Proton Collaborative Group

GU003-10 Phase III Study of Image Guided Radiation Therapy with or without Androgen Suppression for Intermediate Risk Adenocarcinoma of the Prostate

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PROTOCOL SIGNATURE PAGE

GU003-10

Phase III Study of Image Guided Radiation Therapy with or without Androgen Suppression for Intermediate Risk Adenocarcinoma of the Prostate

Protocol Version: September 22, 2016

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, OR TO THE PROTON COLLABORATIVE GROUP OFFICE

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SCHEMA

STRATIFY

T stage
T1-T2a
T2b- T2c

PSA
<10
> = 10 & < = 20

Gleason score
≤ 6
7

RANDOMIZE

Arm I: Radiation Therapy Alone
1) Conformal Proton Radiation Dose:
2.5 Gy (RBE) five days a week in 28 treatments over 5.5-6.5 weeks (total dose: 70 Gy (RBE))
2) High dose radiation with IMRT alone:
1.8 Gy five days a week in 45 treatments over 9-10 weeks (total dose: 81 Gy)
3) Intraoperative LDR brachytherapy and IMRT:
100 Gy Pad103 implant and IMRT 1.8 Gy five days a week in 25 treatments over 5-6 weeks (total dose: 45 Gy)

Arm II: Radiation Therapy and Androgen suppression for 6 Months (Androgen suppression must start 8-10 weeks prior to the start of radiation therapy)
Radiation as mentioned above **PLUS**
Androgen suppression for 6 months

Patient Population: Adenocarcinoma of the prostate with at least one intermediate risk feature including T2b or T2c, Gleason score 2-7, or a PSA 10-20 ng/ml. No high risk features such as T3, Gleason score of > 7, or PSA >20 are allowed.

Eligibility Criteria: (See Section 3.0 for complete eligibility)

- Adenocarcinoma of the prostate clinical stages T1-T2c (AJCC Criteria 7th Ed.). Histological confirmation within 365 days prior to randomization.
- Prostate Specific Antigen (PSA) values 0-20 ng/ml obtained prior to biopsy or at least 21 days after biopsy.
- Gleason score 2-7.
- No pelvic lymph nodes > 1.5 cm in greatest dimension unless the enlarged lymph node is biopsied and negative.
- No invasive cancer within 5 yrs (see section 3.2.10). 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.
- Prior androgen suppression therapy is not allowed.
- Must be able to start treatment within 56 days of registration.
- Signed study specific IRB approved Informed Consent.
- Use of a tissue spacer, rectal balloon or water between the rectum and the prostate.

Required Sample Size: 192

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].

The results for intermediate risk patients with surgery or standard dose radiation are not encouraging. Soloway et al., published the results of surgery for clinical T2b patients. The surgery alone group had a freedom from biochemical failure (FBF) of 68% at 5 years [2]. At the same time FBF was only 59% for patients with a biopsy Gleason score of 7 [3]. Hull et al., reported the multi-institutional experience of several major academic centers managing prostate cancer with surgery[4]. Freedom from biochemical failure for patients with a biopsy Gleason score of 7 was 60% at 5 years. Similarly, results from standard dose radiation are far from optimal. Kestin et al., found a FBF failure of 48% for patients with a biopsy Gleason score of 7, 37% for PSA range of 10 to 20, and 49% for clinical T2 patients treated with low dose radiation[5].Kuban et al., reported a 39% FBF for standard dose radiation (70Gy) for patients with a PSA >10 at 8 years[6].

Results with high dose radiation therapy for patients with Gleason score of 7 have been encouraging. Merrick et al. has published results of 95% FBF at 8 years[7]. Similarly, Demanes et al., have published results of 89% FBF and 96% clinical control at 5 years with high dose radiation[8].

Doses used in these brachytherapy protocols may be difficult to reach with external radiation. Brachytherapy procedures combined with external radiation yield some of the best results available, with moderate morbidity. Demanes et al., have published grade 3 or higher urinary problems in 8% of cases, including 2 cases of grade 4 toxicity (1%). Urinary incontinence was seen in 4% of cases in his study[9].

1.2 Rationale for Using Proton Radiation Therapy

Proton radiation therapy will be employed to deliver high doses safely. Using the dosimetric advantages of proton therapy, we expect to 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]. Zietman et al., phase III proton dose escalation trial showed good biochemical controls for intermediate risk patients of 87.4% at 5 years [15].

1.3 Rationale for Image Guidance

The prostate is a mobile organ in the pelvis. It is subject to movement 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 [16, 17]. Furthermore, the use of prostate fiducial markers will improve prostate positioning decreasing necessary margins for treatment [18, 19] . Image guidance approaches have been proven to be useful to limit toxicity [20, 21]. 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 [22-24]. These studies 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 [25-31]. We propose to employ high dose proton radiation for the treatment of prostate cancer patients.

1.5 Rationale for Hypofractionated Radiation Therapy

Prostate cancer has been found to have a low α/β [32-34]. 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 hypofractionated high dose rate scheme [35]. Kupelian et al., found excellent results employing a hypofractionated approach similar to the one proposed in this protocol [36]. We propose to employ a hypofractionated strategy with our image guided treatment to further improve cancer control and decrease toxicity.

1.6 The Use of Androgen Suppression

Contemporary results with high dose radiation for intermediate risk prostate cancer patients yield high biochemical control rates [36-39]. Androgen suppression has proven to improve results for high risk patients. Therefore it is possible that androgen suppression can further improve the results reported with high dose radiation alone for intermediate risk prostate cancer patients [37, 40-42] D'Amico published improved survival for a phase III trial with the use of androgen suppression and low dose radiation for a patient population comprised of both intermediate and high risk patients [43, 44]. We propose to combine short term androgen suppression to high dose radiation in a mildly hypo-fractionated approach. The RTOG 9408 study revealed a benefit with 4 months of androgen deprivation for intermediate risk prostate cancer patients.

1.7 Prioritization

Proton beam therapy should be able to deliver higher doses with acceptable chronic toxicity. Better immobilization, decreased set up error, and decreased PTV uncertainty will increase the real dose delivered to the prostate and area at risk. Furthermore, improved dose deposition with proton therapy will increase the definition of the high dose region. The treatment protocol will allow us to deliver higher doses to the prostate and areas at risk, potentially improving results while limiting toxicity. The combination of androgen suppression and radiation

therapy may have a synergistic effect further improving freedom from failure for this patient population.

2.0 OBJECTIVES

2.1 Primary Objective

To determine if androgen suppression along with high dose radiation therapy will result in a higher freedom from failure (FFF) than high dose radiation therapy without androgen suppression.

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) [45] discounting bounces per investigator discretion, or the start of salvage therapy including androgen suppression.

2.2 Secondary Objectives

2.2.1 After completion of radiation therapy, determine the incidence of:

- Grade 2 or greater GU and GI toxicity at 6 months (CTCAE Version 4)
- Quality of life issues following completion of radiation therapy
- Impotence after the use of radiation therapy at 3 years
- Freedom from biochemical failure (FFBF) at 5 years
- Clinical failure: local and/or distant at 5 years
- Salvage Androgen Deprivation use (SAD) at 5 years
- Progression free survival: using clinical, biochemical and SAD as events at 5 years
- Overall survival at 5 years
- Disease-specific survival at 5 years

2.2.2 Determine the impact of radiation therapy on quality of life at 2 years.

2.2.3 Determine GI and GU toxicity at 3 years.

2.2.4 Determine prostate and normal structure movement during RT with the use of scans.

2.2.5 Correlate pathologic and radiologic findings with outcomes at 5 years.

2.2.6 Correlate PSA and free PSA levels with outcomes at 5 years.

2.2.7 Correlate testosterone levels and variation with proton therapy and outcomes at 5 years.

2.2.8 Develop a quality assurance process for prostate proton therapy.

2.2.9 Prospectively collect information that will help to define dose-volume relationships of normal structures with acute and chronic toxicity at 3 years.

2.2.10 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.

2.2.11 Possibly 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 of randomization) at intermediate risk for reoccurence determined by at least one of the following:

Gleason Score	7
PSA	> = 10 and < = 20
T stage	T2b – T2c

3.1.2 Clinical stages T1-T2c N0 M0 as staged by the treating investigator (AJCC Criteria 7th Ed.- appendix III).

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 2-7. *> 6 cores are strongly recommended.*

3.1.4 PSA values ≤ 20 ng/ml within 90 days prior to randomization. Obtained prior to biopsy or at least 21 days after prostate biopsy.

3.1.5 ECOG performance status 0-1 (appendix II) assessed within 90 days of randomization.

3.1.6 Patients must sign IRB approved study specific informed consent.

3.1.7 Patients must complete all required pre-entry tests listed in section 4.0 within the specified time frames.

3.1.8 Patients must be able to start treatment within 56 days of randomization.

3.1.9 Patients must be at least 18 years old.

3.1.10 For brachytherapy, an IPSS ≤ 21, or ≤ 17 if the patient is on medications to improve urination.

3.1.11 For brachytherapy, prostate volume must be less than 55cc prior to AS.

3.2 Conditions for Patient Ineligibility

3.2.1 Pelvic lymph nodes > 1.5 cm in greatest dimension unless the enlarged lymph node is biopsied and negative.

3.2.2 Previous prostate cancer surgery to include: prostatectomy, hyperthermia and cryosurgery.

3.2.3 Previous pelvic radiation for prostate cancer.

3.2.4 Previous androgen suppression therapy for prostate cancer.

3.2.5 Active rectal diverticulitis, Crohn's disease affecting the rectum or ulcerative colitis (non-active diverticulitis and Crohn's disease not affecting the rectum are allowed).

3.2.6 Prior systemic chemotherapy for prostate cancer.

3.2.7 History of proximal urethral stricture requiring dilatation.

3.2.8 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 or to have a biopsy if needed).

3.2.9 Major medical, addictive or psychiatric illness which in the investigator's opinion, will prevent the consent process, completion of the treatment and/or interfere with follow-up. (Consent by legal authorized representative is not permitted for this study).

3.2.10 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).

3.2.11 History of myocardial infarction within the last 6 months.

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 radiation treatment must be completed at PCG member institutions in the United States.

4.0 PATIENT ASSESSMENTS

4.1 Study Parameters

Assessments	Pre-treatment	Weekly During RT	End of RT	Follow-Up[c]						At Failure
				3 mos	6 mos	12 mos	18 mos	Year 2 – 5 Annually	Year 7+ Every other year	
History Assessment	X[a]			X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
DRE	X[a]									X[b]
Medication Assessment	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessment (CTCAE v4)	X[a] Baseline Survey	X		X	X	X	X	X	X	X
ECOG performance status	X[a]									X
Histological evaluation	X[e]									
Directed prostate biopsy	X[e]									X[b]
EPIC, IPSS	X[a]			X	X	X	X	X	X	X
PSA *(at least 21 days after prostate biopsy OR prior to biopsy)*	X[a]		X[b]	X	X	X	X	X	X	X
CT or MRI prostate/pelvis (planning)	X[f]									
CT or MRI pelvis (diagnostic)	X[f]									X
Fiducial markers placement	X									
Bone scan	X[b]									X[b]
Urethrogram	X[d]									
Start androgren suppression	X[g]									

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. recommended at time of CT simulation if no MRI is available.
e. within 365 days prior to randomization; 12 core biopsy preferred. If less than 6, re-biopsy is strongly recommended
f. prior to radiation treatment
g. for arm II only- must start 8-10 prior to the start of proton therapy

4.2 Criteria for Biochemical Recurrence

4.2.1 Biochemical failure is defined as 2ng/ml above the current nadir discounting bounces per the investigator's discretion. Date of failure is the date of the PSA measurement.

4.3 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:

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

4.3.2 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.

4.3.3 Freedom from Local Failure/Persistence: This will be one of the secondary 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 rebiopsy.

4.3.4 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 nadir discounting bounces per the investigator's discretion. The date of failure is the date of the abnormal PSA reading.

4.3.5 Biochemical failure: At the time of PSA failure a transrectal 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.

4.4 Quality of Life (QOL)

4.4.1 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 patients are excluded from the QOL requirements of the protocol.

4.5 Follow-Up

4.5.1 Patients will be followed unless the study is terminated by the Study Chair. 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.

5.0 REGISTRATION / RANDOMIZATION

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 on the PCG website

(http://pcgresearch.org, PCG Member Portal) may be used to document eligibility and place 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 randomized through the PCG Electronic Data Capture (EDC) system. Patients can be randomized only after eligibility criteria are met.

5.5 The initial 3 cases from the institution will be centrally reviewed by a PCG Medical Physicist and the Study Chair or designee prior to start of treatment. *Further cases from the institution will also be reviewed periodically for quality assurance. See the Study Procedures Manual (SPM) for details.*

6.0 RADIATION THERAPY

NOTE: Radiation protocol treatment must begin within 56 days after randomization for arm 1 and 8-10 weeks after starting LHRH agonist treatment in arm 2.

6.1 Radiation Dose and Volumes for Proton Therapy

6.1.1 Total dose for proton therapy alone will be 70 Gy (RBE) in 2.5 Gy (RBE) treatments over 5.5-6.5 weeks. The prescription dose is the minimum dose to 95% of the planning target volume and a minimum dose of 90%.

6.1.2 Volumes are as follows for proton therapy **with** a rectal balloon and with or without a tissue spacer:

CTV 1= Prostate + proximal seminal vesicle
PTV 1= 2mm posterior and 3mm elsewhere
PTV eval (OTV) – PTV1 and 5mm Left and Right (if lateral beams or follow beam orientation)

6.1.3 Volumes are as follows for proton therapy **without** a rectal balloon and with or without a tissue spacer:

CTV 1= Prostate + proximal seminal vesicles
PTV 1= 5mm posterior and 6mm elsewhere
PTV eval (OTV) – PTV1 and 2mm Left and Right (if lateral beams or follow beam orientation)

6.2 Radiation Dose and Volumes for IMRT/Photon Therapy

6.2.1 Total dose for photon therapy alone will be 81 Gy in 1.8 Gy treatments over 9 weeks. The prescription dose is the minimum dose to 95% of the planning target volume and a minimum dose of 90%.

6.2.2 Volumes are as follows for photon therapy with a rectal balloon (with or without a tissue expander):

Field 45 Gy:

CTV 1= Prostate + proximal seminal vesicle
PTV 1= 2mm-3mm posterior and 3-4mm elsewhere

Field 36 Gy

CTV 2= Prostate + Gross disease
PTV 1= CTV 2mm-3mm posterior and 3mm-4mm elsewhere

6.3 Radiation Dose and Volumes for Brachytherapy and IMRT/Photon Therapy

6.3.1 The total dose for the IMRT part will be 45 Gy in 1.8 Gy fractions. The prescription dose is the minimum dose to 95% of the planning target volume and a minimum dose of 90%.

6.3.2 Prescription for real time LDR brachytherapy will be prostate D90 of 100Gy.

6.3.3 Volumes are as follows for brachytherapy and photon therapy with a rectal balloon (with or without tissue expander):

Field 45 Gy:

CTV 1= Prostate + proximal seminal vesicles
PTV 1= CTV 2mm posterior and 3mm elsewhere

Brachytherapy:

Prostate D90 of 100Gy

6.4 Equipment and Physical Factors

6.4.1 Radiation will be delivered using the available radiation equipment. Non-opposed 5-7 field IMRT arrangement is recommended for IMRT (if used) and opposed lateral oblique fields are recommended for the proton component (also see section 6.11.2). However, different field arrangements or number of fields can be used as required for optimal PTV coverage.

6.5 Localization Simulation and Immobilization

6.5.1 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 $\leq$ 2mm cuts through the region of interest (prostate and seminal vesicles), 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. T2 sequence 3D with a $\leq$ 2mm spacing is recommended.

6.5.2 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).

6.5.3 Immobilization: Patients will be immobilized for the treatment in a supine position, using an appropriate customized immobilization device. An inflatable rectal probe may be inserted to displace the posterior rectal wall from the radiation beam and immobilizing the prostate. One hundred (100) cc of saline 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.

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

6.5.5 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.

6.5.6 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.

6.6 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 recommended.

Orthogonal x-rays: Orthogonal images (kV images) are recommended for prostate-position correction. X-rays in the beam orientation are recommended. Inter-beam position verification will be done as described before.

6.7 Error Verification

6.7.1 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.

6.7.2 3D volumetric guidance: Cone beam CT, CT on rails, MRI, ultrasound or any other means of guidance can be employed. Image guidance with fiducial markers are required to participate in the study.

6.8 Dose Calculations

6.8.1 Tumor doses will be 1.8 to 2.5 Gy/Gy (RBE) given usually once a day five to six 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. LDR dose would be 100Gy to the prostate D90.

6.8.2 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 3 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.

6.9 Critical Normal Structures

6.9.1 Clinical Target Volume. CTV is the prostate and seminal vesicles 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 prostate volumes. 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 prostate volumes. 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.

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

6.9.3 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.

6.9.4 Rectal wall: is defined inferiorly from the ischial tuberosities and superiorly 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.

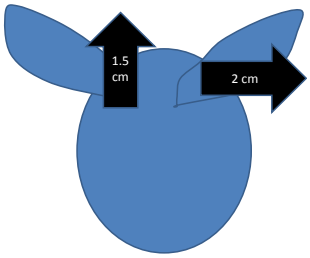
6.9.5 Bladder: should be contoured in its entirety. The wall is defined using a 3 mm contraction on the external bladder contour.

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

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

6.9.8 Rectal wall high dose: The portion of the rectal wall is within the PTV.

6.9.9 Seminal vesicle: For either CT or MRI, the seminal vesicles will include the proximal 1.5cm superiorly and the most medial 2 cm. Both distances will be defined based on the location of the prostate-seminal vesicle junction.



6.10 Normal Tissue Constraints (NTC)

6.10.1 Normal tissue constraints (NTC) to define dose.

Table 2a: **Proton Therapy**

Structure	Constraint	Minor deviation	Major deviation
Rectum	V44 <35%	V44 <40%	V44 ≥ 40%
	V60 <15%	V60 <20%	V60 ≥ 20%
Bladder	V71 <8cc	V71 <12cc	V71 ≥ 12cc
Femoral heads	V40 <1 cc	V40 <2 cc	V40 ≥ 2cc
PTV	Min dose PTV	99.5% >66.5 Gy(RBE)	
PTV eval	PTV Coverage	95% to 70 Gy (RBE)	

Table 2b: **IMRT/Photon Therapy Alone**

Structure	Constraint	Minor deviation	Major deviation
Rectum	V70 <10%	V70 >10%	V70 >20%
	Max < V105%		V106 >1cc
Bladder	V70 <10%	V70 <12%	V70 >20%
	Max <V105%		V106 >1cc
Femoral heads	Max <V55 Gy		>V55 max point
PTV	Min dose PTV ≥90%		Min dose PTV ≤90%
PTV	V100 95-97%		V100 <94% or ≥100%
PTV	V100 <110%		V100 >110%

Table 2c: **IMRT/Photon Therapy and Brachytherapy**

Structure	**Constraint**	**Minor deviation**	**Major deviation**
Rectum	V40 <10%	V40 >10%	V40 >20%
	Max <V105%		V106 >1cc
Bladder	V40 <10%	V40 <12%	V40 > 20%
	V105% <1cc		V106 >1cc
Femoral heads	Max <V55 Gy		≥V55 max point
PTV	Min dose PTV ≥90%		Min dose PTV ≤90%
PTV	V100 95-97%		V100 <94% or ≥100%
PTV	V100 <110%		V100 >110%

Table 2d: **Real Time LDR Brachytherapy**

Structure	**Constraint**	**Minor deviation**	**Major deviation**
Rectum	V100 <1cc		V100 >2cc
Prostate D90	>90%		D90<85%

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 dmax <55 Gy.

6.10.2 Doses will be adjusted employing normal tissue constraints and a minimum of 90% of the initial prescription can be used for treatment. The maximum dose without a major deviation will be used for treatment.

6.10.3 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.

6.11 Proton Planning

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

6.11.2 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.

6.11.3 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.

6.11.4 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.

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

6.11.6 Smearing: PTV will be smeared 1.2cm.

6.12 Quality Assurance (Physics check)

6.12.1 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).

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

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

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

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

6.12.6 **Beam characteristics.** 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.

6.13 Proton Unavailability

For subjects treated with proton radiation, if proton beam therapy is not available, photon therapy may be used at the discretion of the treating physician for not more than 7 treatments of 2.5 Gy (17.5 Gy). If more than 7 treatments of photon therapy is required, the subject will be withdrawn from the protocol.

6.14 Treatment Interruptions

Proton radiation treatment should be delivered for 28 treatments over 5.5 -6.5 weeks. Total treatment time >10 weeks is considered a major deviation and is not accepted in the protocol. If treatment interruption is not of medical necessity, arrangements for IMRT photon therapy should be made. IMRT alone should be delivered for 45 treatments over 9-10 weeks. Brachytherapy with IMRT should be delivered for 25 treatments over 5-6 weeks. Unplanned interruptions, consecutive or not, for more than 5 treatment days (Monday – Friday) are not allowed. Treatment breaks of 4 days are acceptable (i.e. Friday-Monday). Treatment breaks ≥5 treatment days are considered major deviations and are not accepted.

6.15 Radiation Toxicity

The Common Toxicity 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 9.1*

6.16 Radiation Adverse Event Reporting

See Appendix III

7.0 DRUG THERAPY

7.1 Dose Definition

Androgen suppression (AS), will be administered to patients randomized to arm 2. AS will begin 8 – 10 weeks prior to the start of RT for a total of 6 (+/- 2) months. Luteinizing Hormone–Releasing Hormone (LHRH) agonist therapy will consist of analogs approved by the FDA (or by Health Canada for Canadian institutions) e.g. leuprolide, goserelin, buserelin, or triptorelin and may be given in different combination such that the total LHRH treatment time is 6 months (+/- 2 months). For example, LHRH agonist injection(s) may be given as a single 4-month injection, a 4-month injection and one to two 1-month injection(s), two 3-month injections, one to three 1-month and a 3-month injection (4-6 months total), four to six 1-month injections, or a 6-month injection.

7.1.1 Duration of treatment

As outlined above, AS, for arm 2, will be for a duration of 6 months (+/- 2 months). RT will start 8-10 weeks after AS. AS will have a total duration between 4-8 months. AS total duration shorter than 4 months or longer than 8 months is not allowed in the protocol.

7.1.2 The use of concurrent anti-androgen medications such as bicalutamide (Casodex) or flutamide (Eulexin) is allowed but not recommended.

7.1.3 Calcium and Vitamin D supplementation

Patients who are randomized to receive androgen suppression therapy are encouraged to take calcium at 500-1200 mg/day and vitamin D at 400-800 IU/day during androgen suppression therapy; however, these supplements are not required.

7.2 Study Agents: LHRH Agonists

7.2.1 Description

LHRH agonists are long-acting analogs of the native LHRH peptide and are effective at reducing serum testosterone. Analogs approved by the FDA (or by Health Canada for Canadian institutions) can be used in this study.

7.2.2 Administration

LHRH analogs are administered with a variety of techniques, including subcutaneous insertion of a solid plug in the abdominal wall (Zoladex), intramuscular injection (Lupron), subcutaneous injection (Eligard), or insertion of a long-acting cylinder that slowly releases the agent (Viadur). The manufacturer's instructions should be followed.

7.2.3 Adverse Events

Consult the package insert for comprehensive toxicity information. Class-related toxicity is generally a manifestation of the mechanism of action and related to low testosterone levels. In the majority of patients testosterone levels increase above normal in the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. The most common side effect of LHRH analogs is vasomotor hot flashes; weight gain, edema, bone pain, thrombosis, and gastrointestinal disturbances can occur. Other side effects include impotence and loss of libido, depression, dizziness, loss of bone density, anemia, increased thirst and urination, unusual taste in the mouth, skin redness or hives, pain at injection site, muscle mass and strength loss, hair changes, penile length and testicular volume loss, increased cholesterol, hypertension, diabetes exacerbation, emotional lability, nausea, vomiting, and rarely allergic generalized rash and difficulty breathing.

7.2.4 Storage

LHRH analogs should be stored as directed by the commercial supplier.

7.2.5 Supply

Commercially available. (NOTE: Buserelin is not commercially available in the United States. It is commercially available for use in Canada and other countries outside of the United States).

7.3 Drug Accountability

Total duration of treatment must be recorded. Drugs are commercially available and will not be supplied for this study by the sponsor. Follow institutional policy for drug accountability of commercial drugs.

7.4 Criteria for Discontinuation of Protocol Treatment

Protocol treatment may be discontinued for any of the following reasons:

- Progression of disease
- Unacceptable adverse events at the discretion of the treating physician(s)
- A delay in beginning protocol treatment > 56 days
- Use of photon therapy for greater than 7 treatments (if receiving proton therapy)

- Decision to continue LHRH /androgen therapy for greater than 8 months

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 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.

9.1.1 Antidiarrheals

Antidiarrheals, such as loperamide hydrochloride or diphenoxylate-atropine, may be used as needed. The amounts of the drug(s) and dates used should be documented as much as possible.

9.1.2 Antispasmotics

Antispasmotics, such as oxybutynin or tolterodine tartrate, may be used as needed. The amounts of the drug(s) and dates used should be documented as much as possible.

9.1.3 Alpha Blockers

Alpha blockers, such as doxazosin mesylate, terazosin hydrochloride or tamsulosin hydrochloride may be used as needed. The amounts of the drug(s) and dates used should be documented as much as possible.

9.1.4 Analgesics

Analgesics is a broad category, including non-narcotic and narcotic agents. The use of non-narcotic 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.

9.1.5 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.

9.1.6 Rectal Bleeding

Grade 2-3 rectal bleeding should receive medical management for >3 months before plasma coagulation is considered. **Laser fulguration should not be used.**

10.0 TISSUE/SPECIMEN SUBMISSION

10.1 Biopsy Failure

10.1.1 Biochemical failure is defined as 2ng/ml above the current nadir discounting bounces per the investigators discretion. Date of failure is the first date of the elevated 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 Prostate volume will be recorded from imaging studies at the time of failure.

10.2 Pathology Review

12 cores are recommended. 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.

11.0 DATA COLLECTION

Patients must be registered and randomized 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 randomization and electronic case form (eCRF) completion can be found in the Study Procedures 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 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.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Endpoints

12.1.1 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 $\geq$ 2 ng/ml over the current nadir PSA)[45] discounting bounces per investigator discretion, or the start of salvage

therapy including androgen suppression. A log-rank test will be used to investigate the primary endpoint.

12.1.2 Secondary Endpoints:

- Assessment of grade 2 or higher GU and GI toxicity at 6 months.
  Assessment will be performed using NCI-CTCAE version 4 criteria. Descriptive measurements of frequency will be compiled. Comparison of frequencies and severity between group arms will be performed via chi-square tests or Fisher's exact tests dependent on statistical assumptions for analysis.
- Assessment of GI and GU toxicity at 3 years.
  Assessment will be performed using NCI-CTCAE version 4 criteria. Descriptive measurements of frequency will be compiled. Comparison of frequencies and severity between group arms will be performed via chi-square tests or Fisher's exact tests dependent on statistical assumptions for analysis.
- Assessment of biochemical failure.
  Kaplan-Meier survival analysis will be used to assess freedom from biochemical failure for entire study population with log-rank test for comparison of strata and group arms.
- Assessment of local/distant failure.
  Kaplan-Meier survival analysis will be used to assess freedom from local/distant failure for entire study population with log-rank test for comparison of strata and group arms.
- Assessment of distant metastasis.
  Descriptive measurements of frequency will be compiled. Comparison of frequencies and severity between group arms will be performed via chi-square tests or Fisher's exact tests dependent on statistical assumptions for analysis.
- Assessment of quality of life.
  Summation of relative scores for quality of life 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 group arms using t-tests or Mann Whitney U tests depending on the distribution of the data.
- Assessment of impotence.
  Summation of relative scores for sexual function items (items 31 through 39) 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 group arms using t-tests or Mann Whitney U tests depending on the distribution of the data.
- Assessment of salvage androgen suppression use.
  Kaplan-Meier survival analysis will be used to assess salvage androgen deprivation use for entire study population with log-rank test for comparison of strata and group arms.
- Assessment of survival (overall, progression-free and disease-free).
  Kaplan-Meier survival analysis will be used to assess survival for entire study population with log-rank test for comparison of strata and group arms.
- Development of quality assurance process for prostate proton therapy.

Descriptive measures as well as Cox regression techniques will be implemented to track process quality.

- Correlation of PSA, free PSA, and Testosterone levels/variation with outcomes. Rank-Biserial correlation will be used to assess relationships between dichotomous and ordinal (ranked by severity) outcomes.
- Correlation of pathologic and radiologic findings with outcome. Pearson's correlation will be performed for continuous and dichotomous bi-variate analysis. Spearman's rank order correlation will be performed on non-parametric distributed or ordinal measures. Cox regression techniques will be performed with outcome regressed onto variables of interest.
- 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.
- Define dose volume relationship of normal structures with toxicity. Descriptive measurements of frequency will be compiled. Comparison of frequencies and severity between group arms will be performed via chi-square tests or Fisher's exact tests dependent on statistical assumptions for analysis.
- Potentially, future research of pathologic risk factors.
- Possible comparison of an IMRT plan with the proton therapy radiation plan.

12.2 Sample Size Determination

The phase III study is designed to test whether the 5-year FF following radiation treatment is superior for radiation and androgen suppression. The sample size is determined to be able to detect a difference of 15% between the two arms. The expected 5-year FF for the radiation alone arm at 5-years is 80% and 95% for the androgen supression arm. Thus, 162 patients are required for accrual within 4 years for a 0.80 power and a 95% confidence. Considering 10% ineligible cases and/or lack-of-data, the total sample size needed is 179 patients.

This trial makes use of blocked stratified sampling, utilizing a total of eight stratum, with four strata per study arm, in two study arms. An even distribution of patients over the eight strata with random blocking of the two treatments in each stratum requires an increase in sample size to $N = 192$ patients. Ninety-six patients will be allocated to each of the two study arms.

Six blocks in each of the eight stratum will contain four randomly assigned patients each. Thus, a total of 192 patients will be enrolled and randomized for study. If ≥ 29 failure events are found in either arm, the trial will be stopped since the projected maximum failure rate for either arm is >30%.

12.3 Accrual and Study Duration

It is expected that it will take approximately five years to complete the study enrollment. The analysis for Freedom from failure will be carried out at a median follow up of 5 years as defined in section 12.2.

12.3.1 Early Stopping of Study

Guidelines for possible early termination of the trial: A group sequential monitoring rule using the O'Brien-Fleming approach will be utilized. A total of three interim analyses will be conducted,the first at the accrual of 96 patients into the study, the second at the accrual of 144 patients into the study and the final at the accrual of 192 patients and a median of 5 years of follow up. The alpha level for rejection of the null hypothesis of equivalent treatments will be divided and allocated over the two interim analyses and final analysis as shown in section 12.3.2. The final analysis will be done at a median follow up of 5 years.

12.3.2 Early Stopping Table

Interim Analysis Number	**Cumulative Patient Accrual (n) at Time of Interim Analysis**	**Critical Value (Z-statistic) for Rejection of H_0**	**α for Rejection of H_0**
1	96	3.438	0.0006
2	144	2.431	0.0151
Final	192	1.985	0.0471

12.4 Analysis Plan

12.4.1 Interim Reports

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

- Patient accrual rate with projected completion date of the trial.
- Status of compliance of treatment per protocol.
- Frequencies and severity of grade 4+ toxicities, including deaths.

12.4.2 Analysis of Severe Late Toxicity

For reporting, the highest toxicity for any patient will be used for the analysis and dated at the time of occurrence. A cumulative incidence approach will be used as well as specific time cut-offs. A potential minimum of 1 year of follow up is required for all cases. 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.

12.4.3 Estimation of Secondary Endpoints Related to the Efficacy

Outcome endpoints will be analyzed with the use of a cumulative incidence approach.

12.5 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 the preponderance of patients 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.

13.0 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 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). One copy of the signed informed consent document and authorization will be given to the patient, and the investigative site will retain the original document. (If original consent is electronically saved it must be a verified copy of the original). 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.

13.1 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 folder in a password protected form. 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 CRFs 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 CRA, or sponsor representatives.

13.2 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 if the treatment is delivered regardless of the arm. The risks of the treatment or the acute or long term side effects with tight margins, MRI registration, image guidance and thorough quality treatment assurance should be lower than with conventional treatment as delivered 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

ECOG PERFORMANCE SCALE

0 Fully active, able to carry on all predisease 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, Clinical (T)

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).

Regional Lymph Nodes Clinical (N)

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

Regional Lymph Nodes, Pathologic (N)

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 with 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)

Anatomic Stage/Prognostic Groups (Clinical & Pathologic)

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 REPORTING

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 GU003-10 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

Reporting Adverse Events
Adverse Event collection is included in PCG's Electronic Data Capture (EDC) system for the GU003-10 protocol. Additional information regarding data entry can be found in the Study Procedures Manual.

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.

For the GU003-10 protocol, ONLY SAE's possibly, probably or definitely related to protocol therapy are collected. ***In addition, the GU003-10 protocol also requires all protocol 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 GU003-10 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 event collection is available in the SPM.