Cover Page

Clinical Protocol: Stereotactic Body Radiation Therapy and Short-Term Androgen Ablation for Intermediate-Risk, Localized Adenocarcinoma of the Prostate

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Phase: Phase I/II

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Time required to complete the study accrual: The study is expected to begin June 2013 and be completed August 2015.

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1.0 BACKGROUND AND RATIONALE

Radiation therapy is an effective and frequently utilized modality for the treatment of clinically localized prostate cancer. Traditionally, external beam radiation has been delivered in a fractionated manner using daily doses of 1.8-2.0 Gy. This daily dose was derived from early animal experiments and clinical experience, supported by mathematical models of normal tissue and tumor response to fraction size. The most widely used of these models is the linear-quadratic formula, which predicts responses to different fraction sizes based on the alpha/beta ratio of any given tissue.[1]

One of the main motivations for delivering a treatment at low dose rate or with many fractions is that late-responding normal tissue are generally more sensitive than early-responding tissues (i.e. tumor) to increases in fraction size. So increasing the number of fractions generally spares late-responding tissues more than the tumor. This can be quantified in terms of the alpha/beta (α/β) ratio :

• Small alpha/beta (α/β) ratio (2-4 Gy), typical of late sequelae, means high sensitivity to large doses given per fraction.
• Large alpha/beta (α/β) ratio (>8 Gy), typical of tumor control, means low sensitivity to fractionation changes.

It is generally assumed that the mechanistic basis for the different fractionation response of tumors and late-responding normal tissues relates to the larger proportion of cycling cells in tumors. But prostate tumors contain unusually small fractions of cycling cells.[2] Brenner and Hall as well as Duchesne and Peters have reasoned that prostate tumors might *not* respond to changes in fractionation in the same way as other cancers; both papers hypothesize that prostate tumors might respond to changes in fractionation or dose rate more like a late-responding normal tissue.[3,4] In mathematical terms, the suggestion is that the alpha/beta ratio for prostate cancer might be low, comparable to that for late-responding tissues or even lower. Previous estimates of alpha/beta ratios of normal tissue and tumor tissue have generally been 3 and 10, respectively. Recent evidence has estimated the alpha/beta ratio of prostate cancer to be as low as 1.5. If these hypotheses are true, then the optimal therapeutic ratio for prostate cancer would be achieved using daily doses higher than 2 Gy.[5]

Recent clinical reports have demonstrated excellent results utilizing high dose, short course radiation (or hypofractionated) therapy for prostate cancer. The typical treatment course lasts between 35 and 40 treatments for a course of definitive treatment for prostate cancer. Integrating the calculations suggested above, recent studies have evaluated using a definitive course of therapy in a much shorter time period with stereotactic body radiation therapy (SBRT). SBRT incorporates higher doses of radiation over a short time course. Recent publications by King and Boike demonstrate the increasing utility of this technology in the treatment of prostate cancer.[6,7] King and colleagues demonstrated the safety and utility of a 5 day course of radiation therapy using the CyberKnife for SBRT treatment in a Phase I-II prospective study.[6] The dose utilized was 7.25 Gy in 5 fractions. Grade 3 or greater rectal toxicity was seen in only 2 of 32 patients, and 78% of patients achieved a PSA nadir of ≤ 0.4 ng/mL at a minimum follow-up of 12 months. Boike and his colleagues in a separate Phase I-II study used three different dose regimens of 45 Gy, 47.5 Gy, and 50 Gy in 5 fractions.[7] Grade 3 or greater GI toxicity was seen in ≤ 2% of patients and grade 3 or greater GU toxicity was seen in ≤ 4% of patients. The study noted 100% PSA control by the nadir + 2 ng/mL (ASTRO Phoenix) criteria with a short follow-up of 12-30 months. Both of these studies with short

followup suggest safe and successful treatment of prostate cancer with hypofractionated radiation utilizing SBRT.

A useful formalism in clinical radiation oncology is using the biologically equivalent dose (BED) equation to compare different fractionation schemes: $[(n \times d \times (1 + d/(\alpha/\beta)]$ where n=fraction number and d = dose per fraction. The table below compares the effective doses of different fractionation schemes based on the alpha/beta ratios discussed earlier. If the alpha/beta ratio for prostate is between 1.5-3.0, then the King regimen, 7.25 Gy x 5, should be at least as effective or more effective for *tumor control* than 90 Gy given in conventional 2 Gy fractions. Put in another way, if we assume an alpha/beta ratio of 1.5 for the prostate, as shown in the table below we would be able to deliver a BED of 211 Gy, as opposed to 187 Gy with standard fractionation (80 Gy in 2 Gy fractions).

	Fraction Size (Gy)	# Fractions	Acute (10)	Prostate (1.5)	Prostate (3)	Late (3)	Total dose (Gy)
Conventional	2	40	96	187	133	133	80
Conventional	2	45	108	210	150	150	90
Boike	10	5	100	383	217	217	50
Yoshioka	6	9	86	270	162	162	54
King	7.25	5	63	211	124	124	36.25

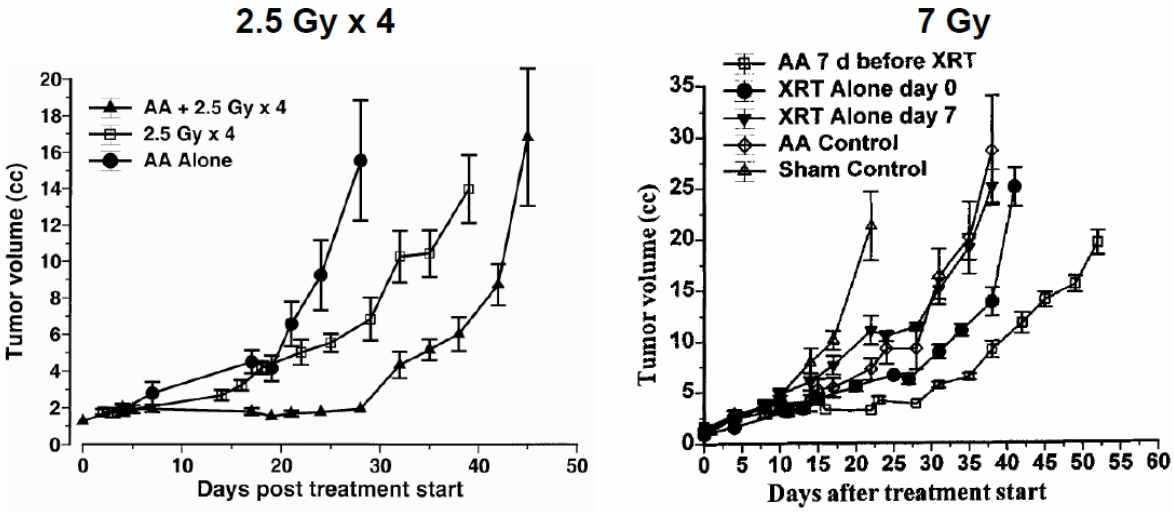
Just as important is the fact that acute and late effect biologically equivalent doses would be lower with the fractionation scheme 7.25 Gy x 5 fractions. Using the BED equation the dose regimen used by King and colleagues is calculated to be iso-effective for late effects to a conventionally fractionated total dose of 74 Gy, a lower dose than what is typically used in definitive external beam treatment currently (which is 78-80 Gy). Furthermore, the study from King and colleagues suggested that patients with every other day fractions had a statistically significant lower rate of GI and GU complications.[6] Taken altogether, in theory, the King fractionation regimen could offer a higher dose for elimination of the patient's prostate cancer while potentially reducing the side effects currently associated with standard fractionation radiotherapy.

Although the results of these hypofractionation studies are promising, they require further validation. If the hypothesis that prostate cancer alpha/beta ratio is lower than normal tissue is correct, then the optimal fractional dose is likely to be even higher than the doses tested thus far, but if incorrect, the result may be increased normal tissue toxicity.

The above studies, while demonstrating an acceptable toxicity profile and good efficacy, were completed primarily in low risk prostate cancer patients. That is, patients in whom there is a greater than 90% biochemical progression free survival after treatment. However, intermediate risk prostate cancer have a known lower biochemical progression free survival and cause specific survival and strategies composed of conventional fractionated radiation alone are not sufficient. RTOG 9408 demonstrated an improved 10 year biochemical progression-free survival with the addition of 4 months (2 months neoadjuvant and 2 months concurrent) of combined androgen deprivation therapy (ADT) with standard fractionated radiation therapy versus standard fractionated radiation alone (74% versus 59%, respectively).[8] This has since become the standard of care for patients with intermediate

risk prostate cancer. Consequently, the vast majority of patients with intermediate risk prostate cancer at our institution are treated with short term androgen deprivation therapy and 8 weeks of external beam radiation. In spite of excellent results with SBRT in the low risk prostate cancer population, no studies have addressed androgen deprivation therapy with SBRT in the intermediate risk population. As shown in the figure below, preclinical data suggests that high dose per fraction of 7 Gy with androgen ablation may have equal and potentially more potent tumoricidal effects then more standard fractionated radiation doses given in 2.5 Gy fractions.[9] Recent clinical data looking at such an approach was published recently by Yoshioka and colleagues who performed a retrospective analysis of patients treated at their institution with high dose rate (HDR) brachytherapy to 54 Gy in 9 fractions and 6 to 12 months of androgen deprivation.[10] While brachytherapy and SBRT may not be well compared in terms of their toxicity profile, the 5-year PSA control rate in intermediate risk patients treated with this protocol was 93%. Toxicity was also very favorable with no grade 4 or 5 toxicities and only $\leq$5% manageable acute and late GI and GU toxicity. [10]

SBRT Dose and Androgen Ablation



Preclinical SBRT dose of 7 Gy synergizes with AA as well as 2.5 Gy x 4 (potentially more durable response)

2.0 OBJECTIVES

2.1 Primary objectives:

Assess 5-year biochemical failure free rate (BFFR) associated with the combined hypofractionated dose regimen and ADT. The BFFR is defined as a binary indicator whether

PSA has increased by 2 ng/ml or more above the nadir PSA any time before the end of 5 years.

2.2 Secondary objectives:

1) Assess the incidence of grade 3 or greater late GU and GI toxicity and self-reported quality of life data.

2) Assess clinical and pathologic control rates associated with the combined hypofractionated dose regimen and ADT using Kaplan-Meier estimates.

3) Collect dose/volume and imaging data to allow normal tissue complication probability modeling and targeting assessment for patients treated with hypofractionated radiation therapy.

4) Collect whole blood to perform correlative studies for serum cytokine profiling and future biomarker studies.

3.0 PATIENT SELECTION: The target population will be patients with a diagnosis of adenocarcinoma of the prostate who are seen in consultation in the Department of Radiation Oncology (approximately >1000 patients per year).

3.1 Eligibility criteria

- Age >18 years old
- Histologically confirmed, locally confined adenocarcinoma of the prostate
- Patient must fit D'Amico intermediate-risk criteria by clinical stage (T2b-T2c), PSA (10-20 ng/mL), and/or Gleason score (Gleason 7).
- The patient has decided to undergo external beam radiation as treatment choice for his prostate cancer.
- Signed study-specific consent form prior to registration

3.2 Exclusion criteria

- Stage T3-4 disease.
- Gleason 8 or higher score.
- PSA > 20 ng/ml.
- IPSS >15
- Clinical or Pathological Lymph node involvement *(N1).*
- Evidence of distant metastases *(M1).*
- Radical surgery for carcinoma of the prostate.
- Previous Chemotherapy unless intervention was greater than 5 years from beginning treatment for prostate cancer.
- Pelvic radiation therapy.
- Previous or concurrent cancers other than basal or squamous cell skin cancers or superficial bladder cancer unless disease free for at least 5 years.
- History of inflammatory bowel disease.
- Major medical or psychiatric illnesses which, in the investigator's opinion, would prevent completion of treatment and would interfere with follow up.

- Myocardial infarction or cerebrovascular accident within one year from consultation, or other major vascular risk factor which would prevent a patient from receiving appropriate androgen deprivation therapy.[11]
- Liver function tests (LFTs) greater than twice the upper limit of normal.

4.0 PRETREATMENT EVALUATIONS

4.1 Subject Screening Procedures:

- History and physical (including digital rectal examination).
- Histological diagnosis and Gleason score provided on the pathology report. All patients, per institutional policy, will have pathology reviewed at Johns Hopkins.
- Prostate specific antigen *(PSA)* within 4 months prior to registration.
- CT scan or MRI of the pelvis within 6 months prior to registration*. Lymph nodes evaluated negative by imaging methods will be classified as NX. Only nodes evaluated negative by surgical sampling will be classified as N0.
- Bone scan within 2 months prior to registration*.
- Cardiovascular risk assessment if the patient is determined to be "high risk" for a vascular event.
- Quality of life measures: IPSS, SHIM, and modified EPIC bowel questionnaires (See Appendix A, B, and C for questionnaires).

* CT/MRI and bone scan optional except for the patients who are:

1. Gleason 4+3
2. >50% cores positive
3. >1 intermediate risk factor (GS 7, PSA $\geq$10 and T2b-T2c).

4.2 Registration procedures

4.2.1 Subject Identification: Patient confidentiality will be maintained in accordance with Health Information Portability and Accountability Act (HIPAA) guidelines. All participants must sign an informed consent that will describe the objectives of the study and potential risks. All patient data reported on the case reports forms will be identified by the patient's initials and study code number only. Patients shall not be identified by name. This should serve to protect the confidentiality of subjects enrolled on the trial. Clinical data and records for all subjects studied including history and physical findings, laboratory data, and results of interventions are to be maintained by the investigators in a secure, locked location. Computerized data will require password authorization(s) for access.

4.2.2 Description of the Recruitment Process: Potential patients will be approached by investigators as identified on the protocol and approved by the IRB. Recruitment is expected to be initiated in the clinic, as patients will most likely be approached during routine visits for standard clinical care. Discussions regarding trial participation and study specifics will take place in private areas. Patients will be provided with the IRB approved consent form and will be given as much time as needed to consider study participation, resulting in multiple visits or calls with study staff, if necessary.

4.2.3 Description of the Informed Consent Process: Only physicians who are also investigators or research nurses listed on the project will perform the informed consent interview. During the informed consent interview the interviewer (investigator physician or

research nurse) will take as much time as needed to ensure that the potential subject understands the research project and also clearly understands that he does not have to participate in this project to receive his cancer treatment at Johns Hopkins. If the patient decides to enroll into the research project he will sign an informed consent form. One will be for his own records, one will be kept in the Clinical Research Office at Johns Hopkins, and the third one will be kept in his medical records.

4.2.4 Registration Procedures

Eligible patients will be entered on study centrally at the Johns Hopkins Hospital by the Study Coordinator.

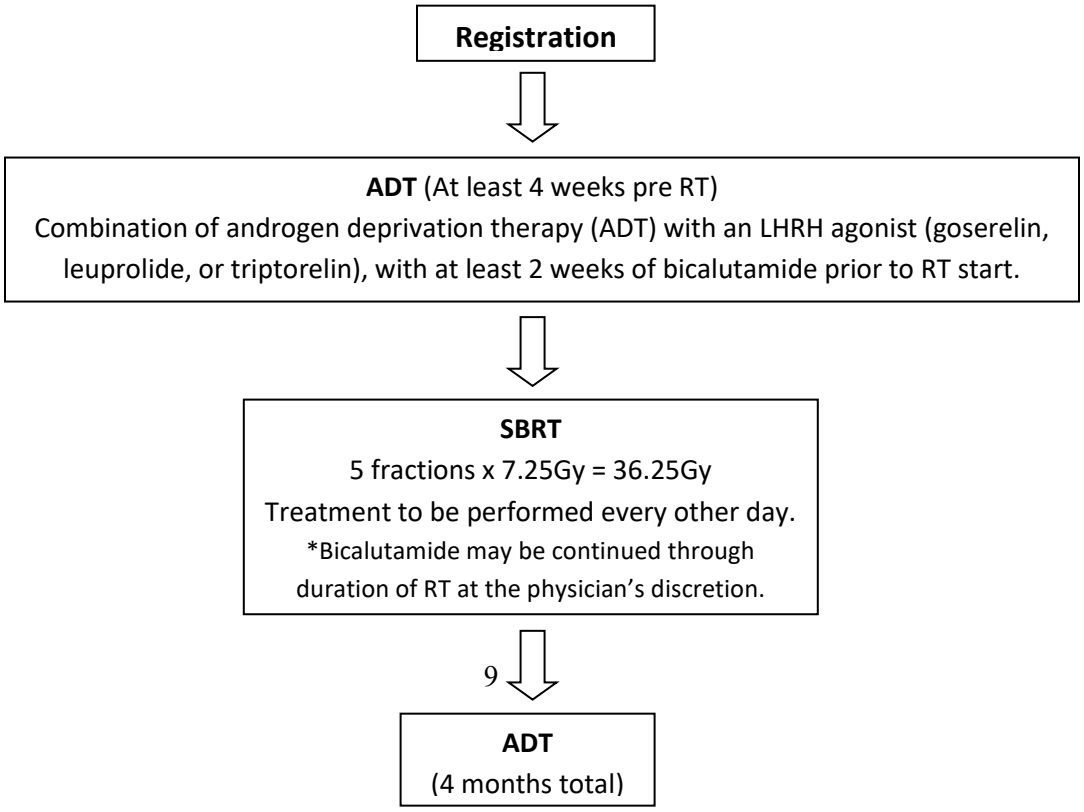
To register a patient, the following documents should be completed by the research nurse or data manager and sent to the Coordinating Center Study Coordinator via fax or email.

- Source documentation verifying eligibility (PHI will be redacted)
- Eligibility checklist
- Signed patient consent form

If the patient is deemed eligible for the study, the Study Coordinator will register the patient and assign a study number. This registration will be confirmed by a mass email sent out by the Coordinating Center Study Coordinator to all participating sites.

5.0 RADIATION THERAPY AND RESEARCH INTERVENTIONS

Rather than receiving combined 40 fractions of radiation over 8 weeks and 4 months of ADT, patients enrolling on the study will receive combined radiation in 5 fractions over 2 weeks and 4 months of ADT (≥ 1 month prior to radiation therapy). There will be no alteration in what patients experience in a treatment session other than a longer (estimated at 2-3 minutes for VMAT and 30 minutes for CyberKnife) duration of beam-on time. A schema of the treatment plan is presented below:



5.1 Simulation procedure

5.1.1 Prior to simulation, patients will undergo transrectal or transperineal insertion of at least 3 gold seeds to improve accuracy in daily prostate alignment and decrease residual positioning errors. Seed placement will occur at least 1 week prior to CT simulation and should aim for at least 1 seed at each of the follow 3 locations: right apex, right base, and left mid prostate. Patients are strongly recommended to ask their referring urologist to place the seeds. If the patients referring urologist is unavailable then the patient will be scheduled for seed placement at Johns Hopkins. However, fiducials are optional if additional image guidance is being used.

5.1.2 Patients will undergo CT simulation and an MRI simulation is preferred but not necessary in the Department of Radiation Oncology. Patients will undergo CT simulation at two time points. The first CT simulation is standard of care and will occur prior to radiation therapy. The second will occur during radiation therapy anytime after the third fraction. The second CT simulation is a Quality Assurance (QA) procedure to confirm if there is any rotation occurring with the prostate in relation to the seeds placed. Second CT simulation is not necessary if patient did not have fiducial placement. CT slice thickness of 3mm will be used.
Simulation is to be performed in the supine position, with either an alpha cradle or adaptable leg bolster. Patients will be instructed to empty their rectum prior to simulation, and to have a moderately full bladder (drink 30 cc of water 30-60 minutes prior to simulation). Oral contrast will be utilized at the discretion of the treating physician, but in general is discouraged given the confounding effect on dose calculation in the radiation planning algorithm due to heterogeneity correction.
In order that extreme rectal filling not be present at the time of the planning CT scan as well as during treatment, patients will be advised to:
a) Take 2 tablespoons of magnesium hydroxide (milk of magnesia) beginning 2 days before the date of simulation as well as 6-12 hours prior to daily treatment.
b) Use gas-reducing agents (such as simethicone or Bean-O) and avoid gas-producing foods in order to minimize presence of rectal gas during therapy (as described in handouts provided by nursing staff at consultation).
If a patient is determined to have a distended rectum at the time of initial scanning, patient will be given opportunity to evacuate and a repeat CT scan performed until treating physician determines it is satisfactory.

5.1.3 A rectal balloon may be inserted at simulation and during daily therapy to minimize variability in rectal contents/dosimetry.[12]

5.2 Target and Normal Tissue Volumes
The target volume definitions are, for the most part, based upon the *ICRU Report 58, Dose and Volume Specification for Reporting Interstitial Therapy*.
a) Gross Target Volume (GTV): The GTV is the entire prostate, as well as any extraprostatic spread visualized on imaging or clinical examination.
b) Clinical Target Volume (CTV): In the case of intermediate risk disease, the CTV will include the prostate and will also encompass the proximal 1 cm of seminal vesicle (overlap of seminal vesicle with 1 cm expansion on prostate; in Pinnacle this can be accomplished by contouring entire seminal vesicle, then using auto-expand ROI function with prostate as ‘source’ and seminal vesicle turned on as ‘avoid exterior’).

c) Planning Target Volume (PTV): The PTV is the CTV plus 3-5 mm margin expansion in all directions except posteriorly, for which a 1-3 mm expansion will be utilized.
d) Rectum will be contoured from approximately the level of the bottom of the ischial tuberosities (where the rectum joins the anal canal) superiorly to the rectosigmoid junction (generally below the sacroiliac joints, or until the rectum no longer is adjacent to the sacrum which is typically greater than 10 cm).
e) Anus (the inferior-most 3cm of the anorectal canal, or 10 slices on 3mm CT cuts)
f) Penile bulb (contoured on the proximal/superior 3 slices or 1cm on CT)
g) Bladder (entire bladder)
h) Small bowel (contoured up to the level of the top of the sacroiliac joints)
i) Femoral heads

ROI designation	Description
GTV	Gross Tumor Volume (prostate)
CTV	Clinical Target Volume (Prostate plus expansion)
PTV	Planning Target Volume (CTV plus expansion)
Bladder	Bladder
Bulb	Penile bulb
Rectum	Rectum
Anus	Anus
SV	Seminal Vesicles
Femur right	Right Femur
Femur left	Left Femur

5.3 Treatment planning

Intensity-modulated radiation will be utilized to achieve a plan meeting the criteria for dose coverage of the PTV and minimizing dose to critical structures. Dose-volume histograms (DVHs) must be generated for all critical normal structures.

5.3.1 Compliance criteria

a) No variation (total coverage): Prescription isodose covers greater than or equal to 95% of the PTV and 99-100% of the CTV.
b) Minor variation (marginal coverage): Prescription isodose coverage between 90-95% of the PTV and 95-98.9% of the CTV.
c) Major variation: Prescription isodose coverage less than 90% of PTV or less than 95% of CTV.

5.3.2 Dose constraints

Based on an alpha/beta ratio of 3 for rectum and bladder late toxicity, as well as dose constraints for rectal and bladder toxicity as determined from prior studies with conventional fractionation, dose constraints for rectum will be:
a) no more than 50% of rectum receives greater than 50% of the prescribed dose
b) no more than 20% of rectum receives greater than 80% of the prescribed dose
c) no more than 10% of rectum receives greater than 90% of the prescribed dose
d) no more than 5% of rectum receives greater than 100% of the prescribed dose
e) Dose constraints for bladder will follow the same dose constraints as those outlined above for the rectum.

f) femoral head DVH goal is no more than 5% of femoral head receives greater than 40% of the prescribed dose [6]

5.3.3 Dose Heterogeneity
a) IMRT/VMAT - Maximum dose to the PTV volume should not exceed prescription dose by more than 7% (1 cc <38.78 Gy). Maximum point dose to critical normal structures outside the PTV including unspecified tissue should not exceed prescription dose by more than 5% (1 cc <38.06 Gy).
b) CyberKnife - Maximum dose to the PTV volume should not exceed prescription dose by more than 20% (1 cc <43.5 Gy). Maximum point dose to critical normal structures outside the PTV including unspecified tissue should not exceed prescription dose by more than 5% (1 cc <38.06 Gy).

5.4 Image-guided and adaptive therapy

5.4.1. If volumetric modulated arc therapy (VMAT) is used then the patient will be aligned with the fiducials* and/or daily cone beam CT scan on the treatment machine. If a rectal balloon is used and requires adjustment, images will be re-taken to ensure appropriate set-up. At the completion of each rotation of the treatment gantry, another kV image and/or CBCT will be taken to ensure set-up accuracy prior to the initiation of the next rotation. A total of three rotations of the gantry will comprise a single day of treatment (2.42 Gy per rotation with three rotations producing a total dose of 7.25 Gy per day).

*Fiducials is optional if additional image guidance is being used

5.4.2. If the CyberKnife is used then image-guided treatment will proceed using the near real-time tracking features of system. The CyberKnife consists of a 6-MV linear accelerator mounted on a robotic arm. A unique feature of the CyberKnife image-guidance system is that the robotic arm is automatically repositioned to track the target using stereoscopic in-room kV x-ray source and a pair of amorphous silicon flatpanels.

5.5 Androgen Deprivation Therapy (ADT)
Androgen deprivation therapy, also known as hormonal ablation, is designed to inhibit the effects of testosterone on prostate cancer cells. This will be accomplished by medications designed to block testosterone production in the hypothalamus (goserelin/leuprolide/triptorelin) and medications designed to block testosterone receptors at the cell surface (bicalutamide). Each of these drugs is approved by the FDA for the treatment of prostate cancer. Goserelin, leuprolide, or triptorelin will be used for four months (≥ 1 month prior to radiation therapy), with at least two weeks of bicalutamide prior to start of RT. Bicalutamide may be continued through the duration of radiation at the physician's discretion. Doses and drug information may be found at the websites below:

- Goserelin (Zoladex®) – http://www1.astrazeneca-us.com/pi/zoladex3_6.pdf
- Leuprolide (Lupron®) - http://pitap.abbott.com/lupron3month22_5mg.pdf
- Triptorelin (Trelstar®) - http://pi.actavis.com/data_stream.asp?product_group=1684&p=pi&language=E
- Bicalutamide (Casodex ®) - http://www1.astrazeneca-us.com/pi/casodex.pdf

5.6 Patient management during treatment

All patients will be seen one time by the radiation oncologist during treatment. Radiation reactions will be recorded with attention toward the following:
a) Rectal or small bowel symptomatology (cramping, diarrhea, rectal urgency, hematochezia)
b) Bladder symptomatology (frequency, urgency, nocturia, dysuria)
c) Radiation dermatitis
d) Side effects will be treated based on the discretion of the radiation oncologist, and documentation kept in the medical record. Rectal side effects such as diarrhea may be treated with diphenoxylate or loperamide. Bladder or rectal spasms can be treated with anticholinergic agents or tolterodine. Irritative or obstructive voiding symptoms can be managed with alpha-blockers or phenazopyridine.

6.0 PATIENT ASSESSMENTS

6.1 Study Parameters

- H&P – at initial consult and following treatment protocol
- PSA – At baseline, 3 and 6 months after treatment, then every 6 months until 3 years, and then annually until year 5
- Testosterone – At baseline, 3 and 6 months after treatment, then every 6 months until 3 years, and then annually until year 5
- Bone Scan - at baseline*
- Pelvic CT or other lymph node assessment - at baseline*
- Symptom assessment (IPSS, SHIM, modified EPIC sheet, as per Appendix I) – At baseline, 3 and 6 months after treatment, then every 6 months until 3 years, and then annually until year 5
- Serum ALT, AST and AP at baseline and one month following initiation of ADT.
- Optional Blood draw collected at baseline and at 3 and 24 months following treatment completion. Patients who have initiated ADT prior to consent for optional blood samples will be ineligible to give extra blood samples.
- Seed placement of at least 3 gold seeds at least 1 week prior to first CT simulation if additional image guidance is not being used
- CT simulation will occur prior to radiation treatment as standard of care and then again during radiation any time after fraction 3 as a QA procedure for monitoring prostate rotation in relation to seed placement. However, second CT simulation after fraction 3 is only necessary if patient had fiducial placement.

* CT/MRI and Bone scan optional except for the patients who are:

1. Gleason 4+3
2. >50% cores positive
3. >1 intermediate risk factor (GS 7, PSA $\geq$10 and T2b-T2c).

Safety run-in phase
A phase I trial of SBRT in prostate cancer (n=45) composed of 60% intermediate-risk, localized patients where 22% of men were treated with androgen deprivation has been recently reported (ref. 7). This trial used considerably higher SBRT doses than our current trial (9-10 Gy x5 versus 7.25 Gy x5) and still reported no Grade 3 or 4 GI or GU acute toxicities (<90 days). Therefore, we believe our more modest SBRT fractionation scheme of 7.25 Gy x5 is likely safe in combination with androgen deprivation. To ensure that this combination is safe, the first six patients will be treated and analyzed for toxicity for 3

months after radiation. Six patients will be enrolled at the proposed dose of SBRT and androgen deprivation therapy and if 0 or 1 patient experiences a dose limiting toxicity (DLT) then this regimen will be considered safe (note: accrual will continue while the interim analysis is being conducted). If >1 patient experiences a DLT than this regimen will be considered unsafe and the trial will stop at this point. DLT for the purpose of calculation of the maximum tolerated dose (MTD) includes medically unmanageable Grade 3 or any Grade 4 toxicity with an *attribution* of probably related to protocol intervention (see section 10.2).

6.2 Follow-up Schedule

6.2.1 Patients will be assessed at three months and at six months after treatment, then every 6 months until 3 years, then annually until year 5. The patient will be off study after 5 years.

6.2.2 Patients who develop a rise in PSA of greater than 25% and of at least 0.3 ng/ml compared to the prior PSA will have PSA drawn every 3 months until PSA either returns to nadir value or rises to a value 2 ng/ml or more above the nadir. The nadir PSA is defined as the lowest PSA value after initiation of treatment. Time of failure will be the date of the first PSA that is 2 ng/ml or more above the nadir.

6.2.3 At any point in time, patients may undergo biopsy for histopathologic assessment of disease response, if there is evidence of recurrence.

7.0 STUDY CALENDAR

	Pre-treatment	Radiation[14]	Follow-Up[16] (in time post radiation treatment)										
			1 mo	2 mo	3 mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	Year 4	Year 5
Initial Consult	X												
Consent	X												
History and Physical	X				X	X	X	X	X	X	X	X	X
Digital Rectal Exam[15]	X				X	X	X	X	X	X	X	X	X
Biopsy[12]													
Histological Diagnosis[1]	X												
MRI *	X[3]												
Pelvic CT scan *	X[3]												
Bone scan *	X[4]												
Cardiovascular risk assessment	X[5]												
Quality of Life measures[6]	X				X	X	X	X	X	X	X	X	X
Toxicity assessment[9]	X	X			X	X	X	X	X	X	X	X	X
Biomarker blood draw (optional)	X				X				X				
Serum ALT, AST, and AP[10]	X												
Seed placement[7]	X												
CT Simulation[17]	X	X											
PSA[11]	X[2]				X	X	X	X	X	X	X	X	X
Testosterone	X				X	X	X	X	X	X	X	X	X
LHRH agonist[13]	X	X	X	X									
Bicalutamide[8]	X	X	X	X									

[1]Histological diagnosis and Gleason score provided on the pathology report. All patients, per institutional policy, will have pathology reviewed at Johns Hopkins

[2]PSA within 4 months prior to registration

[3]CT scan or MRI of the pelvis within 6 months prior to registration. Lymph nodes evaluated negative by imaging methods will be classified as NX. Only nodes evaluated negative by surgical sampling will be classified as N0.

[4]Bone scan within 2 months prior to registration

[5]Cardiovascular risk assessment if the patient is determined to be "high risk" for vascular event – prior MI or stroke within 5 years

[6]IPSS (less than 16 or patient is excluded from trial participation), SHIM, and modified EPIC bowel questionnaires

[7]At least 1 week prior to simulation, patients will undergo transrectal or transperineal inserting of at least 3 gold seeds to improve accuracy in daily prostate alignment and decrease residual positioning errors. However, if additional image guidance is being used, fiducials will be optional.

[8]At least two weeks of bicalutamide at the initiation of hormone therapy and may be continued through the duration of radiation at the physician's discretion.

[9]Patients will be seen one time by the radiation oncologist during treatment

[10]Serum ALT, AST and AP collected before the initiation of ADT and one month (+/- 14 days) following initiation of ADT

[11]Patients who develop a rise in PSA of greater than 25% and of at least 0.3 ng/ml compared to prior PSA will have PSA drawn every 3 months until PSA either returns to nadir value or rises to a value 2 ng/ml or more above the nadir. The nadir PSA is defined as the lowest PSA value after initiation of treatment. Time of failure will be the date of the first PSA that is 2 ng/ml or more above the nadir.

[12]At any point in time, patients may undergo biopsy for histopathologic assessment of disease response, if there is evidence of recurrence.

[13]Androgen deprivation therapy will be given for 4 months total, (must be given ≥ 1 month prior to the start of radiation therapy)

[14]Radiation will be given in 5 fractions over 2 weeks (treatment to be performed every other day)

[15]Rectal exam is required at baseline. During follow-up it is at the discretion of the treating physician

[16] Follow-up appointments for 1 month, 2 months, and 3 months have a +/- 7 day tolerance window and all other follow-up appointments have a +/- 30 day tolerance window.
[17] CT simulation will occur prior to radiation therapy and then again during radiation therapy as a QA procedure after fraction 3 only if patients had fiducial placement.
*CT/MRI and bone scan optional except for the patients who are: 1. Gleason 4+3 2. >50% cores positive 3. >1 intermediate risk factor (GS 7, PSA $\geq$10 and T2b-T2c).

8.0 DATA ANALYSIS AND SPECIAL CONSIDERATIONS

8.1 Primary Analysis:

The primary objective is to estimate the 5-year biochemical failure free rate (BFFR) associated with the combined hypofractionated dose regimen and ADT. The BFFR is defined as a binary indicator whether PSA has increased by 2 ng/ml or more above the nadir PSA any time before the end of 5 years. The primary analysis will be performed by first obtaining the Kaplan-Meier (K-M) estimate of the biochemical failure free survival, and then estimating the 5-year biochemical failure free rate (BFFR) from this K-M curve together with 95% confidence interval. Greenwood formula will be used to calculate the variance of K-M estimate.

8.2 Secondary objectives:

8.2.1. Assess the incidence of grade 3 or greater late GU and GI toxicity and self-reported quality of life data.

Kaplan-Meier estimate of the incidence of grade 3 or greater late GU and GI toxicity will be constructed together with 95% confidence interval. Patient reported quality of life will be summarized using means and standard deviation for continuous measures, the contingency tables for categorical measures.

8.2.2 Assess clinical and pathologic control rates associated with the combined hypofractionated dose regimen and ADT.

Assessments will be performed 3 and 6 months after treatment and then every 6 months until 3 years, then annually until year 5. These rates will be estimated from Kaplan-Meier curves together with 95% confidence intervals.

Disease-Free Survival, measured from the date of enrollment to the date of documented progression or date of death using Kaplan-Meier estimates. Progression will be documented by PSA, bone scan, or biopsies.

Time to Local Progression (TLP) will be measured from the date of enrollment to the date of documented local progression using Kaplan-Meier estimates. Patients with new palpable abnormality on digital rectal examination or PSA failure at any point in time will also be offered biopsy to distinguish between local and distant failures. Patients who do not undergo biopsy will be censored at the last point of time they were considered locally controlled by digital rectal examination and PSA and considered not evaluable for further assessment.

Time to Distant Failure (TDF) will be measured from the date of enrollment to the date of documented metastastic disease. Patients who have negative biopsy following PSA failure or palpable abnormality will be considered to have only distant failure.

Overall survival (OS), measured from date of enrollment to date of death using Kaplan-Meier estimates. Every effort will be made to document the cause of death.

8.2.3 Collect dose/volume and imaging data to allow normal tissue complication probability modeling and targeting assessment for patients treated with hypofractionated radiation therapy and ADT.

Voxel level dose distribution, normal tissue complication, and tumor control will be collected. All images will be co-registered and normalized. Functional principal component analysis will be used to develop dose response and tumor control models.

8.2.4 To explore the changes in serum levels of inflammatory and angiogenic cytokines as biomarkers of treatment response, we will use Bioplex 200 technology to batch analyze a 27 cytokine panel in paralllel at baseline and after 3 and 24 months of completing treatment. The blood collected in one 8 ml serum separation tube (BD vacutainer, lavender-top) will be allowed to stand 45-60 minutes and processed within one hour. The tube will be centrifuged at 1200g for 10 min in a swing out rotor (approximately 2500rpm). The serum will be transferred into a clean empty 15ml tube using Pasteur pipette. The serum will be aliquoted into 1.05 ml volume in each cryopreservation vial and stored in –80^{o}C or -20^{o}C freezer. We will process the samples as described previously by our Co-I Dr. Drake[13]. Briefly, The Bioplex 200 (Bio-Rad, Hercules, CA) platform will be used to determine the absolute concentration (in pg/ml) of 27 target proteins in banked sera samples. A multiplexed bead-based immunoassay is performed in duplicate for each serum sample following the manufacturer's protocols and using the supplied cytokine standards. The concentration of each cytokine will be determined using a 5-parameter log curve fit using the supplied software. The Human 27-plex panel includes validated assays for IL-1b, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12(p70), IL- 13, IL-15, IL-17, eotaxin, basic FGF, G-CSF, GM-CSF, IFNg, IP-10, MCP-1, MIP1a, MIP1b, PDGF-BB, vascular endothelial growth vactor (VEGF), and TNFa. This data will be correlated with primary and other secondary objectives.

8.3 Sample size

The primary endpoint is the 5-year biochemical failure free rate (BFFR) associated with the combined hypofractionated dose regimen and ADT. All patients will be followed for at least 5 years. We expect to observe 5-year BFFR 85% or higher. The annual dropout rate is expected to be at most 1% ~ 2% (or cumulative 5 year dropout rate is less than 10%). If 100 patients will finish 5 year follow up, the width of 95% confidence interval of BFFR will be less than 0.14. To incorporate the dropout rate, the total required sample size will be 110.

8.4 Safety monitoring.

An early stopping boundary will be used to test the hypotheses H0: Rt≤10% versus H1: Rt>10% where Rt is the rate of grade 3 or greater on either GU or GI toxicity. We derive the one-sided stopping boundary using exact binomial test: at the first stage with 50 patients recruited, if 12 or more patients have experienced grade 3 or greater toxicity with an *attribution* of probably related (see section 10.2), the trial will be stopped. Otherwise, the trial will continue to recruit all 100 patients. If no more than 16 patients out of total 100 patients have experienced grade 3 or greater toxicity as detailed previously, the treatment is considered safe for further investigation. Based on EAST 5 (Copyright © 2009 Cytel Inc) Bionomial one-sample exact test for single proportion, this stopping rule gives 87% power to reject unsafe treatment regime if the true toxicity rate is 20%.

9.0 ACCRUAL AND STUDY DURATION

Of approximately 90 patients per month seen in consultation for prostate cancer each month in the department of radiation oncology (East Baltimore, Green Spring Station, Sibley and Suburban sites total), we anticipate approximately 25% of patients to be eligible. All eligible patients will be offered enrollment on the study, and we estimate a 30% accrual rate with 5% dropout rate, resulting in an average of at least 7 patients enrolled per month. The planned study open date is June 2013 for the East Baltimore site and May 2014 for Sibley and Suburban sites. The projected closure date of accrual is August 2015. The total length of the study would be from June 2013-August 2020.

10.0 REPORTING OF ADVERSE EVENTS

10.1 General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v 4.0) and the LENT-SOMA criteria.[14] The CTCAE v 4.0 is available at http://ctep.cancer.gov/reporting//ctc.html.

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by participants will be collected and recorded from initiation of study, throughout the study, and within 5 years post radiation therapy. Participants who experience an ongoing adverse event related to a study procedure beyond 5 years post RT will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

10.2 Definitions

Adverse Event (AE): An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

Serious Adverse Event: means an event that is
- fatal
- life-threatening
- persistent or significantly disabling or incapacitating
- inpatient hospitalization or prolongation of hospitalization

• congenital anomaly or defect and/or
• a significant medical incident (considered to be a serious study related event because, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.)

Events not considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

Important Adverse Event: means an event, although not a Serious Adverse Event, which still presents an undesirable occurrence that interferes with the subject's usual activities and may be persistent or require treatment. (For example, serious rash, cough, or fever.)

Expectedness:

- Expected: Expected adverse events are those that have been previously identified as resulting from administration of protocol intervention. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, package inserts or is included in the informed consent document as a potential risk.
- Unexpected: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, package inserts or when it is not included in the informed consent document as a potential risk

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

10.3 Reporting Procedures

10.3.1 General
All adverse events will be captured on the appropriate study-specific case report forms (CRFs).

10.3.2 All **fatal** events, both **expected and unexpected**, must be reported to the JHM IRB within a time period as specified by current institutional guidelines after the PI learns of the event, whether or not the PI believes the event to be related to the study. All other events, which are both **serious** and **unexpected**, must be reported to the JHMI IRB within a time period as specified by current institutional guidelines after the PI learns of the event. Events which are **serious** but **expected**, should be reported as part of the continuing review

application. If any of these Serious Adverse Events requires a change to the protocol or consent form, the PI must make those changes promptly and submit the revised documents to the JHM IRB.

10.3.3 **Important** Adverse Events that are **unexpected** must be reported to the JHM IRB within a time period as specified by current institutional guidelines. If the Important Adverse Event requires changes to the protocol or consent form, the PI must make those changes promptly and submit the revised documents to the JHM IRB.

10.3.4 All other **unexpected** Adverse Events or changes to the protocol and consent form must be reported to the JHM IRB, within a time period as specified by current institutional guidelines

10.4 Following a Study Related Adverse Event

If a patient experiences an adverse event while on study, the following steps will be taken:
1) Establish the cause and severity of the adverse event and determine if said event is related to study participation.
2) Principal Investigator will decide what treatment(s), if any, is/are required.
3) Depending on the type and severity of adverse event, an appropriate follow-up schedule will be constructed which will allow for determination of event outcome.
4) Patient will be followed by principal investigator until the adverse event has resolved.

11.0 DISPOSITION OF DATA

Clinical records for all subjects studied including history and physical findings, laboratory and clinical data, and operative and dosimetric records are to be maintained by the investigators in a secure location at Johns Hopkins Cancer Center. Any records that are stored electronically will be password protected and only those who are involved in the research will have a password. These records are to be stored for a minimum of 8 years after last clinical visit.

12.0 PROTOCOL MODIFICATIONS

All revisions or amendments (that are not required for immediate patient safety) to the protocol must be approved by the Johns Hopkins Institutional Review Board prior to implementation.

13.0 DEPARTURES FROM PROTOCOL

If there is a departure from the Clinical Protocol, the Principal Investigator will notify in writing the local IRB at Johns Hopkins at the time of annual review (continuing review). The research coordinator will keep a log of all deviations/departures that occur on this project and this log will be reviewed by the research team on a monthly basis. During the review the research team will discuss corrective action plans to minimize future deviations/departures. If there are departures to the protocol that effects patient safety the principal investigator will notify in writing the IRB within 24 hours of discovering the departure/deviation.

14.0 CRITERIA FOR WITHDRAWAL FROM STUDY

Patients may be withdrawn from the study for the following reasons:
a) Consent for participation is withdrawn
b) Noncompliance to study procedures

c) Development of intercurrent, non-cancer related illness that prevents either continuation of therapy or regular follow-up.

15.0 ROLES AND RESPONSIBILITIES OF STUDY PERSONNEL

Principal Investigator: Oversees all aspects of the trial. Recruits and consents patients and administrates protocol specific procedures. Provides medical care to research subjects during the conduct of the study. Follows and advises regarding the treatment of adverse events. Reports SAE's to the IRB within the required time frame. Amends the trial as necessary to reflect unforeseen adverse events, new scientific data and for the general integrity of the study. Monitors the trial. Is ultimately responsible for the conduct of protocol.

Co-Investigators: If a physician**:** can recruit and consent patients and can administrate protocol specific procedures. Can provide medical care to research subjects during the conduct of the study. Has input on the course of action for adverse events.
If not a physician**:** Collaborates with the Principal Investigator according to area of expertise.

Research Nurses: Executes protocol specific procedures requiring nursing qualifications. Provide nursing care to research subjects during the conduct of the study. May consent patients for study enrollment.

Data Manager/Study Coordinator: Collects data from subject's medical records and codes it onto the study's case report forms. Notifies principal investigator of any deviations that he/she finds while managing the data. Prepares annual IRB renewals and termination report upon study completion, assists with management of regulatory issues governing the trial. Monitors the trial.

16.0 PARTICIPATING SITE GUIDELINES

This study will be conducted in accordance with the Sidney Kimmel Comprehensive Cancer Center's Coordinating Center Protocol.

Patient Registration

Prior to protocol enrollment and initiation of treatment, subjects must sign and date an IRB approved consent form. All patients must be registered centrally at the Sidney Kimmel Comprehensive Cancer Center.

To register a patient, the following documents must be completed and faxed (443-287-8354) or e-mailed to the Coordinating Center:

- Signed patient consent form
- Registration Form
- Copies of pertinent lab results, pathology reports, etc. (*please specify what source documents are required to confirm eligibility, if applicable*)

The Coordinating Center will review the documents to confirm eligibility. To complete the registration process, the Coordinating Center will:

- assign a patient study number
- register the patient on the study with the Sidney Kimmel Comprehensive Cancer Center's Clinical Research Office
- fax or e-mail the patient study number to the participating site.

Multicenter Guidelines

Protocol Chair

The Protocol Chair is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE)
- Reviewing data from all sites.

Coordinating Center

The Coordinating Center is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Registering all patients with the Coordinating Center by submitting patient registration form, and signed informed consent promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

Quality Assurance

This is a Level I study under the SKCCC Data Safety Monitoring Plan. Data Monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee at SKCCC. The Coordinating Center PI and study team at Johns Hopkins will conduct semimonthly teleconferences with all the sub-sites participating. Dr. Joseph Herman from Johns Hopkins will serve as the unbiased and impartial internal physician monitor and will attend these semimonthly teleconferences. These conferences will include a comprehensive overview (across all sites) of SAE's, AEs, regulatory, enrollment, data capture, and overall study progress.

Authorized representatives of the Coordinating Center may visit participating sites to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

Data Submission

Completed case report forms along with their corresponding redacted source documentation must be transmitted by secure facsimile report, email, or internet database to the Coordinating Center monthly. Case report forms will be provided to participating sites by the Coordinating Center.

Adverse Event Reporting

Definition of Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical trials, from the time of signing an informed consent, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no trial treatment has been administered.

Definition of Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any trial phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Protocol Chair

The Protocol Chair is ultimately responsible for the required reporting of all adverse events.

Coordinating Center

The Coordinating Center is the central location for the collection and maintenance of documentation of adverse events and is responsible for submitting adverse event reports to the Protocol Chair promptly. The Coordinating Center will maintain documentation of all adverse event reports for each participating site. Adverse event reports submitted to the Coordinating Center must be signed and dated by the participating site's Principal

Investigator. The Coordinating Center will provide appropriate forms to be used by all participating sites for reporting adverse events. Information to be provided must include:

- Subject ID number, and initials
- Date of the event
- Description of the event
- Description of site's response to the event
- Assessment of the subject's condition
- Subject's status on the study (on study, off study, etc.)
- Attribution of event to study drug

Participating Sites

Participating sites are responsible for reporting adverse events to their IRB according to its specific requirements and to the Coordinating Center as follows:

Fatal Events whether anticipated or unanticipated, and whether or not related to the study must be reported to the Coordinating Center within **24 hours** of the participating site Principal Investigator's learning of the event.

Serious and Unanticipated Adverse Events as defined above must be reported to the Coordinating Center within **24 hours** of the participating site Principal Investigator's learning of the event.

Other Serious Adverse Events which may result in a change to the protocol, informed consent, or risk to subjects as specified in the protocol must be reported within **three (3) working days** of the participating site Principal Investigator's learning of the event.

Adverse Events which result in no change to protocol, informed consent, or risk to subjects must be reported to the Coordinating Center on a monthly basis.

Adverse event reports are to be faxed to the Coordinating Center at 443-287-8354. Follow-up reports are faxed, mailed, or sent electronically to the Coordinating Center as necessary.

The investigator must also report follow-up information about SAEs within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided within the same time frames described above.

All SAEs must be collected whether or not they are considered causally related to the investigational product. Investigators and other site personnel are responsible for reporting all casually related SAEs to their IRB and the Protocol Chair.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 IRB: Prior to initiating the study, the Principal Investigator must obtain written approval to conduct the study from the appropriate IRB. Should changes to the study protocol become necessary, protocol amendment will be submitted in writing to the IRB by the Principal Investigator for IRB approval prior to implementation.

17.2 Informed Consent: All potential candidates for the study will be given a copy to read of the Informed Consent for the study. The investigator will explain all aspects of the study in lay language and answer all the candidate's questions regarding the study. If the candidate desires to participate in the study, he/she will be asked to sign the Informed Consent. No study procedures will be performed on a patient until after they have signed the informed consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

17.3: The principal investigator will ensure that the study is conducted in compliance with the protocol and according ICH Guidelines for Good Clinical Practices, the Declaration of Helsinki, and all regulatory and institutional requirements, including those for patient privacy, informed consent, Institutional Review Board approval and record retention.

18.0 DATA SAFETY AND MONITORING PLAN

The principal investigator, co-investigator radiation oncologist, research nurses, and study coordinator will review the data on a regular basis through regularly scheduled study team meetings. This trial will be audited annually by the central clinical research office at Johns Hopkins as well as by the Hopkins Safety Monitoring Committee.

This is a DSMP Level I study under the SKCCC Data Safety Monitoring Plan (12/06/2012). The Clinical Research Office QA Group will perform an audit after the first subject has been treated and then periodically depending on the rate of accrual and prior audit results. All trial monitoring and reporting will be reviewed annually by the SKCCC Safety Monitoring Committee. The PI is responsible for monitoring the study. Data must be reviewed to assure the validity of data, as well as, the safety of the subjects. The PI will also monitor the progress of the trial, review safety reports, and clinical trial efficacy endpoints and to confirm that the safety outcomes favor continuation of the study. The PI will be responsible for maintaining the clinical protocol, reporting adverse events, assuring that consent is obtained and documented, reporting of unexpected outcomes, and reporting the status of the trial in the continuing renewal report submitted to the IRB and to the trial monitoring review group. Content of the continuing renewal report at a minimum should include year-to-date and full trial data on: accrual and eligibility, protocol compliance, treatment administration, toxicity and ADR reports, response, survival, regulatory compliance, compliance with prearranged statistical goals. The report should be submitted in a timely manner according to the schedule defined by Johns Hopkins Medicine Institutional Review Board.

19.0 LIST OF DATA COLLECTION SHEETS

IPSS Scoring Form
EPIC questionnaire
SHIM questionnaire

20.0 REFERENCES

1. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol.* Aug 1989;62(740):679-694.

2. Haustermans KM, Hofland I, Van Poppel H, et al. Cell kinetic measurements in prostate cancer. *Int J Radiat Oncol Biol Phys.* Mar 15 1997;37(5):1067-1070.

3. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys.* Mar 15 1999;43(5):1095-1101.

4. Duchesne GM, Peters LJ. What is the alpha/beta ratio for prostate cancer? Rationale for hypofractionated high-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys.* Jul 1 1999;44(4):747-748.

5. Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumors really low? *Int J Radiat Oncol Biol Phys.* Jul 15 2001;50(4):1021-1031.

6. King CR, Brooks JD, Gill H, Pawlicki T, Cotrutz C, Presti JC, Jr. Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. *Int J Radiat Oncol Biol Phys.* Mar 15 2009;73(4):1043-1048.

7. Boike TP, Lotan Y, Cho LC, et al. Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer. *J Clin Oncol.* May 20 2011;29(15):2020-2026.

8. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med.* Jul 14 2011;365(2):107-118.

9. Joon DL, Hasegawa M, Sikes C, et al. Supraadditive apoptotic response of R3327-G rat prostate tumors to androgen ablation and radiation. *Int J Radiat Oncol Biol Phys.* Jul 15 1997;38(5):1071-1077.

10. Yoshioka Y, Konishi K, Sumida I, et al. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: five-year results of an extreme hypofractionation regimen with 54 Gy in nine fractions. *Int J Radiat Oncol Biol Phys.* Jun 1 2011;80(2):469-475.

11. Levine GN, D'Amico AV, Berger P, et al. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *CA Cancer J Clin.* May-Jun 2010;60(3):194-201.

12. D'Amico AV, Manola J, Loffredo M, et al. A practical method to achieve prostate gland immobilization and target verification for daily treatment. *Int J Radiat Oncol Biol Phys.* Dec 1 2001;51(5):1431-1436.

13. Zabransky DJ, Smith HA, Thoburn CJ, et al. Lenalidomide modulates IL-8 and anti-prostate antibody levels in men with biochemically recurrent prostate cancer. *Prostate.* Apr 2012;72(5):487-498.

14. Pavy JJ, Denekamp J, Letschert J, et al. EORTC Late Effects Working Group. Late Effects toxicity scoring: the SOMA scale. *Int J Radiat Oncol Biol Phys.* Mar 30 1995;31(5):1043-1047.

APPENDIX A

INTERNATIONAL PROSTATE SYMPTOM SCORE (I-PSS)

Name _____ Date _____

	Not at all	Less than 1 time in 5	Less than half time	About half the time	More than half the time	Almost always
1. Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
3. Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Urgency Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
	None	1 time	2 times	3 times	4 times	5 times or more
7. Nocturia Over past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5

Total I-PSS Score_____

(questionnaire continued on next page)

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly satisfied	Mixed -About equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with the urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Urinary incontinence	Rarely or never	About once a week	More than once a week	About once a day	More than once a day
Over the past 4 weeks, how often have you leaked urine?	0	1	2	3	4

Urinary incontinence	Total control	Slight occasional leakage after voiding	Occasional leakage associated with urgency	Some control but frequent uncontrollable leakage	No control at all, constant leakage
Which best describes your urinary control?	0	1	2	3	4

Patient Signature _____

APPENDIX B

Sexual Health Inventory for Men

Name _____ Date _____

Circle the number of the response that best describes your own situation. Please be sure that you select one and only one response for each question, describing your experience **over the past 6 months**.

Check here if you use one of the following: Viagra, Cialis, Levitra (please answer questions according to your condition when taking the medication)_____

OVER THE PAST 6 MONTHS: (CHECK HERE IF YOU HAVE NOT BEEN SEXUALLY ACTIVE _____)

1. How do you rate your confidence that you could get and keep an erection?

Very low	Low	Moderate	High	Very high
1	2	3	4	5

2. When you had erections, how often were your erections hard enough for penetration (entering your partner)?

No sexual activity	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than, half the time)	Almost always or always
0	1	2	3	4	5

3. How often were you able to maintain your erection after you had penetrated (entered) your partner?

Did not attempt intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than, half the time)	Almost always or always
0	1	2	3	4	5

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

Did not attempt	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
0	1	2	3	4	5

5. When you attempted sexual intercourse, how often was it satisfactory for you?

Did not attempt intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than, half the time)	Almost always or always
0	1	2	3	4	5

Total Score _____ Patient Signature _____

APPENDIX C

BOWEL HABITS
The next section is about your bowel habits and abdominal pain.
Please consider **ONLY THE LAST 4 WEEKS.**

Name _____ Date _____

	Never	Rarely	About half the time	Usually but not always	Always
1. How often have you had rectal urgency (felt like you had to pass stool, but did not) **during the last 4 weeks?**	0	1	2	3	4
2. How often have you had uncontrollable leakage of stool of feces?	1	2	3	4	5
3. How often have you had crampy pain in your abdomen, pelvis or rectum **during the last 4 weeks**?	1	2	3	4	5
4. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) **during the last 4 weeks**?	1	2	3	4	5
5. How often have you had bloody stools **during the last 4 weeks**?	1	2	3	4	5
6. How often have your bowel movements been painful **during the last 4 weeks**?	1	2	3	4	5
7. How often do you have to wear pads or diapers because of leakage of stools or mucus from your rectum?	1	2	3	4	5
8. How often do you take anti-diarrheal medication (such as Imodium or Lomotil)?	1	2	3	4	5
9. Overall, how often have your bowel habits been a problem for you **during the last 4 weeks**?	1	2	3	4	5

10. How many bowel movements have you had on a typical day **during the last 4 weeks**?		2 or less	3-4	5 or more	

Total score _____ Patient Signature _____