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A Phase II Trial of Hypofractionated Radiation Therapy for Prostate Cancer with High Risk Features after Radical Prostatectomy

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Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, protocol document, consent form, regulatory issues, forms completion and submission	Rad Onc Study Coordinator

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List of Abbreviations

3DCRT	3-D Conformal Radiation Therapy
AE	Adverse Event/Adverse Experience
AS	Androgen Suppression
CBCT	Cone Bean CT
CFR	Code of Federal Regulations
CRF	Case Report Form
CTV	Clinical Target Volume
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IBTR	Ipsilateral breast tumor recurrence
IMRT	Intensity Modulated Radiation Therapy
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
OAR	Organs At Risk
PHI	Protected Health Information
PI	Principal Investigator
PTV	Planning Target Volume
QOL	Quality of Life
RBE	Relative biologic effectiveness
RT	Radiation Therapy
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
XRT	X-ray Radiation Therapy

SCHEMA

SCHEMA

Group I : Adjuvant radiation
PSA <0.2 ng/ml and patients must have one of the following: + margins, ECE, or SVI.

Group II : Salvage radiation (prostate bed)
PSA ≥0.2-<2

Group III : Salvage radiation (metastatic)
PET positive pelvic or abdominal LN or bone lesions

S T R A T I F Y

Conformal Radiation

Group I:

Adjuvant: Dose: 30 Gy (RBE); 6 Gy (RBE) in 5 treatments >36 hours apart over 2 weeks.

Group II:

Salvage: Dose: 32 Gy (RBE); 6.4 Gy (RBE) in 5 treatments >36 hours apart over 2 weeks. AS x 6 months

Group III:

PET + disease: A maximum of three targets can be treated (plus the prostatic fossa, if clinically indicated). Only pelvic or abdominal LN or bone lesions. AS x 18 months
Dose to prostatic fossa (): Dose: 32 Gy (RBE); 6.4 Gy (RBE) in 5 treatments >36 hours apart over 2 weeks with AS x 18 months.

Dose to pelvic or abdominal LN metastases: Dose: 30 Gy (RBE); 6 Gy (RBE) in 5 treatments >36 hours apart over 2 weeks with AS x 18 months.

Dose to bone metastases: Dose: 20 Gy (RBE) in 1 treatment with AS x 18 months.

Patient Population: Adenocarcinoma of the prostate after radical prostatectomy with one or more high risk features including seminal vesicle invasion, extracapsular extension, positive margins, and a PSA ≥0.2 and <2 ng/ml.

Eligibility Criteria:

Note: The list below is for screening only. See Section 3.0 for complete eligibility.

- Adenocarcinoma of the prostate pathologic stages pT2-T3b, N0-N1,Nx, M0-1 (AJCC Criteria 8th Ed.).
- For PSA <0.2 ng/ml,patients must have one of the following: + margins, ECE, or SVI.
- Gleason score 2-10.
- No history of non-prostatic invasive cancer within 5 yrs (see section 3.2.10). Cutaneous basal cell or squamous cell carcinomas are permitted.
- ECOG performance status of 0-2.
- No previous pelvic radiation or systemic chemotherapy for prostate cancer.
- Prior androgen suppression therapy is allowed if the total duration is less than 6 months.
- Must be able to start treatment within 120 days of registration.
- Signed study specific IRB approved Informed Consent.
- International Prostate Symptom Score (IPSS) ≤25.

1.0 BACKGROUND

1.1 Hypofractionated Treatment

In several phase 3 randomized trials, radiation after radical prostatectomy with or without androgen suppression had improved overall survival or progression free survival for patients with one or more high risk features including seminal vesicle invasion, extracapsular extension, positive margins, and a PSA ≥0.2 and <2 ng/ml. However, these studies have employed standard fractionation delivered over 6-7 weeks. [1-5] The relatively long duration of this treatment limits access to care and strains the system by increasing radiation utilization. Furthermore, Brenner and Hall have postulated that relatively high doses of radiation were necessary to maximize tumor control with standard fractionation.[6] Similar to treatment for adenocarcinoma of the intact prostate, higher doses in the postprostatectomy setting have been associated with improved outcomes.[7,8] In order to deliver higher biologic equivalent dose (BED) and increase access to care, treatment could be delivered over five visits by employing stereotactic body radiation therapy (SBRT). SBRT is a highly precise technique that delivers a higher BED to the target while minimizing doses to the organs at risk. This improvement in the in the therapeutic windown is possible due to the low α/β of prostate cancer in relation to the surrounding tissue. This treatment approach is extremely attractive since fewer fractions with higher BED can decrease radiation equipment utilization, improve access to care, increase patient convenience, and potentially improve cancer outcomes.

Several randomized trials have tested hypofractioned regimens based on the low α/β of prostate cancer.[9-16] These randomized trials compared moderate hypofractionation employing doses of 2.4-3.4 Gy vs. standard fractions of 1.8-2.0 Gy per fraction and have demonstrated the safety of this approach. In the same manner, a hypofractionated approach after surgery can allow for faster treatment delivery while delivering biologically lower doses to normal tissue.

For this study, we propose an SBRT hypofractionated approach to post-prostatectomy radiation treatment. Based on the proposed α/β of 1.5 for prostate cancer, 32 Gy in 6.4 Gy fractions (5 treatments) would be dose equivalent to 72 Gy in 2.0 Gy fractions (36 treatments). At the same time, due to the lower α/β of prostate cancer compared to normal tissue, lower equivalent doses can be delivered to the rectum and bladder. In this case, based on an α/β of 3.5 for normal tissue, a biological dose of only 58 Gy would be delivered to the portions of rectum and bladder

receiving full dose. Thus, a relative benefit of 14 Gy would be seen compared to normal fractionation. The proposed normal tissue α/β of 3.5 Gy is well-documented in the literature [17-19] and supported by the results of several hypofractionation trials.[9-16] This study attempts to demonstrate the safety of hypofractionation for prostate cancer with high risk features after surgery.

Biologic considerations

On the basis of published data, 32 Gy RBE in 5 treatments is equivalent to 72 Gy RBE in 2 Gy fractions.[18,20,21] If the α/β of normal tissue >1.5 Gy, the resulting BED to the normal tissue will be lower than the dose delivered with standard fractionation. Consequently, toxicity should be lower; the opposite should also be true. We feel conformable with the selected dose of 32 Gy given that (1) it is a lower dose than our experience with 38 Gy in 7.6 Gy fractions for intact prostate cancer, (2) clinical data is available for the fractionation, and (3) it is supported by the available literature.[16,22]

Rationale for the dose employed

The effect of hypofractionation on cancer and normal tissue as predicted by Brenner and Hall [6] applies equally for treating intact prostate tumors or recurrences within the prostatic fossa. Brenner and Hall's predictions have been verified by multiple randomized trials of moderate and SBRT hypofractionated schedules that have shown low rates of adverse events.[9-16] Based on the clinical data from these trials, the linear quadratic equation can be tailored to determine the dose equivalent over 5 treatments.

Dose fractionation has been studying extensively in attempts to maximize the therapeutic window treating prostate cancer with radiotherapy. Since the α/β for prostate cancer has been defined at approximately 1.5, hypofractionated regimens can deliver high biologic doses to the target relative to the surrounding normal tissue. As can be seen in the table below, the clinical data fit very well for a α/β of 1.5 for tumor control and 3.5 for OAR. This is also similar to the data from the European Institute of Oncology, where they reported on the results of 34 consecutive cases treated to primary and or oligometastatic disease. They delivered a dose of 30 Gy in 5 fractions to the prostatic fossa, 33 Gy in 3 fractions to at-risk lymph node regions, and 36 Gy to the oligometastatic bone lesions. The analysis ''per treatment site'' showed that all treatments for metastatic lesions (100%) were free of acute toxicity, with high rates of freedom

from toxicity for lymph node (94%) and anastomosis treatments (75%).[23]

SBRT treatment to spine or extra-axial bone lesions has been very successful with very low toxicity and excellent outcomes.[24-27] Single fraction doses of 20 Gy or higher frequently have been used successfully.[24-27]

Treatment of lymph node metastasis from prostate cancer with SBRT has been found to be safe and efficacious.[26-32] Interestingly, in a paper from Ost et al, they found that the predominant pattern of failure for prostate cancer nodal disease was still oligometastatic usually within a nodal region.[28] SBRT can often be offered again in the future for these patients who continue to have a low burden of oligometastatic disease. In order to account for this observation, we would mandate the use of AS for 18 months for patients with nodal metastatic disease treated on this protocol, which should decrease the number of events and allow for subsequent SBRT treatment for patients that presented with localized failure within a nodal region or bone.

Equivalent doses for different hypofractionated prostate studies

Trial	Author	Arm	Dose	N	Fx	Per week	Weeks	Tumor EQD2	OAR EQD2
Italian	**Arcangeli**	1.0	80.0	40.0	2.0	5.0	8.0	80.0	80.0
		2.0	62.0	20.0	3.1	5.0	4.0	81.5	74.4
CHHip	**Dearnaley**	1.0	74.0	37.0	2.0	5.0	7.4	74.0	74.0
		2.0	60.0	20.0	3.0	5.0	4.0	77.1	70.9
		3.0	57.0	19.0	3.0	5.0	3.8	73.3	67.4
HYPRO	**Aluwini**	1.0	78.0	39.0	2.0	5.0	7.8	78.0	78.0
		2.0	64.6	19.0	3.4	3.0	6.3	90.4	81.0
Fox Chase	**Pollack**	1.0	76.0	38.0	2.0	5.0	7.6	76.0	76.0
		2.0	70.2	26.0	2.7	5.0	5.2	84.2	79.1
MDACC	**Hoffman**	1.0	75.6	42.0	1.8	5.0	8.4	71.3	72.9
		2.0	72.0	30.0	2.4	5.0	6.0	80.2	77.2
Ontario	**Lukka**	1.0	64.0	32.0	2.0	5.0	6.4	64.0	64.0
		2.0	52.5	20.0	2.6	5.0	4.0	61.9	58.5
Australia	**Yeoh**	1.0	64.0	32.0	2.0	5.0	6.4	64.0	64.0

			2.0	55.0	20.0	2.8	5.0	4.0	66.8	62.5
PCG GU002	**Vargas**		1.0	79.2	44.0	1.8	5.0	8.8	74.7	76.3
			2.0	38.0	5.0	7.6	5.0	1.0	98.8	76.7
Duke	**Lewis**			65	26	2.5	5.0	5.2	74.3	70.9
Proposed		P. Fossa (salvage)		32.0	5.0	6.4	5.0	1-2	72.2	57.6
		P. Fossa (adjuvant		30	5	6	5	1-2	64.3	51.8
		LN		30	6	6.0	5.0	1.0	64.3	51.8
		Bone		20	1	20	1.0	1.0	NA	NA

Prostate fossa

The primary endpoint of this study would be freedom from failure at 5years. Based on the failure definition used in the SWOG, EORTC 22991, ARRO, RTOG 9601, and GETUG AFU 16 a PSA of 0.5 ng/ml or above would be used. [1-5] SWOG 8794 reported a freedrom from failure of 75% with adjuvant radiation at 5-years. They defined PSA failure as a PSA of 0.5 ng/ml or higher for patients with an undetectable PSA. [3,33] The RTOG 9601 study in general used a PSA failure definition of a raise of 0.3ng/ml above the nadir.[5] GETUG AFU-16 defined a PSA failure as a PSA of 0.5ng/ml above nadir, and the 5-year freedom from failure was 80%.[4] Based on the results of the randomized studies mentioned before we selected a PSA cut off of 0.5ng/ml to define failure, any local or distant failure or the re-initiation or initiation of salvage AS.

Ost and others pooled individual patient data from different institutions treating oligometastatic prostate cancer. For patients that present with oligometastatic disesase the 5-year freedrom from failure was 20% in this publication.[29] We will use the same definition of a PSA of 0.5ng/ml or higher, clinically progressive disease, or the re-start of androgen suppression.

Summary

Multiple clinical trials as detailed in the table above support the role of hypofractionation for prostate cancer. Although the biologic principles governing the role of hypofractionation for prostate cancer remain the same for an intact prostate or after a radical prostatectomy, the use of hypofractionation after a radical prostatectomy remains experimental. The current study attempts to address a crucial need: to define the role of hypofractionation for prostate cancer after radical

prostatectomy. The current study would be able to determine, with an acceptable upper bound confidence interval, freedom from failure rates for patients who receive hypofractionated radiation after a radical prostatectomy. Exploratory objectives include chronic/late toxicity, among others (see section 2.2). Late toxicity rates in the current study should be lower than published rates for a more protracted fractionation, as biologic equivalent doses delivered to organs at risk in the current hypofractionated study are lower than those employed with standard protracted fractionation.

2.0 GOALS

2.1 Primary Objective

To determine if SBRT would result in similar freedom from failure (FFF) than standard fractionation photon therapy.

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 (PSA ≥ 0.5 ng/ml over the current nadir PSA), or the start/re-start of salvage therapy including androgen suppression.

2.2 Exploratory 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)
- Grade 3 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.
2.2.3 Determine overall GI and GU toxicity.
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.
2.2.6 Correlate pre-RT PSA levels with outcomes.
2.2.7 Correlate variation in proton therapy or x-ray dosimetry and outcomes.
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.

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 prostate cancer with high risk features after prostatectomy and their potential effect on outcomes.

2.2.11 Possibly compare dosimetric parameters of 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 at the time of surgery

3.1.2 Pathologic stages T2-T3b, N0-Nx-N1, M0-1 as staged by the pathology report (AJCC Criteria 8th Ed.- appendix II).

3.1.3 One or more high risk features including: seminal vesicle invasion, extracapsular extension, positive margins, or a PSA post surgery between 0.2 and <2.0

3.1.4 PSA values < 2 ng/ml within 90 days prior to enrollment. Obtained at least 6 weeks after surgery.

3.1.5 ECOG performance status 0-2 (appendix II) assessed within 90 days of enrollment.

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 (AS or radiation) within 120 days of study registration.

3.1.9 Patients must be at least 18 years old.

3.2 Conditions for Patient Ineligibility

3.2.3 Previous pelvic radiation.

3.2.4 Prior androgen suppression therapy for prostate cancer for more than 6 months

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, to have a biopsy if needed, or place markers).

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 or decompensated CHF 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.

4.0 TEST SCHEDULE

4.1 Study Parameters

Assessments	Pre-treatment	End of RT	Follow-Up[c]				At Failure
			3 mos (+ 3mo/- 2mos)	12 mos (+/- 3mos)	Year 2 – 5 Annually (+/- 3 months)	Year 7+ Every other year	
History Assessment	X[a]						
DRE	X[a]						X[b]
Medication Assessment	X						
Adverse Events Assessment (CTCAE v4)	X[a] Baseline Survey	X	X	X	X	X	X
ECOG performance status	X[a]						X
Histological evaluation	X						
Directed prostate biopsy	X[d.]						X[b]
Qol,EPIC, IPSS[i]	X[a]		X	X	X	X	X
PSA *(at least 6 weeks after prostate surgery)*	X[a]		X	X	X	X	X
Testosterone	X[e.]						
CT or MRI prostate/pelvis	X[b]	X[e.]	X[e]	X[e]	X[e]	X[e]	X[b]
Fiducial markers placement	X[d.]						
Bone scan	X[b]						X[b]
PET scan	X[b]						X[b]
Start androgren suppression	X[g]						

a. within 90 days prior to enrollment.
b. highly recommended if PSA ≥0.2 ng/ml.
c. follow-up schedule: at 3 months and at 12 months for the first year; yearly up to year 5; every 2 years thereafter. See SPM for additional information on follow up visit windows.
d. recommended (not mandatory).
e. as clinically indicated.
g. if PSA ≥0.2 ng/ml after surgery AS can have started 0-6 months prior to inclusion in the trial.
i. IPSS is included within the Quality of Life (QoL) EPIC questionnaire, QoL survey's collected clinically as indicated.

4.2 Criteria for Biochemical Recurrence

4.2.1 Biochemical failure is defined as 0.5ng/ml above the PSA prior to start AS. If the PSA before radiation was <0.2 ng/ml a PSA of 0.50 ng/ml or higher will be considered a biochemical failure. Date of failure is the date of the PSA measurement.

4.3 Measurement of Effect/Response

4.3.1 No Evidence of Disease (NED): No evidence of disease on physical exam, and imaging studies, and freedom from biochemical recurrence.

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

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

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, imaging, or by prostate rebiopsy.

4.3.4 Freedom from PSA Failure: Biochemical failure is defined as 0.5ng/ml above the PSA prior to start AS or radiation. If the PSA before radiation was <0.2 ng/ml a PSA of 0.5 ng/ml will be considered a biochemical failure. The date of failure is the date of the abnormal PSA reading.

4.3.5 Imaging : At the time of PSA failure, local failure, or distant metastasis, a pelvic MRI, bone scan, or PET are highly recommended

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 STRATIFICATION FACTORS

5.1 patients will stratify by their clinical scenario following radical prostatectomy into 3 groups.

5.2 Group I: PSA after surgery <0.2 ng/ml and one high risk feature either positive margins, extracpauslar extension, or seminal vesicle invasion. PSA has to be undetectable if patients are receving AS or <0.2 ng/ml if AS naive.

5.3 Group II: PSA after surgery ≥0.2 ng/ml and <2 ng/ml and no evidence of distant disease or positive LN on imaging studies or surgical pathology. PSA has to be undetectable if patients are receving AS piror to enrollment or <2 ng/ml if AS naive.

5.4 Group III: PET + disease in up to 3 areas including the pelvic or abdominal LN, and or bone. The prostate fossa can be treated as an additional site, if not previously treated. PSA has to be undetectable if patients are receving AS prior to enrollment or <2 ng/ml if AS naive.

6.0 REGISTRATION / ENROLLMENT

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

6.2 Verify the patient meets the eligibility criteria prior to enrollment. The protocol-specific eligibility checklist provided. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

6.3 Patients can be enrolled only after eligibility criteria are met.

7.0 PROTOCOL TREATMENT
RADIATION THERAPY

7.1 Radiation Dose and Volumes for x-rays or Proton Therapy

7.1.1 Total dose for **prostate fossa** will be 30 (Group I) or 32 (Group II-III) Gy or Gy (RBE) in 5 treatments >36 hours apart over 2 weeks. The prescription dose is the minimum dose to 95% of the optimization target volume or PTV (x-rays) and a minimum dose of 90% to the OTV or PTV.

Total dose for **lymph node lesions** for proton therapy alone will be 30 Gy or Gy (RBE) in 6 Gy or Gy (RBE) treatments >36 hours apart over 2 weeks. The prescription dose is the minimum dose to 95% of the optimization target volume or PTV (x-rays) and a minimum dose of 90% to the OTV or PTV.

Total dose for **bony lesions** for proton therapy alone will be 20 Gy or Gy (RBE) in a single fraction treatment over one day to the GTV.. For bony lesions a CTV2 would be generated covering 1cm inside the bone or the remainder of vertebral body as per contouring guidelines.[34] Please see section 7.1.4. Dose to the OTV2 or PTV 2 would be 16Gy in a single fraction. The prescription dose is the minimum dose to 95% of the OTV1-2 or PTV1-2 (x-rays) and a minimum dose of 90% to the OTV or PTV.

7.1.2 Prostate fossa Volumes are as follows for photon or proton therapy **with** or **without** a rectal balloon:

CTV = Prostate fossa + seminal vesicle volume
PTV = 5mm in all directions
OTV (protons only) = PTV + 3mm Left and Right (if lateral beams or follow beam orientation)
STV = PTV + 5mm all around

7.1.3 Lymph node Volumes are as follows for photon or proton therapy with or without a rectal balloon:

CTV = lymph node positive on PET + lymph node seen on the planning CT
PTV = 5mm in all directions
OTV (protons only) = PTV + 3% in the beam direction (follow beam orientation)
STV = OTV + 5mm all around, excluding small bowel

7.1.4 Bone target Volumes are as follows for photon or proton therapy with or without a rectal balloon:

CTV1 = bone lesion on PET + bone lesion seen on the planning CT.
CTV2= CTV 1 +1cm inside the bone or based on PET changes. For lesion in the vertebral bodies please follow the **contouring guidelines**[34]
PTV1 = CTV1 + 5mm in all directions. For spine lesions PTV = CTV + 1mm in all directions.
PTV2 = CTV2 + 5mm
OTV 1-2 (protons only) = PTV 1-2 + 3% in the beam direction (follow beam orientation). OTV should not include the spinal cord + 1mm
STV = OTV + 5mm all around, excluding small bowel or spinal cord

7.1.5 Seminal vesicle bed volume

Should include the proximal seminal vesicles (SV) for most cases defined as the proximal 1cm of the SV remanent. In cases of positive seminal vesicle involvement the whole remanent seminal vesicle should be included as well as the removed seminal vesicle area. The volume of the seminal vesicle treated will be at the discretion of the physician.

7.2 Radiation Dose and Volumes for IMRT/Photon Therapy

7.2.1 Total dose for photon therapy alone will be the same dose as for proton therapy given in Gy. Coverage would be as defined above to the PTV

7.2.2 Volumes are as defined above for the PTV

7.3 Equipment and Physical Factors

7.3.1 Radiation will be delivered using the available radiation equipment. 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.

7.4 Localization Simulation and Immobilization

7.4.1 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 ≤ 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. T2 sequence 3D with a ≤ 2mm spacing is recommended. For patients in group III, fusion of the PET scan is required for target identification and localization.

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

7.4.3 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 decreasing movement of the rectum. One hundred (100) cc of saline is recommended to be used on a daily basis if a balloon is to be used. Balloon inflations or placement techniques may vary, as well as, water use or volume.

7.4.5 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.

7.4.6 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 fossa position will then be verified based on prostate fossa markers employing the techniques described below. If fiducial markers are not available cone-beam CT or CT on rails or other form of volumetric imaging is necessary.

7.6 On-line Daily Guidance Correction

We do realize that for an individual patient, 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) can be used for fiducial markers. It can also be used to define bone targets.
Volumetric guidance: Cone beam CT or CT rails can be used if fiducials are not available to define the prostate fossa or the LN target volume.

Daily image guidance:

Prostate fossa: aligment would be done using the fiducial markers. If fiducial markers are not available volumetric guidance is necessary. Aligment of the prostate fossa would be done considering the position of the anterior rectal wall.

Lymph nodes: Kv guidance can be used if fiducial markers are available. If no fiducials are available volumetric guidance is necessary.

Bone lesions: Kv guidance or volumetric guidance can be used.

7.7 Error Verification

7.7.1 MRI cine: MRI cine can be done to determine intra-fraction motion.

7.7.2 3D volumetric guidance: Cone beam CT, CT on rails, MRI, ultrasound or any other means of guidance can be employed.

7.7.3 Real time tracking can be used when available.

7.7.4 Fluro is recommended when available to document fiducial stability and intrafraction error

7.8 Dose Calculations

7.8.1 Target doses will be Gy/Gy (RBE) given usually once a day for five treatments >36 hours apart over 2 weeks. Gy (RBE) equivalence will be based on the most recent proton biologic equivalent dosimetric calculations and review of the most current literature.

7.8.2 Dose Volume Histograms (DVH) for the prostate fossa and important critical normal structures will be calculated. The different dose constraints will be reported.

7.9 Critical Structures

7.9.1 Clinical Target Volume. CTV is the prostate and seminal vesicles as defined by MRI or CT. Contouring guidelines can be used a prosposed by the RTOG or TROG [redacted] [35] [36]In summary:

For CT or MRI definition:

- *Inferior CT:* Urethrogram is recommended. The prostate fossa will be contoured starting on average 0.8 cm above the urethral beak if a urethrogram is used.
- *Inferior MRI:* the contours would start about 6mm below the vesico-urethral anastomosis.[36] If the a prostate apical margin is found the volumes would start about 1cm below. Alternatively 2-4mm below when the urethra is at the level of the elevator ani muscle (hour glass sign).
- *Anterior:* To the posterior edge of the symphysis pubis
- *Posterior:* the volume would be close to the rectum and around the anterior quarter of the rectum.
- *Lateral:* The elevator ani muscles that form the urogenital diaphragm should not be included laterally. Coronal CT views will be used to determine appropriate prostate contouring.
- *Superior:* The proximal 1cm of the 21emnant seminal vesicles should be included in the prostate fossa volumes. For positive seminal vesicle involvement the whole seminal vesicle bed should be included. Different seminal vesicle volumes can be used based on the clinical risk factors as determined by the treating physician.

7.9.1.1 CTV for Group 3.

Additional CTVs are allowed in group 3. A total of 3 additional targets can be treated. **PET CT** information would be used for target definition.

Lymph node (LN) targets:

The LN as defined by the PET information would be contoured in the planning CT using both the information and postion of the LN on the PET

CT and in the planning CT. The resulting CTV would be union of the information in the PET-CT and the planning CT.
Bone targets:
The bone targets would be contoured in the planning CT using both the information and position of the lesion on the PET CT or MRI and in the planning CT. The resulting CTV would be union of the information in the PET-CT and the planning CT. If the bone target is in the vertebral body the lesion would be contoured included the region of interest as defined by International Spine Radiosurgery Consortium Consensus Guidelines for Target Volume Definition in Spinal Stereotactic Radiosurgery

7.9.3 Preplan. The number of slices will be recorded. Slice spacing will be ≤ 2mm at the prostate fossa level, and 2-5mm elsewhere.

7.9.4 Rectum: is defined inferiorly from the ischial tuberosities and superiorly to the sigmoid flexure. The wall will be defined using an average thickness of 3mm (optional). Sagittal MRI or CT view should be used to verify volume definition.

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

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

7.9.7 Small bowel: Individual loops should be contoured including 3 cm above and below the taget or targets.

7.9.8 Organs at risks (OAR): additional OAR would be contoured based on the location of the targets.

7.9.9 Spot target volume STV:

7.10 Normal Tissue Constraints (NTC)

7.10.1 Normal tissue constraints (NTC) to define dose.

Table 2a: **Radiation Therapy**

Structure	**Constraint**	**Minor deviation**	**Major deviation**
Rectum	V30 <15%	V30 <40%	V30 ≥ 40%
Bladder	V33 <8cc	Record in cc	
	V30 <50cc	Record in cc	
	Max dose	Record in Gy	
Femoral heads	V40 <1 cc	V40 <2 cc	V40 ≥ 2cc
OTV or PTV			
	Min dose > 90%		Min dose < 85%
	Max dose	Record in Gy	
	D95% = 100%		D95% = <94%
Small bowel	Max dose	Record in Gy	
	V30Gy	Record in Gy	
	Max dose = 35Gy	Record in Gy	Max dose >35Gy

Salvage

Large bowel	Max dose	Record in Gy	
	V30Gy	Record in Gy	
	Max dose = 38Gy	Record in Gy	Max dose >38Gy
Spine	Max dose	14Gy	
Lung	V20	record	V20 >25%
	mean	record	

7.10.2 **The maximum dose without a major deviation will be used for treatment.**

7.10.3 In cases of major normal tissue constraint deviation, patients will be notified. No major NTC deviations are allowed in the protocol.

7.11 Planning

7.11.1 **MRI fusion:** Initial automatic fusion will be done based on bony anatomy. Soft tissue registration will then be done in the sagittal plane at midplane of the symphysis pubis. Attention would be paid to the prostate fossa/rectal interface. If fiducial markers are available they should be used for registration.
PET CT fusion: automatic fusion based on bony or soft tissue anatomy would be done for all sites, at physician discretion.

7.11.2 For proton planning, two un-opposed lateral fields are recommended. More fields can be used as necessary. The minimum number of beams necessary to meet the required treatment parameters should be used.

7.11.3 Uniform dose distribution by means of pencil beam, spot scanning, double scatter or other delivery methods is acceptable.

7.11.4 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 OTV with 95% IDL is required.

7.11.6 Smearing: PTV will be smeared 1.2cm if double scattered is used.

7.11.7 **Spot target volume**: would exclude the spinal cord without exceptions, and the small bowel.

7.11.10 X-ray planning: Patients can be treated to the PTV with x-ray treatment either IMRT, SBRT, ARC, 3D or any other form of volumetric planning is allowed. IGRT is mandatory for all x-ray treaments and can consist of x-rays or conebeam.

7.12 Quality Assurance (Physics check)

7.12.1 Daily online imaging will be performed during radiation therapy

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

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

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

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

7.13 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.

7.14 Treatment Interruptions

Group I or II: Proton radiation treatment should be delivered for 5 treatments over 1-2 weeks. Total treatment time >2 weeks is considered a **major deviation** and is not accepted in the protocol. If treatment interruption is not of medical necessity, arrangements for photon therapy should be made. Unplanned interruptions, consecutive or not, for more than 5 treatment days (Monday – Friday) are not allowed. Treatment should be completed within 2-weeks regadarless of the reason.

Group III: Prostate fossa treatment would be delivered as defined above for Group I or II. Treatment to the LN or bone targets would be done as specified in the protocol. LN treatment can be done over 1-2 weeks at the preference of the physician. Bone treatments would be done in a single treatment.
Treatments can be done during, before or after the prostate fossa treatment. All sites treated should complete treatment within 6 months at the discretion of the treating physician.

7.15 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*

7.16 Radiation Adverse Event Reporting

See Appendix III

7.20 DRUG THERAPY- ANDROGEN SUPPRESSION

7.2.1 Dose Definition

Androgen suppression (AS), will be administered to patients stratify to group II and group III. AS ideally will begin before the start of radiation treatment. **Acceptable range is 0 – 6 months prior to the start of RT.** Thus, patients could

have received AS prior to enrollment in the protocol for up to 6 months. Patients should start AS prior to the start of radiation therapy if mandated by protocol. Patients should start treatment within 120 days from the date of enrollment and AS per protocol can be started any time between the date of enrollement and the start of radiation. Total acceptable AS durations per protocol can be seen in the table below.

Acceptable range for the total duration of AS for each group

	Recommened Duration AS	Acceptable Range
Group I	0	0 months
Group II	6 months	3 - 12 months
Group III	18 months	6 - 24 months

Patients receiving AS outside of the range will be considered to have a major deviation and a deviation report will need to be filled out. Patients will be continued to be monitored in the study and data will be analyzed based on intention to treat and also analyzed excluding patients with AS given outside of the acceptable range.

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 duration is as specified above. 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, for a total duration of 6 months.

7.2.2 The use of concurrent anti-androgen medications such as bicalutamide (Casodex) or flutamide (Eulexin) is allowed.

7.2.3 Calcium and Vitamin D supplementation
Patients who are 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.

7.2.4 Androgen suppression prior to enrollement is allowed. AS can be started up to 6 months before enrollement in group II and group III. Although not recommended AS is allowed for Group I, for up to 6 months.

7.2.5 Androgen suppression duration correction for AS use prior to enrollement. AS would be continued for the regular duration of AS in their specific group to the total duration that was specified in the protocol not counting the duration of the AS prior to enrollment; 6 months for Group II; or 18 months for Group III.

7.3 Study Agents: LHRH Agonists

See section 14

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 > 60 days

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

8.0 Radiotherapy Dose Modifications Based on Adverse Events

This study has no pre-specified interruptions due to adverse events. Treatment interruptions are discouraged. No dose modifications should be done for treatment interruptions.

9.0 Ancillary Treatment/Supportive Care

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 Adverse Event (AE) Reporting and Monitoring

10.1 Definitions

Adverse Event- An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event – Any grade 4 or 5 adverse event as defined by CTC AE v4.0. Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include in general:

- Death
- Life threatening adverse experience where emergent lifesaving treatment is necessary.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)- Any unanticipated problem or adverse event that meets the following three criteria:

Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND** Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND

Related: A problem or event is "related" if it is possibly related to the research procedures.

Preexisting Condition- A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant

findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

10.2 Recording Adverse Events

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting unless as otherwise stated in the table below.

All appropriate treatment areas 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://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.21 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected and if the adverse event is related to the medical treatment or procedure. With this information, determine whether the event must be reported as an expedited report (see Section 10.3).

10.22 Assessment of Attribution
Only G4 or G5 adverse events will require an attribution. Any change in the grade of an adverse event within the list of monitored AEs will be recorded and considered to be related to treatment. Any new adverse not listed occurring within the Radiated area or in close proximity will be graded and attribution defined by the study PI.
Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the treatment and the adverse event.

10.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

a. Serious Adverse Events will be reported as part of regular adverse event reporting mechanisms via the data capture system and logged for review reporting.

10.31 Investigator Reporting: Notifying the Mayo IRB:

The IRB requirements reflect the guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) in early 2007 and are respectively entitled “Guidance on Reviewing and

Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subject Protection."

10.311 According to Mayo IRB Policy any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO must be reported to the Mayo IRB as soon as possible but no later than 5 working days after the investigator first learns of the problem/event.

10.312 Non-UPIRTSO – the investigator reports problems or events that do NOT meet criteria of an UPIRTSO in summary format at the time of the next continuing review. The investigator monitors the severity and frequency of subsequent non-UPIRTSOs.

Consider the following information to collect when developing any forms for documentation of adverse events.
Example
Information collected on the adverse event worksheet (and entered in the research database):

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

10.4 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation	Grading scale (if not CTCAE)
General	Pain	X	X	CTCAE
GI	Rectal hemmorrhage	X	X	CTCAE

	Diarrhea	X	X	CTCAE
	Proctitis	X	X	CTCAE
GU	Frequency	X	X	CTCAE
	Urgency	X	X	CTCAE
	Obstruction	X	X	CTCAE
	Incontinence	X	X	CTCAE
	Retention	X	X	CTCAE

10.5 Submit via appropriate *reporting mechanisms* the following AEs experienced by a patient and not specified in Section 10.4:

10.52 Grade 4 and 5 AEs regardless of attribution to the study treatment or procedure.

10.53 Grade 5 AEs (Death)

10.531 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure

10.532 Any death more than 30 days after the patients last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

11.0 TREATMENT EVALUATION

11.1 Failure

11.1.1 Biochemical failure is defined as 0.5ng/ml above the PSA before treatment or a PSA of 0.5ng/ml if PSA was <0.2ng/ml before treatment. Date of failure is the first date of the elevated PSA measurement.

11.1.2 Imaging at failure is recommended:
MRI, Bone scan, and or PET

11.1.4 Biopsies of the site of failure can be directed by radiology images such as MRI or PET.
11.1.5 Patients will be evaluated at baseline, then according to the Assessment Schedule (Section 4.0)
11.1.6 At the time of reevaluation, patients will be classified in the following manner:
11.1.7 No evidence of disease (NED).
11.1.8 Recurrence of disease (REC). Consider biopsy of the site and PET scan.
11.1.9 The site of recurrence (or failure) will also be collected and classified as nodal pelvic, nodal abdomen, bone, prostate fossa, or PSA failure alone.
11.1.10 Secondary Treatment. The date of the first retreatment and extent of retreatment post recurrence (i.e. secondary resection, re-irradiation for primary disease, AS, Chemo), will be collected. Pathology, if available, and operative reports are required to be submitted per Section 18.0.

12.0 Descriptive Factors

12.1 Post surgical pathology: positive margins, seminal vesicle invasion, extracapsular extension, Perinerural invasion
12.2 Post surgical lymph node dissection: number removed, number positive.
12.3 Gleason score
12.4 Pre-treatment PSA
12.5 PET findings: location of disease sites
12.6 PET findings biopsy

13.0 Treatment/Follow-up Decision at Evaluation of Patient

Follow-up data will collected and entered after the observation phase outlined in section 4.0. If the patient is still alive after 5 years have elapsed from the on-study date, the patient would be followed every 2-years for life.

13.1 Patients who have a recurrence while receiving therapy or during observation will continue to be followed.
13.2 Patients who discontinue treatment or observation for reasons other than recurrence will contijnue to be followed.
13.3 Patients who will not receive any radiation treatment or who will receive radiation treatment outside of the facility were they signed consent will be removed from the protocol.
13.4 A patient is deemed ineligible if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will be removed from the protocol.

If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary. The patient will be removed from the protocol.

13.5 A patient is deemed a cancel if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

None to be collected.

15 Drug Information

15.1 Description

LHRH agonists are long-acting analogs of the native LHRH peptide and are effective at reducing serum testosterone. Analogs approved by the FDA can be used in this study.

15.2 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.

15.3 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.

15.4 Storage

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

15.5 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).

15.6 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.

16 Statistical Considerations and Methodology

16.1 Study Endpoints

16.1.1 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), the start/re-start of salvage therapy including androgen suppression, and biochemical failure (PSA $\geq$ 0.5 ng/ml).

16.1.2 Secondary Endpoints:

- Assessment of acute grade 2 or higher and grade 3 or higher GU and GI toxicity. Assessment will be performed using NCI-CTCAE version 4 criteria. Descriptive measurements of frequency will be compiled.
- Assessment of grade 2 or higher and grade 3 or higher GI and GU toxicity at 3 years.
  Assessment will be performed using NCI-CTCAE version 4 criteria.
- Assessment of local/distant failure.
- Assessment of distant metastasis.
- 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.
- 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.
- Assessment of salvage androgen suppression use.
- Assessment of survival (overall, progression-free and disease-free).

16.1.3 Exploratory endpoints:

- Development of quality assurance process for prostate proton therapy.
- Correlation of pathologic and radiologic findings with outcome.
- Estimation of prostate and normal structure movement.
- Define dose volume relationship of normal structures with toxicity.
- Potentially, future research of pathologic risk factors.
- Possible comparison of an IMRT plan with the proton therapy radiation plan.
- Different iterim analysis can be done at the discretion of the PI. The time of the interim analysis would be defined by the PI based on the accrual numbers, the type of analysis to be done and the follow up of the group to be studied.

16.2 Statistical Design

This phase II study is designed to determine whether the 5-year FF following hypofractionated radiation treatment is similar to published results in the adjuvant and salvage setting. Failure will be assessed at 5 years. Success will be defined as freedom from failure at 5 years and Groups I/II will be evaluated separately from Group III.

Group I/II:
The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 61%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen would be 80%. The following Simon's Optimum design uses 37 evaluable patients (in Groups I/II) to test the null hypothesis that the proportion of successes is at most 61%.

In RTOG 9601, the experimental arm 5-year freedom from failure (FFF) was 80% and for the control arm was 50%. This translated into a 30% absolute difference between arms and a small 5% improvement in overall survival (OS) after 10-years. Our upper bound confidence interval of 20% is smaller than the difference in RTOG 9601. Thus, our trial would be able to detect a difference in freedom from failure that is acceptable, less than 20%, and within an acceptable long term OS difference, less than 5%.

Our power analysis was based on absolute numbers since relative changes may show a potentially large difference that may not be clinically relevant. In this manner, a difference between 1% and 5% may be seen as a relative 5 fold change (500%). However, the difference remains clinically irrelevant.

Group III:
For Group 3, we would like to see an improvement in the freedom from failure published in the literature by employing PET staging for all cases and AS for at least 6 months.
The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 20%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen would be 47.5%. The following Simon's Optimum design uses 19 evaluable patients (in Group III) to test the null hypothesis that the proportion of successes is at most 20%.

For this patient population, we need about a 30% freedom from failure benefit at 5-years to be able to detect a long term clinically relevant absolute survival benefit. Thus, our upper bound confidence interval of 27.5% is in line with the difference in failure rates that is necessary for a meaningful clinical finding. Similar to Group I and II above, an absolute difference of 30% should translate into a 5% long term survival benefit (RTOG 9601). Relative changes were not used since a difference between 1% and 5% may be seen as a relative 5 fold change (500%). However, the difference remains clinically irrelevant.

16.21 Decision Rules:

Group I/II:
16.211 If 27 or fewer successes are observed in the first 37 evaluable patients, we will consider this regimen to be ineffective in this patient population. If 28 or more successes are observed in the first 37 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this patient population.

Group III:

If 7 or fewer successes are observed in the first 20 evaluable patients, we will consider this regimen to be ineffective in this patient population. If 8 or more successes are observed in the first 20 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this patient population

16.213 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process.

16.22 Sample Size

The one-stage design to be utilized is fully described in Section 16.21 for Groups I/II and Group III. A minimum of 56 (Group I/II: 36, Group III: 20) evaluable patients will be accrued to this phase-II study unless undue toxicity is encountered. We anticipate accruing an additional 6 patients (Group I/II: 4, Group III: 2) to account for ineligibility, cancellation, major treatment violation, or other reasons. Maximum projected accrual is therefore 62 patients in all groups.

16.23 Power and Significance Levels

Groups I/II

Assuming the number of successes is binomially distributed, the significance level is 0.05 and the probability of declaring that this regimen warrants further studies (i.e. statistical power) under various success proportions and the probability of stopping accrual can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is …	0.61	0.65	0.70	0.75	0.80
Then the probability of declaring that the regimen warrants further studies is…	0.04	0.11	0.29	0.55	0.81

Group III

Assuming the number of successes is binomially distributed, the significance level is 0.05 and the probability of declaring that this regimen warrants further studies (i.e. statistical power) under various success proportions and the probability of stopping accrual can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is …	0.20	0.275	0.35	0.425	0.475
Then the probability of declaring that the regimen warrants further studies is…	0.04	0.20	0.46	0.73	0.86

16.3 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.

16.4 Analysis Plan

The analysis for this trial will commence at the planned timepoints (see 16.2) and at the time the patients have become evaluable for the primary endpoint. Such decision will be made by the Statistician and Study chair, availability of data for secondary endpoints, and the level of data maturity.

16.41 Primary Analysis: The primary analysis will be to estimate FFF rate at 5 years. Events for FFF will be defined as any of the following:

- First occurrence of clinical failure (local recurrence, regional recurrence, or distant metastasis)
- Biochemical failure by PSA > 0.5 ng/ml over the current nadir PSA
- Start/re-start of salvage therapy including androgen suppression

All patients meeting eligibility criteria who have signed a consent form and who have begun treatment will be evaluable for the primary analysis.

16.411 Estimation: The proportion of successes (number of patients achieving FF at 5 years) will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner [74].

16.412 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence limits.

16.42 Secondary Analysis

16.421 Adverse Events:
Protocol toxicity will be measured using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The use of CTCAE grading for urinary toxicity might be misleading. Patients are commonly prescribed α-2 blockers as a measure to decrease urinary frequency and urgency, but most patients will not have urinary retention or any threatening complication if the medication is not used. Other publications have modified the CTCAE grading of grade 2 AEs to accommodate this inconsistency. Here, we will use the strictest definition, that is, any use of a prescription or over-the-counter medication over baseline will be considered a grade 2 AE. The use of CTCAE may also be misleading for grade 3 toxicity as the definition usually includes the need for medical/operative intervention, transfusion, or hospitalization. However, given the ambiguity of hospitalization criteria across the country, in this trial we require an intervention or transfusion to define a grade 3 event. All patients who were registered to the study and started treatment will be included in the acute adverse event analysis. The maximum grade for each type of acute AE will be recorded for each patient. Data will be summarized as frequencies and relative frequencies. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. The proportion of patients with grade 2 or higher GU and GI toxicity at 6 months will be estimated by the number of patients experiencing a grade 2 or higher GU and GI event divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner [74]. Similarly, grade 3 or higher GU and GI events will be estimated along with overall toxicity.

16.422 *Locoregional control*: The cumulative incidence of locoregional recurrence will be estimated using a competing risks method (Gooley et al.). The competing risks will be distant prostate cancer recurrence and death.

16.423 Events of interest including: 1) Impotence after the use of radiation therapy at 3 years, 2) FFBF at 5 years, 3) Salvage androgen deprivation use (SAD) at 5 years will be estimated as the number of patients experiencing the event of interest divided by the total number of evaluable patients. 95% confidence intervals will be calculated for each estimate.

16.424 Cause specific survival: The CSS will be estimated with a Kaplan-Meier estimator and curve. Estimates will be given for specific time points along with 95% CIs.

16.425 *Overall survival*: The OS will be estimated with a Kaplan-Meier estimator and curve. Estimates will be given for specific time points along with 95% CIs.

16.43 Exploratory Analyses:

16.431 *Quality of life*: Patients will complete the Expanded Prostate Index Composite (EPIC)and AUA before treatment, during routine follow-up visits at 3, 12, 18, and 24 months, and yearly after completion of treatment. EPIC is a validated instrument that measures urinary, bowel, and sexual function and bother. To statistically evaluate change over time, responses will be grouped by system and assigned a numeric score. The difference in mean scores will be assessed with the t-test. Multi-item scale scores will be transformed linearly to a 0 to 100 scale, following scoring instructions for the EPIC. Lower numbers correspond to worsening function and increased bother. To assess changes in health-related QOL from baseline, a clinically significant difference will be defined as half of a SD and at least a 10-point change. A clinically significant change in AUA scores will be defined as a change of 5 points or more. Scale score trajectories over time will be examined using stream plots and mean plots with standard deviation error bars overall. Analysis will include percent change from baseline using t-tests and generalized linear models to test for changes at each time point and non-zero slope respectfully.

16.432 Prostate and normal structure movement will be described during RT . Data will be summarized by frequencies and mean (SD) or median values.

16.433 Variables of interest including 1) Pathologic, radiologic findings, 2) pre-RT PSA levels, 3) Proton therapy and x-ray dosimetry levels will be compared to outcomes and described in Groups I/II and III separately. Data will be summarized by frequences and mean (SD) or median values. Continuous variable will be compared using unpaired t tests and nonimal variables will be compared using contingency tables and Chi square analyses.

16.5 Data & Safety Monitoring

16.51 The study chair(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules: The stopping rules specified below are based on knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- If 11 or more patients in the first 30 treated patients experience a grade 3 or higher adverse event at least possibly related to treatment at any time.
- After the first 30 patients have been treated: if ≥ 35% of all patients experience a grade 3 or higher adverse event at least possibly related to treatment at any time following the completion of protocol treatment.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event

16.6 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 84 months after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the median follow-up is 5 years.

16.7 Inclusion of Women and Minorities

16.71 This study will be available to all eligible patients, regardless of race, or ethnic origin.

16.72 There is no information currently available regarding differential effects of this regimen in subsets defined by race, or ethnicity, and there is no reason to expect such differences to exist.

16.73 The geographical region served by the Mayo Clinic, has a population which includes approximately 5% 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.

Accrual Estimates by Gender/Ethnicity/Race

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	2	2
Not Hispanic or Latino	0	60	60
Ethnic Category: Total of all subjects	0	62	62
American Indian or Alaskan Native	0	1	1
Asian	0	1	1
Black or African American	0	9	9
Native Hawaiian or other Pacific Islander	0	1	1
White		50	50
Racial Category: Total of all subjects	0	62	62

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

16.6 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.

16.7 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.

17.0 Pathology Considerations

Review of the pathology at the treating institution is recommended
SVI, positive margins, extracapsular extension, LN removed and positive LN number, extranodal extension.

The PI must make study data accessible to the CRC, 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 CRC. If the original documents are not available any written or verbal communication, or clinical documentation would be considered source documentation. However, **pathology report is necessary.**

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s) -

CRF	**Treatment** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after registration
Patient Eligibility	
Demographics	
On-Study	
Pathology Surgery[1]	
Imaging reports[1]	
PSAs[1]	
Dates and doses of AS use[1]	
Any medical record[1]	
Adverse Events- Baseline	
Patient Status: Baseline	

[1]Given the difficulties to find original reports of PSAs or AS use, or staging imaging studies, any written or verbal communication by the patient or treating physician or any medical record were this information is consigned would be considered our primary source of information.

18.3 Data Handling and Record Keeping

18.31 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

(This information is contained within the Mayo IRB Informed Consent Template Section 14)

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission

to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

18.32 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Source documents are kept in a secure location that is locked and requires approved access. Given the difficulties to find original reports of PSAs, AS use, staging imaging studies, any written or verbal communication by the patient or treating physician or any medical record were this information is consigned would be considered our primary source of information.

18.33 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction. If a cell data point is not recorded it will be considered N/D.

18.37 Records Retention

The investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The investigator will retain the specified records and reports for;

1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" [redacted]

19.0 Study Finances

19.1 Costs charged to patient: routine clinical care

19.2 Other budget concerns: The Mayo Clinic Radiation Oncology Unit is funding the study and will cover costs related to running the study that are not covered by Marley.

20.0 Publication Plan

The principal investigators hold primary responsibility for publication of the results of this study and approval from the principal investigators must be obtained before any information can be used or passed on to a third party. The principal investigator would maintain control and use of all data used in the study during the study and after the study has been completed.

20.1 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. 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 may 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.

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, 8TH EDITION

DEFINITION OF TNM

Primary Tumor, Clinical (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
	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 found in one or both sides, but not palpable
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	Extraprostatic tumor that is not fixed or does not invade adjacent structures
	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.

Primary Tumor, Pathologic (pT)

pT2	Organ confined
pT3	Extraprostatic extension
pT3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
pT3b	Tumor invades seminal vesicle(s)
pT4	Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Regional Lymph Nodes Clinical (N)

NX	Regional lymph nodes were not assessed
N0	No positive regional lymph nodes
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 assessed
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)

Stage Group	T	N	M	PSA	Grade Group	Gleason
I	T1a-c	N0	M0	PSA < 10	1	Gleason ≤ 6
	T2a	N0	M0	PSA < 10	1	Gleason ≤ 6
	T2	N0	M0	PSA < 10	1	Gleason ≤ 6
IIA	T1a-c	N0	M0	PSA ≥ 10, < 20	1	Gleason ≤ 6
	T2a	N0	M0	PSA ≥ 10, < 20	1	Gleason ≤ 6
	T2	N0	M0	PSA ≥ 10, < 20	1	Gleason ≤ 6
	T2b-c	N0	M0	PSA < 20	1	Gleason ≤ 6
IIB	T1-2	N0	M0	PSA < 20	2	Gleason 7
IIC	T1-2	N0	M0	PSA < 20	3	Gleason 7
	T1-2	N0	M0	PSA < 20	4	Gleason 8
IIIA	T1-2	N0	M0	PSA ≥ 20	1-4	Any Gleason
IIIB	T3-4	N0	M0	Any PSA	1-4	Any Gleason
IIIC	Any T	N0	M0	Any PSA	5	Gleason 9 or 10
IVA	Any T	N1	M0	Any PSA	Any Grade	Any Gleason
IVB	Any T	Any N	M1	Any PSA	Any Grade	Any Gleason

*Note: When either PSA or grade group is not available, grouping should be determined by T category and/or either PSA or grade group, 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 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 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 study, ONLY SAE's possibly, probably or definitely related to protocol therapy are collected. ***In addition, the 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 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 [redacted]. 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.

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12. Hoffman KE, Voong KR, Pugh TJ, et al. Risk of late toxicity in men receiving dose-escalated hypofractionated intensity modulated prostate radiation therapy: results from a randomized trial. Int J Radiat Oncol Biol Phys 2014;88:1074-84.
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14. Pollack A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. J Clin Oncol 2013;31:3860-8.
15. Yeoh EE, Botten RJ, Butters J, Di Matteo AC, Holloway RH, Fowler J. Hypofractionated versus conventionally fractionated radiotherapy for prostate carcinoma: final results of phase III randomized trial. Int J Radiat Oncol Biol Phys 2011;81:1271-8.
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