5 If available, different imaging and biologic-imaging studies can be used to define different structures. DVH will be performed as needed.

6.10.6 Beam characteristic - The penumbra as defined by the 20-80% isodoseline in a 10x10 field at a depth in water of 25cm should be less than or equal to 8mm.

6.11 Proton Unavailability

If proton beam therapy is not available, photon therapy may be used at the discretion of the treating physician for not more than 10 treatments of 1.8 Gy (18 Gy) in the standard fractionation arm and for not more than 1 treatment of 7.6 Gy in the hypo-fractionation arm. A larger photon component is not allowed on protocol and patients should be withdrawn from the protocol.

6.12 Treatment Interruptions

Treatment should be delivered for 44 treatments over 8.5-9 weeks. Unplanned interruptions, consecutive or not, for more than 5 treatment days (Monday-Friday) are not allowed. Treatment breaks $\geq$ 5 days are considered major deviations and not allowed. If treatment interruption is not of medical necessity, arrangements for IMRT photon therapy should be made.

For subjects randomized to the 5 fraction arm, treatment should be delivered once daily for 5 treatments over 1-2 weeks. Treatments should be planned to be delivered on consecutive days.

6.13 Radiation Toxicity

The Common Terminology Criteria for Adverse Events (CTCAE) v4.0 from the National Cancer Institute (NCI) will be used for toxicity grading. All patients will be seen weekly by the radiation oncologist during radiation therapy. Any observations regarding radiation reactions will be recorded and should include attention toward the following potential side effects:

- Skin reactions such as erythema and moist desquamation.

- Rectal irritation manifesting as diarrhea, rectal incontinence, proctitis or rectal bleeding.
- Bladder toxicity including urinary frequency/urgency, dysuria, hematuria, obstruction, retention and incontinence.
- Presence or absence of erections sufficient for sexual activity and use of medications or mechanical aids to enhance erections should be recorded.

Clinical discretion may be exercised to treat side effects from radiation therapy. *See section 9.2.*

6.14 Radiation Adverse Event Reporting

See Appendix III

7.0 DRUG THERAPY

Not applicable to this study

8.0 SURGERY

Not applicable to this study

9.0 OTHER THERAPY

9.1 Adjuvant Hormone Therapy

Adjuvant hormone therapy is NOT allowed on this randomized trial. The eligibility criteria for this study were chosen to exclude those patients that benefit from the use of hormone therapy in conjunction with radiation therapy. This trial is seeking to measure the effects of two fractionation schedules of radiation therapy on cancer control and toxicity.

9.2 Permitted Supportive Therapy

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.

9.2.1 Antidiarrheals

Antidiarrheals, such as loperamide hydrochloride or diphenoxylate-atropine, may be used as needed.

9.2.2 Antispasmotics

Antispasmotics, such as oxybutynin or tolterodine tartrate, may be used as needed.

9.2.3 Alpha Blockers

Alpha blockers, such as doxazosin mesylate, terazosin hydrochloride or tamsulosin hydrochloride may be used as needed.

9.2.4 Analgesics

Analgesics is a broad category, including non-narcotic and narcotic agents. The use of nonnarcotic agents, such as acetaminophen, non-steroidal anti-inflammatory agents or phenazopyridine hydrochloride for radiotherapy treatment-related pain should be documented as much as possible. Narcotic use as a consequence of treatment should also be recorded.

9.2.5 Erectile Dysfunction

Erectile dysfunction may be treated with medical management (e.g., phosphodiesterase inhibitors), vacuum pumps or other devices as appropriate. The amounts of the drug(s) used and the dates that medical management or the use of mechanical devices was started should be documented.

9.2.6 Rectal Bleeding

Grade 2-3 rectal bleeding should receive medical management for >3 months before plasma coagulation is considered. It is common for rectal bleeding to be controlled with watchful waiting and for it to resolve after 2-years following completion of therapy. Conservative medical measures such as stool softeners and anti-inflammatory agents including steroids are recommended. Laser fulguration should NOT be used.

10.0 PATHOLOGY

10.1 Biopsy at Failure

10.1.1 Biochemical failure is defined as a PSA of 2ng/ml above the current nadir. Date of failure is the date of the PSA measurement.

10.1.2 Prostate biopsy is highly recommended for all patients with:

- post-treatment residual prostate abnormality or growth of a palpable prostate abnormality.
- evidence of nodal and/or distant failure to assist in accurately determining the "true" local control rate.
- after a biochemical failure.

10.1.3 In the absence of a biopsy, such patients will be considered local failures if their exam is abnormal. If their exam is normal, or if they are on long-term androgen suppression therapy, they will be censored at the last point in time that they were considered locally controlled and not considered for further assessment of pathologic local control.

10.1.4 Prostate biopsies can be directed by radiology images such as MRI or PET.

10.1.5 Although not mandatory, prostate volume should be recorded from imaging studies at the time of failure.

10.2 Pathology Review

12 cores are preferred. If less than 6 cores, re-biopsy is strongly recommended. A local pathology review is strongly recommended for patients whose reports come from another institution.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

Assessments	Pre-Entry	Weekly During RT	End of RT	Follow-up (months)[c]								At Failure
				3	6	12	18	24	36	48	60	
History/Physical exam with DRE	X[a]			X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Medication assessment	X[a]	X	X	X	X	X	X	X	X	X	X	X
Toxicity assessment	X[a]	X	X (Arm II/ 5 fx pts only)	X	X	X	X	X	X	X	X	X
ECOG performance status	X[a]											X
Trans-rectal ultrasound with core biopsies	X[d]											
Histological evaluation	X[d]											
PSA- *at least 21 days after prostate biopsy or prior to biopsy*	X[a]		X[b]	X	X	X	X	X	X	X	X	X
CT or MRI pelvis – diagnostic (plus abdomen at time of failure)	X[e]											X
Bone scan	X[b]											X[b]
Bone x-ray or CT (*if bone scan is equivocal*)	X[b]											
Urethrogram – *recommended at time of CT simulation if no MRI is available*	X[b]											
EPIC, IPSS	X[a]			X	X	X	X	X	X	X	X	X
CT or MRI prostate/pelvis (for planning or movement)	X[e]											
Directed prostate biopsy												X[b]
Secondary Pathology review – *if from outside institution*	X[b]											
Physics consultation – *if needed for pacemaker or internal defibrillator*	X											
Fiducial markers placement	X[e]											

a. within 90 days prior to randomization
b. highly recommended
c. follow-up schedule: at 3 months; at 6 months and every 6 months x 3; yearly up to year 5; every 2 years thereafter. See SPM for additional information on follow up visit windows.
d. within 365 days prior to randomization; 12 core biopsy preferred. If less than 6, re-biopsy is strongly recommended.
e. may be done pre-or post randomization but must be done prior to treatment

11.2 Criteria for Biochemical Recurrence

11.2.1 Biochemical failure is defined as a PSA of 2ng/ml above the current nadir. Date of failure is the date of the PSA measurement.

11.3 Measurement of Effect/Response

Prostate tumor dimensions should be assessed by physical exam and recorded on the physicians' note for initial evaluation. After study entry, disease activity evaluations will be made and recorded using the following criteria.

11.3.1 No Evidence of Disease (NED): No evidence of disease on physical exam, imaging studies, or PSA.

11.3.2 Local Failure/Persistence: This rating will be assigned when:

- There is clinical evidence that the prostate gland shows disease progression or recurrence.
- Biopsy proven prostate cancer.

11.3.3 Freedom from Local Failure/Persistence: This will be one of the primary study endpoints. The time to progression will be measured from the date of the start of treatment to the date of documented local failure as determined either by clinical exam or by prostate re-biopsy.

11.3.4 Freedom from PSA Failure: Time in months from start of treatment to PSA failure. This is defined as having a PSA 2ng/ml above the current nadir. The date of failure is the date of the abnormal PSA reading.

11.3.5 Biochemical failure: At the time of PSA failure a trans-rectal ultrasound and prostate biopsies are highly recommended to correlate the true rate of local failure in patients at the time of biochemical failure. Prostate volume will be recorded to determine PSA density.

11.4 Quality of Life (QOL)

Prostate cancer-specific HRQOL (Health Related Quality of Life) as measured by the Expanded Prostate Index Composite (EPIC). The specific EPIC form used for this study is the *EPIC + SF12 and AUSI.* This form includes the required IPSS score. All data for the QOL forms are collected via Electronic Data Capture. Non-English speaking subjects are excluded from QOL requirements.

11.5 Follow-Up Visits

It is highly recommended that patients will be seen in person by the treating investigator for all follow-up visits. If however subjects refuse to return to the clinic, they must be contacted by phone or email to obtain information needed for data collection. Collaborating medical records must also be obtained including records from other treating physician exams. Any failure to contact subjects for follow-up must be clearly documented in the source record.

12.0 DATA COLLECTION

Patients must be registered through the PCG Electronic Data Capture (EDC) system. All required study information will be entered and verified in the EDC system. Detailed guidelines for patient registration and electronic Case Report Form (eCRF) completion can be found in the EDC Manual. Timelines for data submission must be followed closely in order to assure human subject safety.

The PI must make study data accessible to the Clinical Research Associate (CRA), to other authorized representatives of the study chair, and to the appropriate regulatory authority inspectors. The data in the EDC will be checked against source documents by the CRA.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint:

Freedom from failure (FFF): The events for FFF will be the first occurrence of clinical failure (local recurrence, regional recurrence, or distant metastasis), biochemical failure by the Phoenix definition (PSA ≥ 2 ng/ml over the current nadir PSA), or the start of salvage therapy including androgen deprivation. A 1-sided 95% confidence interval around the difference in 2-year FFF rate will be used to investigate the primary endpoint. We will compute a 1-sided 95% confidence interval for the difference in 2-year FFF rate between the standard and hypofractionated treatment arms using the exact (Clopper-Pearson) confidence limit. If this confidence limit falls below 4.2%, we will declare the hypofractionated RT treatment non-inferior to standard RT treatment. The interim and final analyses will be conducted when the 75th patient and last patient enrolled have been followed for 2 years. The primary analysis will include all eligible and consented patients who initiate treatment and who are not lost to follow-up before 2 years post randomization. A long-term analysis will be conducted when the last patient enrolled has been followed for 5 years. The study is designed to test whether FFF following hypofractionated radiation treatment is non-inferior compared to the standard RT treatment. To arrive at a non-inferiority margin at 2 years, we first set the non-inferiority margin to be 10% at 5 years (98% 5-year FFF rate in the standard RT treatment arm, and 88% in the hypofractionated arm). To allow for earlier analysis, we plan to conduct the FFF analysis after 2 years of follow-up, so this 5-year non-inferiority margin translates into a 4.2% non-inferiority margin at 2 years assuming exponentially distributed failure times (99.2% 2-year FFF rate in the standard RT treatment arm, and 95% in the hypofractionated arm).

13.1.2 Secondary Endpoint:

Assessment of grade 2 or higher GU and GI toxicity at 6 months and 2 years Assessment will be performed using NCI -CTCAE criteria. Descriptive measurements of frequency (maximum grade) will be compiled. Comparison of frequencies and severity between arms will be performed via chi-square tests or Fisher's exact tests dependent on statistical assumptions for analysis. A cumulative incidence approach may also be used. In such an analysis, all time variables will be defined from the start of radiation treatments to the occurrence of the event. If no event is found, the patient will be censored at the time of the analysis.

13.1.3 Exploratory Endpoints:

- Assessment of quality of life and sexual functioning
  Summation of relative scores for quality of life and sexual functioning items from the Expanded Prostate Cancer Index Composite (EPIC) instrument will

be used to measure each individual's quality of life. The total scores will be compared between arms at 2 years using analysis of covariance adjusting for baseline scores.

- Assessment of biochemical failure
  Kaplan-Meier survival analysis will be used to assess freedom from biochemical failure for the entire study population with log-rank test for comparison of arms.
- Assessment of local/distant failure
  Kaplan-Meier survival analysis will be used to assess freedom from local/distant failure for the entire study population with log-rank test for comparison of arms.
- Assessment of salvage androgen deprivation use
  Kaplan-Meier survival analysis will be used to assess salvage androgen deprivation use for the entire study population with log-rank test for comparison of arms.
- Assessment of survival (progression-free, overall and disease-specific)
  Kaplan-Meier survival analysis will be used to assess survival for the entire study population with log-rank test for comparison of arms.
- Estimation of prostate and normal structure movement
  Descriptive measures (mean, standard deviation, median, range) will be compiled for variables of interest. Norms for arms of the study will be established with 95% confidence limits of the mean on each variable of interest.
- Association of pathologic and radiologic findings with outcome
  Logistic and Cox regression techniques will be used to assess the relationship of pathologic and radiologic findings with outcomes.
- Assocation of PSA, free PSA, and testosterone levels/variation with outcomes
  Logistic and Cox regression techniques will be used to assess the relationship of PSA, free PSA, and testosterone levels/variation with outcomes.

13.2 Sample Size Determination

The study is designed to test whether FFF following hypofractionated radiation treatment is non-inferior to standard RT treatment. We will compute a 1-sided 95% confidence interval for the difference in 2-year FFF rate between the standard and hypofractionated treatment arms using the exact (Clopper-Pearson) confidence limit. If this confidence limit falls below 4.2%, we will declare the hypofractionated RT treatment non-inferior to standard RT treatment. The interim and final analyses will be conducted when the 75^{th} patient and last patient enrolled have been followed for 2 years. The primary analysis will include all eligible and consented patients who initiate treatment and who are not lost to follow-up before 2 years post randomization.

To ensure 80% power and conservatively allowing for up to 15% dropout (due to ineligibility or being lost to follow-up before 2 years post randomization), this study requires 150 patients be randomized, as computed in East v6.3. A long-term analysis will be conducted when the last patient enrolled has been followed for 5

years. We expect minimal loss to follow-up; however, in the event of significant censoring, we may employ time-to-event analysis (Kaplan-Meier and Cox regression) for point estimates, confidence intervals, and arm comparisons. The study is designed to test non-inferiority with a 2-year 4.2% margin in the difference in FFF rates between the two arms with a one sided p value = .05 and a statistical power of 0.80. Randomized allocation to each of the two treatment arms of the study was initially planned as equal (1:1 allocation). However, in order to increase accrual, after accrual of 37 patients at 1:1 allocation the randomized patient allocation scheme was changed to a 2:1 ratio in favor of treatment Arm II. Thus, a total of 150 patients (randomized at a ratio of 1.65:1 once taking into consideration the initial 1:1 ratio and subsequent 2:1 ratio) are required for accrual for 80% power and a 1-sided 95% level of significance including up to 15% dropout due to ineligibility or loss to follow-up. A total of ~57 patients will be allocated to Arm I. A total of ~94 patients will be allocated to Arm II.

This trial makes use of blocked stratified sampling, utilizing a total of 16 possible strata, with 8 strata per study arm. A total of 37 patients were enrolled into the study at the 1:1 allocation, with 19 patients allocated to Arm I, and 18 patients allocated to Arm II. Allocation on the 2:1 ratio in favor of Arm II will necessitate an additional ~75 patients allocated to Arm II, and an additional ~38 patients allocated to Arm I.

13.3 Accrual and Study Duration

It is expected that it will take approximately 5 years to complete the study enrollment. The final primary analysis can be undertaken after the last patient enrolled has been followed for 2 years. A long-term analysis will be conducted when the last patient enrolled has been followed for 5 years.

13.3.1 Early Stopping of Study

This study will incorporate statistical monitoring rules (stopping rules) to serve as guidelines for possible early termination of the trial for both non-inferiority as well as futility. A group sequential monitoring rule using the O'Brien-Fleming approach will be utilized. One interim analyses will be conducted, after 75 patients have been enrolled followed for 2 years. The final analysis will be conducted after the last patient enrolled has been followed for 2 years. The alpha level for rejection of the null hypothesis (difference in FFF rate at 2 years is greater than or equal to 4.2%) in favor of the alternate hypothesis (difference in FFF rate at 2 years is less than 4.2%) will be divided and allocated over two analyses as show in section 13.3.2.

13.3.2 Early Stopping Table

Analysis	Cumulative Patient Accrual (n) at Time of Analysis	P-value for Rejection of H_0	P-value for futility
Interim	75 (followed for 2 years)	0.006	0.363
Final	150 (followed for 2 years)	0.048	NA

13.4 Analysis Plan

13.4.1 Interim Reports

Interim reports will be reviewed by the DSMB/research staff every 6 months to 1 year until the last patient has been entered into the study. In general, the interim reports will contain information about:

- Patient accrual rate with projected completion date of the trial.
- Status of compliance rate of treatment per protocol.
- Frequencies and severity of grade 3+ toxicities, including rate of failures and deaths.

13.4.2 See Section 13.1 and 13.2 for the analysis plan for the primary and secondary endpoints.

13.4.3 Gender and Minorities

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and racial/ethnic minorities in clinical research, we will include patients of any racial/ethnic minority in our study. However, given that the prostate is a male organ, patients for this study will be male.

Based on previous accrual statistics, we project that 81% of the men in the study will be white, 15% black or African American, 3% Hispanic, 0.5% Asian, 0.3% Pacific Islander, and 0.2% American Indian or Alaskan Native.

14.0 Ethical, Regulatory and Administrative Issues

This study will be conducted in full compliance with the Institutional Review Board regulations in 21 CFR 56. This study will be conducted in full compliance with the informed consent regulations in 21 CFR 50. Only staff members who have completed human subject protection training will obtain informed consent from the study participants.

Written informed consent and authorization of use and disclosure of Protected Health Information (PHI), as applicable in the US, must be obtained from each patient before performing any Screening/Baseline evaluations that are specifically study related (outside the scope of routine care). A copy of the signed informed consent document and HIPAA authorization will be given to the patient, and the investigative site will retain either the original *or* an exact copy electronically. The consent document must contain the 20 elements of informed consent described in ICH E6 4.8. The authorization for use and disclosure of PHI must contain the elements required by 45 CFR 164.508 for valid authorizations.

14.1 Study Data Storage and Confidentiality

Raw and collected research data will be stored in locked cabinets at all times. If electronic forms are used they will be kept in a password protected format. Electronic data will be in compliance with FDA CFR Title 21 Part 11.

No study documents will be destroyed or moved to a new location without prior written approval from the sponsor. If the site investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another investigator or the institution where the study was conducted.

All information regarding the nature of the proposed investigation provided by the study chair to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the patient, or the appropriate regulatory authority) must be kept in confidence by the investigator.

The anonymity of participating patients must be maintained. Patients will be identified by their initials and assigned patient numbers in case report forms and other documents submitted off site. Documents that will not be submitted off site and that identify the patient (e.g., the signed informed consent document) must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the sponsor, or sponsor representatives.

14.2 Risk Benefit Assessment

By definition this study is determined as greater than minimal risk. Patients treated in the protocol will have the potential benefit of treatment with state of the art technologies and thorough treatment quality assurance that is not available in common clinical practice. Furthermore, potentially the patient will benefit from treatment in two arms as the trial design is for equipoise. Thus, patients may benefit from the treatment delivered, regardless of the arm. The risks of the treatment or the acute or long term side effects with this technology (proton therapy) and thorough quality treatment assurance should be lower than with conventional treatment as delivered with photon radiation in common clinical practice. However, a data safety monitoring board will review the potential harmful effects of the treatment and stopping rules are in place in the protocol.

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APPENDIX I

PERFORMANCE STATUS SCORING

ECOG PERFORMANCE SCALE

0 Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

5 Dead.

APPENDIX II
AJCC STAGING SYSTEM- PROSTATE, 7TH EDITION

DEFINITION OF TNM

Primary Tumor (T)
Clinical

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy *(e.g., because of elevated PSA)*
T2	Tumor confined within prostate*
T2a	Tumor involves one half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostate capsule**
T3a	Extracapsular extension *(unilateral or bilateral)*
T3b	Tumor invades seminal vesicle*(s)*
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.

*Note:	Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.
**Note:	Invasion into the prostatic apex or into *(but not beyond)* the prostatic capsule is classified not as T3 but as T2.

Primary Tumor
*Pathologic (pT)**

pT2	Organ confined
pT2a	Unilateral, one-half of one side or less
pT2b	Unilateral, involving more than one-half of side but not both sides
pT2c	Bilateral disease
pT3	Extraprostatic extension
pT3a	Extraprostatic extension or microscopic invasion of bladder neck**
pT3b	Seminal vesicle invasion
pT4	Invasion of rectum, levator muscles, and/or pelvic wall

*Note:	There is no pathologic T1 classification
**Note:	Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

APPENDIX II
AJCC STAGING SYSTEM- PROSTATE, 7TH EDITION (CONTINUED)

Regional Lymph Nodes (N)
Clinical

NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Regional Lymph Nodes (N)
Pathologic

pNX	Regional nodes not sampled
pN0	No positive regional nodes
pN1	Metastases in regional node(s)

*Distant Metastasis (M)**

M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node*(s)*
M1b	Bone*(s)*
M1c	Other site*(s)* with or without bone disease

*Note: When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced.

Histologic Grade (G)

Gleason X	Gleason score cannot be processed
Gleason ≤6	Well-differentiated (slight anaplasia)
Gleason 7	Moderately differentiated (moderate anaplasia)
Gleason 8-10	Poorly differentiated/undifferentiated (marked anaplasia)

APPENDIX II
AJCC STAGING SYSTEM- PROSTATE, 7TH EDITION (CONTINUED)

*Anatomic Stage/Prognostic Groups**

Group	T	N	M	PSA	Gleason
I	T1a-c	N0	M0	PSA<10	Gleason ≤6
	T2a	N0	M0	PSA<10	Gleason ≤6
	T1-2a	N0	M0	PSA X	Gleason X
IIA	T1a-c	N0	M0	PSA<20	Gleason 7
	T1a-c	N0	M0	PSA≥10<20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA ≥20	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason ≥8
III	T3a-b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

*When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available.

APPENDIX III

ADVERSE EVENT COLLECTION/REPORTING GUIDELINES

Definitions and Terminology

An adverse event (AE) is defined as any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a protocol-specified medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (e.g., attribution of unrelated, unlikely, possible, probable, or definite). This may be a new event that was not pre-existing at initiation of any protocol-specified treatment/procedure(s), a pre-existing event that recurs with increased severity or frequency subsequent to commencement of any protocol specified treatment/procedure(s), or an event though present at commencement of any protocol-specified treatment/procedure(s) becomes more severe following initiation of these treatment(s)/procedure(s). Each AE is a unique representation of a specific event used for medical documentation and scientific analysis. **For the GU002-10 protocol, only possibly, probably or definitely related adverse events are collected**.

Grading of Adverse Events

Unless specified otherwise, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 is used to grade severity of adverse events. All appropriate site personnel should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

PCG Adverse Event Data Collection Forms

All AEs can be collected on PCG's Data Collection Forms. **For the GU002-10 protocol, only those adverse events related to protocol therapy will be collected.** Contact the PCG Headquarters via telephone or e-mail with any questions concerning AE reporting and PCG AE Data Collection Forms.

SERIOUS ADVERSE EVENT REPORTING GUIDELINES

Definitions and Terminology

A Serious Adverse Event (SAE) is an adverse experience occurring during the course of the study or during planned follow-up that meets any of the following criteria:

- results in death;
- is life threatening (places the patient at immediate risk of death from the experience as it occurred);
- requires inpatient hospitalization (> 24 hours) or prolongs an existing hospitalization;
- results in persistent or significant disability/incapacity (substantial disruption of one's ability to carry out normal life functions);
- or is a congenital anomaly/birth defect.

In addition, the GU002-10 protocol also requires any possibly, probably or definitely related grade 3 and above toxicities to be reported as SAEs.

Medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. Important medical events that may not meet the strict definition of a SAE could still be significant enough to require reporting. For instance, situations that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the SAE definition above. They should also usually be considered serious.

Reporting Serious Adverse Events (SAE)

SAE reporting is safety related, separate from and in addition to data management toxicity reporting requirements on the case report form. For the GU002-10 study, investigators and other site personnel **must report all possibly, probably or definitely related SAEs within 1 business day of discovery of the event.**

SAEs should be reported on an SAE form via email to safety@pcgresearch.org. If email is unavailable, a phone call to PCG Headquarters should be made to alert that an SAE report form will be forthcoming.

It is expected that all information may not be available at the time of the initial SAE report is submitted. A follow-up report with complete information is expected within 10 days of the initial report. As new information related to the SAE is made known to the investigator, the SAE report should be updated and resubmitted to PCG Headquarters. All supporting source documentation, if requested, must be emailed to the CRA at PCG Headquarters as soon as available. SAEs will also be recorded in the PCG Electronic Data Capture system. In addition to notifying PCG, the Investigator is responsible for reporting SAEs to the IRB per their requirements.

Additional information regarding adverse events collection is available in the SPM.