THOMAS JEFFERSON UNIVERSITY

PHASE I TRIAL OF HIGH DOSE RATE BRACHYTHERAPY COMBINED WITH STEREOTACTIC BODY RADIATION THERAPY FOR INTERMEDIATE RISK PROSTATE CANCER PATIENTS

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List of Abbreviations

SBRT Stereotactic Body Radiation Therapy
HDR High dose rate
LDR low dose rate
IMRT Intensity Modulated Radiation Therapy
VMAT Volumetric Modulated Arc Therapy
NCCN National Comprehensive Cancer Network
GI gastrointestinal
GU genitourinary
PSA prostate specific antigen
EBRT externa beam radiation therapy
CREST(calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia)
EPIC Expanded Prostate Cancer Index Composite
MTD maximum tolerated dose
AUA American Urologic Association
DLT dose limiting toxicity
CTV clinical target volume
PTV planning target volume
V_x volume of tissue receiving X Gy of radiation therapy
D_x dose that X volume of tissue is receiving
ICRU International Commission on Radiation Units
Gy Gray
CT computed tomography
QOL quality of life
CRMO Clinical Research Management Office
FDA Food and Drug Administration
KCC Kimmel Cancer Center
DSMC Data and Safety Monitoring Committee
IRB Institutional Review Board
SAE Severe adverse event
AE Adverse event
TJUH Thomas Jefferson University Hospital
CRF Case report forms

Study Summary

Title	*PHASE I TRIAL OF HIGH DOSE RATE BRACHYTHERAPY COMBINED WITH STEREOTACTIC BODY RADIATION THERAPY FOR INTERMEDIATE RISK PROSTATE CANCER PATIENTS*
Short Title	*Using a temporary radioactive implant and short course of radiation to treat prostate cancer*
Protocol Number	*CCRRC # 2012-10* *IRB # 12D.210)*
Phase	*Phase I*
Methodology/Study Design	*Single Arm Dose Escalation Trial*
Study Duration	*28 years (to reach MTD, 5 years including expansion cohort)*
Study Center(s)	*Single-center*
Objectives	*To determine the safety of hypofractionation in combination with a high dose rate implant for men with prostate cancer*
Number of Subjects	*42 (maximum)*
Diagnosis and Main Inclusion Criteria	*Adenocarcinoma of the prostate, T2b-T2c or Gleason score 7 or PSA 10-20 ng/ml, no prior pelvic radiation, KPS>70*
Study Product, Dose, Route, Regimen	*N/A*
Duration of administration	*N/A*
Reference therapy	*IMRT alone or LDR implant with IMRT*
Statistical Methodology	*'3+3' Phase I Design. Data analysis of phase I studies is descriptive. All estimates of dose specific rates (e.g., toxicity) will be presented with corresponding confidence intervals using the exact method.*

1.0 INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures. The primary objective of this study is to determine the safety and toxicity profiles of HDR combined with SBRT. This is a Phase I trial that uses a standard "3+3" design for dose escalation through escalation of radiation dose fraction size with 3 planned dose levels.

1.2 Background and Rationale

Prostate cancer is the most common non cutaneous malignancy diagnosed in the United States [Jemal *et al.*, 2011]. Men with newly diagnosed disease are currently stratified based on their PSA, Gleason score, and DRE into one of three groups: low risk, intermediate risk, or high risk [D'amico *et al.*, 1998]. Low risk is defined as either Gleason score 6 or below, PSA <10, and T1-T2a. Intermediate risk is defined as T2b-T2c or Gleason score 7 or PSA 10-20 ng/ml. High-risk disease is defined as PSA >20 or Gleason >7 or T2c or greater. The current standard non-surgical treatment for men with intermediate risk prostate cancer is radiation therapy [Mohler *et al.*, 2010].

Benefit of Dose Escalation

Recently, there have been multiple phase III trials demonstrating the benefit of radiation dose escalation in the treatment of both low risk, intermediate risk, and high risk prostate cancer [Dearnaley *et al.*, 2007, Al-Mamgani *et al.*, 2008, Kuban *et al.*, 2008, Zietman *et al.*, 2010]. These trials have all used external beam radiation therapy and have set a new standard dose for radiation treatment for men with prostate cancer that has been endorsed by the NCCN.

Dose Escalation with HDR

In addition to increasing the total dose delivered by EBRT, dose escalation can be achieved using brachytherapy. The radiation can be delivered either with low activity radioactive seed sources (termed low dose rate or LDR brachytherapy) or using a temporary implant with a higher activity source (high dose rate or HDR brachytherapy). HDR brachytherapy is a standard of care in the United States and Europe to deliver a radiation boost to the prostate when combined with external beam radiation. Three large studies [Galalae *et al.*, 2002, Demanes *et al.*, 2005, Vargas *et al.*, 2006] including over 500 men received a combination of EBRT and HDR. All reported excellent outcome with PSA progression free survival between 70-90% for men with both intermediate and high-risk disease. Further, the rate of late GI/GU toxicity was quite low as well with late grade 3 GU toxicity ranging from

2.1-6.7%, late grade 4 GU toxicity of 0-1%, late grade 3 GI toxicity of 0-1% and late grade 4 GI toxicity of 0-0.5%.

In addition, a phase III randomized trial compared EBRT alone or EBRT combined with an HDR boost [Hoskin *et al.*, 2007]. This trial demonstrated a significant improvement in actuarial biochemical relapse-free survival is seen in favor of the combined brachytherapy schedule. However, this trial was criticized that the EBRT alone arm had a lower biologic radiation dose than the combined arm. A retrospective study from Memorial Sloan Kettering Cancer Center compared patients who received EBRT alone to 86.4 Gy with those who underwent HDR brachytherapy combined with EBRT [Deutsch *et al.*, 2010]. Dose escalation by adding HDR brachytherapy provided improved PSA relapse-free survival in the treatment of prostate cancer compared with ultra-high-dose EBRT, independent of risk group on multivariate analysis, with the most significant benefit for intermediate-risk patients. Finally, a systemic review of the literature [Pieters *et al.*, 2009] compared results from EBRT alone, EBRT combined with LDR, and EBRT combined with HDR. This study concluded that combination of external beam radiotherapy and HDR brachytherapy results in a superior biochemical control and overall survival.

Biologic Benefit of Hypofractionated Radiation for Prostate Cancer

Radiation effects in prostate cancer cells have been typically studied using clonogenic cell survival curves, which allow cell death to be modeled using a linear quadratic equation. The dose response of tumors and normal tissues to fractionated radiation therapy can be predicted according to a formula: $S= e^{(-\alpha D-\beta D^2)}$, where α and β are the linear and quadratic components of the model. Based upon this model, an alpha/beta ratio can be calculated which allows various dose and fractionation schemes to be compared. The alpha-beta ratio is generally >10 Gy for early-responding tissue such as skin, mucosa, and most tumors and <5 Gy for late responding tissue such as connective tissues and muscles. Recent evidence reveals that prostate cancer has a low alpha/beta ratio, implying that those cells are more sensitive to doses delivered in larger fraction size [Fowler *et al.*, 2001]. Further, given the lower alpha-beta ratio for prostate cancer than bladder and rectal mucosa (where the most significant late toxicity occurs) creates the potential for therapeutic gain with larger fraction sizes [Brenner *et al.*, 2002, Fowler *et al.*, 2003]. Based upon this, there is an increasing trend to reduce the total treatment time by administering higher dose/fraction [Ritter *et al.*, 2009].

Clinical Experience Using Hypofractionation or SBRT in Prostate

There have been a number of phase I trials reporting the use of hypofractionated regimens for the treatment of low and intermediate risk prostate cancer in the (primary) definitive setting [Adkison *et al.*, 2010, Jabbari *et al.*, 2010, Oermann *et al.*, 2010, Boike *et al.*, 2011, King, 2011]. These trials show excellent biochemical

control and toxicity profiles. A five institutional cooperative phase I/II trial that explored the tolerance and efficacy of 3 increasingly hypofractionated radiation regimens with equivalent predicted late toxicity was recently reported in abstract form [Ritter *et al.*, 2009]. A total of 307 men were enrolled and biochemical progression free survival was 95% at 5 years. At 2 years, actuarial rectal bleeding was 8% with all cases resolving either spontaneously or after minor intervention.

Patient Logistical Benefit of Hypofractionation

One caveat with dose escalation to doses between 74-80 Gy is that current radiation therapy treatment is given in daily fractions of sizes of 2 Gy/day and treatments last for approximately 2 months. The prolonged nature of the radiation treatment course has been cited by prostate cancer patients as a primary reason for not choosing RT [Holmboe *et al.*, 2000].

Combination of HDR and hypofractionated radiation therapy

The combination of high dose rate brachytherapy and external beam radiation therapy has been recently published [Morton *et al.*, 2011]. The protocol used a single HDR treatment of 15 Gy followed by EBRT to a dose of 37.5 Gy in 15 fractions. One hundred and twenty three patients were followed for a median of 45 months. Biochemical disease-free survival was 95% and the two year prostate biopsy was positive in only 4% of men. Further, acute grade 3 or higher GU toxicity was experienced by only 2 patients and 1 patient developed a grade 3 late GU toxicity. The grade 3 toxicity was hemorrhagic cystitis that required cysto-prostatectomy; however the patient was also diagnosed with scleroderma and telangiectasia (CREST) syndrome, which is generally a contraindication to radiation therapy and may have been a contributing factor to his toxicity. There was 4% grade 2 GI toxicity consisting of proctitis. Patient reported toxicity using the EPIC tool was notable for decrease in urinary, bowel and sexual domain scores in the first 2 years following treatment, but median urinary and bowel domain scores were not significantly different from baseline at 3 and 4 years.

2.0 STUDY OBJECTIVES

Primary Objective:
The primary objective of this study is to determine the safety and feasibility of delivering HDR brachytherapy with SBRT for the treatment of men with intermediate risk prostate cancer. The maximally tolerated dose (MTD) will thus be determined.

Secondary Objective:

To determine the acute and late hematologic and late nonhematologic toxicity profile of HDR and SBRT combination.

To evaluate dosimetric parameters, including dose-volume factors for bladder and rectum that are associated with HDR and SBRT related toxicity.

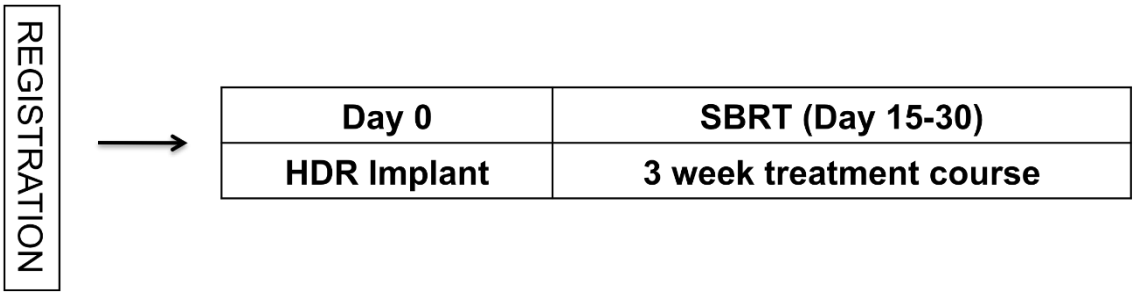
To describe patient-reported outcomes including EPIC and AUA Symptom Index for patients treated HDR and SBRT.

3.0 STUDY DESIGN

This is a single-center, open-label, non-randomized Phase I study in patients with Intermediate risk prostate cancer. We will use standard "3+3" dose escalation design.

3.1 General Design

SCHEMA



*Note: Patients will start radiation therapy 2 weeks after the implant procedure, with the possibility of starting up to 3 weeks afterward (Day 22).

Patients will be accrued in a standard "3+3" dose-escalation design during ongoing dose exploration. Dose escalation will continue until the maximum tolerated dose (MTD), the appropriate dose for Phase II study. During dose exploration, cohorts of 3-6 patients will be treated as a cohort. The initial cohort will be treated at Dose Level 1. The enrollment scheme is a conventional 3 + 3 design. If 0/3 or 1/6 patients initially treated at Dose Level 1 have DLT at the first treatment cycle, the SBRT dose per fraction will be escalated, and the next cohort of 3-6 patients will be treated at Dose Level 2. In like manner, depending on cohort toxicity, the SBRT dose/fraction will be escalated as needed to determine the highest level for which 2 of 6 patients has DLT. The dose level below this level will be declared the MTD. Dose level 3 will be the highest dose for this study and no further dose escalation will be performed. If Dose level 1 has 2 or greater patients with DLT, then dose level -1 will be used. We will allow for an expansion cohort of an additional 30 patients at the MTD dose level.

Planned Dose Levels During Exploration

Dose Level	Pts	Number of Fractions	SBRT Dose/Fraction	HDR Dose	BED tumor[+]	BED Acute	BED Normal Tissue[*]

						Normal Tissue%	
-1	3-6	15	2.5 Gy	15 Gy	113.5 Gy_2	70.3 Gy_2	95 Gy_2
1	3-6	10	3.2 Gy	15 Gy	113.5 Gy_2	66.5 Gy_2	94 Gy_2
2	3-6	7	3.94 Gy	15 Gy	113.5 Gy_2	63.2 Gy_2	92 Gy_2
3	3-6	5	4.78 Gy	15 Gy	113.5 Gy_2	60.7 Gy_2	91 Gy_2

+ For tumor alpha beta ratio is 1.5 for prostate

% For normal tissue alpha beta ratio for acute toxicity is 10.

* For normal Tissue alpha beta ratio for late toxicity is 3.

While the number of fractions is being reduced, the overall treatment length will remain unchanged. The dose level -1 (15 fractions) is given daily over 15 treatment days. For dose level 1 (10 fractions), this will also be given over 15 treatment days (3-4 treatments per week). For dose level 2, 2-3 treatments will be given per week over 15 treatment days. For dose level 3, 2 fractions will be given per week for a total length of 15 treatment days. In this trial design, weeks are not specified, as a patient may begin treatment midweek (i.e. Wednesday or Thursday and then treatment would last into a fourth week).

There will be an expansion cohort at the maximum tolerated dose. This will consist of 30 total patients (including the original 3 or 6). This patient number is calculated statistically. Based on the published dose level -1 toxicity, the total toxicity rate is 6.5%. Thus, using a binomial distribution, the probability of seeing a toxicity rate above 10% would be 13% using a 30 patient cohort. This will provide valuable information for a phase II trial.

3.2 Primary Study Endpoints

The primary study endpoint is safety. Toxicities will be Graded according to the National Cancer Institute, Common Toxicity Criteria (NCI, CTC), version 4.0. If

multiple toxicities are seen, the presence of DLT will be based on the most severe toxicity experienced.

For this protocol, DLT will be defined as any of the following events occurring during or within 3 months of radiation treatment attributable to treatment toxicity:

Non- Hematologic: Any Grade 4 toxicity or any grade 3 GU toxicity or Grade 3 diarrhea/nausea/vomiting/stomatitis lasting for more than 7 days despite optimal treatments.

Dose escalation will not occur until three patients at the current dose level have completed the combination of HDR and SBRT and have follow up for 3 months. Late toxicities after the treatment period will not be used to consider dose escalation but will be recorded and reported.

3.3 Secondary Study Endpoints

The secondary endpoint is to assess the late nonhematologic toxicity profile and the acute and late hematologic toxicity profile of HDR and SBRT combination.

The dosimetric parameters, including dose-volume factors for bladder and rectum, will be correlated with acute toxicity.

Multiple patient reported outcome instruments will be used including EPIC, AUA symptom score.

4.0 SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

Adenocarcinoma of the prostate with intermediate risk disease T2b-T2c or Gleason score 7 or PSA 10-20 ng/ml, without metastatic disease

•To rule out metastatic disease, patients must have the following tests:

- Bone scan within 60 days prior to registration
- CT of abdomen/pelvis within 60 days prior to registration

• Karnofsky Performance Status >70

• Age > 18

• PSA blood test within 60 days prior to registration

• Prostate biopsy within 180 days prior to registration

• Within 60 days prior to registration, hematologic minimal values:

  • Absolute neutrophil count > 1,500/mm3

  • Hemoglobin > 8.0 g/dl

  • Platelet count > 100,000/mm3

• Men of childbearing potential must be willing to consent to using effective contraception while on treatment and for at least 3 months thereafter.

• No history of previous pelvic irradiation

4.2 Exclusion Criteria

- History of urological surgery or procedures predisposing to GU complications after radiation, i.e., anastomoses, stricture repair, etc. (will be determined by radiation oncologist)
- History of prior pelvic irradiation
- Documented distant metastatic disease.
- Prior radical prostatectomy or cryosurgery for prostate cancer

4.3 Gender/Minority/Pediatric Inclusion for Research

Women and children will not be entered into this protocol as they do not suffer from prostate adenocarcinoma. There is no exclusion of minorities in this protocol.

4.4 Subject Recruitment and Screening

Subjects will be recruited for the study from investigator or sub-investigator's clinical practices and referring physicians. Patients will be screened based on pathology, PSA values, image studies etc.

4.5 Early Withdrawal of Subjects

Subject may be withdrawn from the study prior the expected completion of that subject if :

Disease progression,

Study closure,

Unacceptable adverse event(s),

Patient decision to withdraw from the study, or

In the judgment of the investigator, further treatment would not be in the best

interest of the patient.

4.5.2 Data Collection and Follow-up for Withdrawn Subjects

Even though subjects may be withdrawn prematurely from the study, it is imperative to collect data on such subjects throughout the protocol defined followup period outlined in the Study Calendar (Appendix IV) for that subject (though careful thought should be given to the full data set that should be collected on such subjects to fully support the analysis). Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study drug. If a subject withdraws consent to participate in the study, attempts should be made to obtain permission to record at least survival data up to the protocol-described end of subject follow-up period. IT MUST BE A HIGH PRIORITY TO TRY TO OBTAIN AT LEAST SURVIVAL DATA ON ALL SUBJECTS LOST TO FOLLOW-UP AND TO NOTE WHAT METHODS SHOULD BE USED BEFORE ONE CAN STATE THE SUBJECT IS TRULY LOST TO FOLLOW-UP (e.g. number of phone calls to subject, phone calls to next-of-kin if possible, certified letters, etc.). A subject who withdraws from the study for any reason prior to completing radiation therapy will not be counted as evaluable for the purposes of the study.

5.0 Radiation Therapy

5.1 HDR

HDR will be performed using intra-operative real time 3D ultrasound planning with Oncentra Prostate under general anaesthesia. Patients will need routine pre-operative work-up and anesthesia pre-assessment as indicated. Standardized template-based catheter configuration will be used, and dwell time optimization performed using ultrasound.

CTV = Prostate + any gross extension
PTV = CTV
Dose Prescription = 15 Gy in single fraction to CTV

Planning Goals:
V100: 95-99%
V90: 99-100%
V150 < 35%
V200: < 11%
Urethra D10: < 118%
Rectal V80 < 0.5 cc

5.2 SBRT

CT Simulation will be performed either same day or day after HDR. Patients will be positioned supine on a flat tabletop with customized thermoplastic mold or footbox. A full bladder and empty rectum will be encouraged. CT images will be obtained with slice thickness of 3 mm from the top of the iliac crests to the perineum.

Target volumes and normal tissue organs will be contoured for IMRT planning. Daily imaging will be performed for target localization. The definition of volumes will be in accordance with ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

Radiation Therapy staff will contour the entire bladder, the rectum from the bottom of the ischium to the sigmoid flexure (usually 11-13 cm), and both femoral heads.

CTV = Prostate + Inferior 2 cm of Seminal Vesicles
PTV = CTV + 0.7 cm all around except 0.5cm posteriorly.

Treatment Technique: IMRT or VMAT with appropriate CBCT image guidance to prostate prior to delivery of each fraction of radiation.

Beam Energy: 10-18 MV

Dose Cohort	Fractions	Fraction Size	Total Dose
-1	15	2.5 Gy	37.5 Gy
1	10	3.2 Gy	32 Gy
2	7	3.94 Gy	27.6 Gy
3	5	4.78 Gy	23.9 Gy

Planning Volumes Constraints

Dose Level	**CTV**	**PTV**		**Rectum**			**Bladder**	**Femoral Heads**
	≥ 99%	**≥ 99%**	**<1%**	**<20%**	**<35%**	**<50%**	**<35%**	**<5%**
-1	V37.5	V35.6	V39.4	V33	V29	V24	V29	V24
1	V32	V31	V32.9	V30.2	V27.7	V24.3	V27.7	V24.3

2	V27.6	V26.7	V28.4	V26.7	V24.5	V21.7	V24.5	V21.7
3	V23.9	V23.2	V24.5	V23.6	V21.7	V19.25	V21.7	V19.25

5.3 Radiation Toxicity

Adverse events include: skin reactions; loss of pelvic hair; transitory fatigue; infertility; impotence that could be permanent; urethral stricuture; small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, rectal bleeding, hematochezia, and bowel incontinence; bladder complications including urinary frequency, dysuria, hematuria, urinary tract infections, and urinary incontinence; injuries to the rectum, bowel, or urinary system that could result in colostomy or other major surgical procedures.

5.4 Radiation Adverse Event Reporting

See Section 8.0 for adverse event reporting instructions.

6.0 STUDY PROCEDURES

All patients will be evaluated by a radiation oncologist. Initial visit will include overall assessment of health as well as determination of eligibility. Pretreatment PSA and staging will be obtained. Prostate volume will be determined based on trans rectal ultrasound performed at biopsy. If ultrasound volume unable to be obtained, then prostate will be measured on CT imaging.

Prior to HDR procedure, the patient will be assessed through pre admission testing to ascertain safety of anesthesia. On the night prior to the procedure, the patient will undergo a bowel preparation consisting of a Fleets enema.

On day of HDR procedure, patient will be intubated and sedated. The patient will be placed in the dorsal lithotomy position and an ultrasound will inserted into the rectum and images will be acquired. The treating radiation oncologist will define the prostate, urethra, and anterior rectal wall. Catheters will be inserted into the prostate and a 3 dimensional treatment plan will be generated. Dwell positions and times will be calculated. The catheters will be connected to the HDR afterloader and the treartment plan will be reviewed and approved by the treating radiation oncologist. After completion of the treatment, the catheters will be removed and 3 fiducial markers will be inserted into the prostate.

The patient will be taken to a post operative recovery area and medically cleared to leave the hospital. The patient will then undergo a CT scan either on the same day or a week after the HDR procedure. The treating radiation oncologist will define the CTV, PTV, bladder, and the rectum. An IMRT/VMAT plan will be generated and reviewed and approved by the treating radiation oncologist.

The patient will return to the department for external beam treatment two weeks (and up to 3 weeks) after the implant procedure. The patient will be seen once per

week by the treating radiation oncologist during external beam therapy. After completion of external beam treatment, the patient will be seen again at first follow up at 1 month or sooner if medically necessary to assess toxicity and then at 3 months after the procedure with a PSA test. The patient will have routine follow up of every 3 months for the first 2 years, 6 months from years 3-4, and then annually with PSA evaluation prior to each of these follow-up visits as is standard of care. See Study Calendar (Appendix IV).

Patients will also be asked to complete two (2) quality of life (QOL) questionnaires, so that patient-reported outcomes can be captured. The questionnaires are the Expanded Prostate Cancer Index Composite (EPIC) and the American Urological Association BPH Symptom Score Questionnaire (AUA Index). Questionnaires should be completed at the follow time points: pre-treatment, 3 months post-RT, 6 months post-RT, 9 months post-RT, 1 year post-RT, then every 3 months for 1 year, then every 6 months for 2 years, and then annually.

7.0 STATISTICAL PLAN

We will use a two-stage accrual design at each radiation fraction size considered. We will initially enter 3 subjects at each radiation fraction size. If none of the three experiences a dose-limiting toxicity we will proceed to the next radiation fraction size. If one of the three experiences that level of toxicity, we will accrue 3 more subjects at that fraction size. If at any time there are two or more dose-limiting toxicities (in the 3-6 subjects) on a given fraction size, we will terminate accrual to the trial. No patient will be treated at a higher fraction size until the 3 or 6 patients have completed their toxicity evaluation period at the current dose. With this plan, a dose with a 50% or greater probability of causing a dose-limiting toxicity has at most a 12.5% chance of satisfying the conditions for dose escalation after the first 3 subjects and at least a 50% chance of stopping at 3. With the two-stages (3-6) together, there is at most a 17.2% chance of escalation.

The maximally tolerated dose (MTD) will then be the last dose studied or the previous dose, based on clinical judgment of the degree of toxicity seen at the last dose. While waiting for the 3 or 6 subjects accrued according to plan to complete their toxicity evaluation period, additional subjects may be accrued at the current dose. These additional subjects will not count towards the formal plan of stopping at two or more toxicity occurrences, but will contribute to the judgment as to the MTD.

Data analysis of phase I studies is descriptive. All estimates of dose-specific rates (e.g.,response and toxicity) will be presented with corresponding confidence intervals using the exact method.

7.1 Sample Size Determination

The total sample size would vary depending upon the DLTs observed and the resulting influence on cohort size and number of dose levels tested. We plan to have 3 dose levels for testing, depending on toxicity, with 3 to 6 patients enrolled at a particular dose level during dose exploration. Once the MTD has been determined, additional patients maybe added. The total sample size will be 3-42 patients.

7.2 Subject Population(s) for Analysis

All-treated population: Any subject in the study that received HDR implant will be followed and analyzed.

8.0 SAFETY AND ADVERSE EVENTS

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 90 days following the last administration of study treatment.

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.

General Physical Examination Findings

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.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the principal investigator at TJUH of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The principal investigator at TJUH should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality as evidenced on CBC should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.4 Stopping Rules

Patients will be taken off study for persistent grade 3 or 4 GI/GU toxicity, or grade 3 or 4 hematological toxicity(ies) that lasts for more than 2 weeks. A patient who withdraws prematurely from the study for any reason either prior to completing

radiation therapy or after completing radiation therapy should be followed per the Study Calendar (Appendix IV) schedule.

8.5 Data and Safety Monitoring Plan

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the compliance and implementation of the KCC data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events by both the assigned Medical Monitor and the KCC DSMC.

8.5.1 Medical Monitoring and AE/SAE Reporting

Every KCC investigator initiated protocol includes requirements for reporting of adverse events based on CTC 4.0. All events are reported to the IRB and Medical Monitor using a password protected web-site. In addition all unexpected and serious adverse events (SAEs) are reported to the TJU IRB and to the Food and Drug Administration (FDA) if applicable. The investigator is required to submit all unexpected and serious adverse events to the TJU IRB and the Medical Monitor within the timeframes outlined in the below table. All AE/SAEs will be reported to the DSMC at the quarterly DSMC review meetings; however, if the Medical Monitor determines corrective action is necessary, and "ad hoc" DSMC meeting will be called. ***Fatal adverse events related to treatment which are unexpected must be reported within 24 hours to the TJU IRB and the DSMC. Fatalities not related to the study drug/device must be reported within 5 days.*** A summary of the reporting requirements for KCC investigator initiated Phase I and Phase II studies are presented below. Reporting requirements for Phase III investigator initiated studies are described in the protocol reviewed by the CCRRC and TJU IRB.

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 and 5
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase 1 - 48 Hours (Death: 24 Hours) Phase 2 - 5 Working Days

Possible Probable Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 working days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase 1 - 48 Hours Phase 2 - 5 Working Days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase 1 and Phase 2 - 48 Hours (Death: 24 Hours)

**NOTE: This table is based on the NCI AE/SAE reporting Guidelines and the TJU IRB Policy and Procedures. Please follow the individual protocol AE/SAE reporting guidelines if more stringent reporting procedures are specified.

8.5.2 Data and Safety Monitoring Committee

Data and Safety Monitoring Committee (DSMC) is the Data and Safety Monitoring Board (DSMB) for the KCC. The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials at the Thomas Jefferson University KCC. The committee meets quarterly to review the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

- The DSMC shall consist of a minimum 14 (including one non-voting member) members (see below) from the Department of Pharmacy (Thomas Jefferson University Hospital), the Clinical Cancer Research Review Committee (CCRRC), Thomas Jefferson University Division of Human Subjects Protection (responsible for the administration of the TJU IRBs), Thomas Jefferson University faculty, external members of the scientific community, and the KCC Clinical Trials Support Office (CRMO).
- The DSMC meets quarterly. Additional DSMC meetings are scheduled based on the nature and number of trials being monitored over a specified time period. The DSMC meets (by conference call) within 24 hours following the notification of an unexpected adverse event felt to be related to the study drug.
- Prior to each DSMC meeting, each board member, is provided a printout of all reported AEs and SAEs occurring during the reporting period for this clinical trial. The principal investigator provides a detailed and comprehensive narrative assessment of current adverse events to date, indicating their possible significance and whether these toxicities have affected the conduct of the trial. DSMC members are provided with the principal investigator's assessment, a written report summarizing adverse events, safety data, and activity data observed during the specified time period described in each protocol, as well as

recommendations from the Medical Monitor. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study.

- A summary of the board's action is sent to each investigator, the CCRRC and TJU IRBs. The DSMC actions may include recommendations/requirements that will lead to improved patient safety and/or efficacy, significant benefits or risks that have developed, or other changes determined to be necessary. The DSMC may also take note of slow accrual or lack of scientific progress, and refer such issues to the CCRRC. The DSMC provides the investigator with the rationale for any decision made. If for any reason the PI of the trial disagrees with the conclusions of the DSMC, the issue will be referred to the Associate Director of Clinical Investigations, who will be responsible for dispute resolution. The DSMC board action is also described in the progress report submitted by the principal investigator as part of the annual review of the protocol by the TJU IRBs. Any action resulting in temporary or permanent suspension of an NCI-funded clinical trial is reported to the NCI program director responsible for that grant by the CRMO with a copy of the communication to the principal investigator.

9.0 DATA HANDLING AND RECORD KEEPING

9.1 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.

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 (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 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.

9.3 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". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

For non-FDA regulated studies, summarize the record retention plan applicable to the study (taking into account any applicable Department, Division or Research Center requirements)

For FDA-regulated studies the following sample language is appropriate:

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10.0 STUDY MONITORING, AUDITING, AND INSPECTING

10.1 Study Monitoring Plan

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

KCC Investigator Initiated Phase I Studies

Phase I studies require continuous monitoring by the PI of the study with quarterly safety and monitoring reports submitted to the CRMO and the DSMC. The investigator is required to submit all unexpected on-site adverse events and serious adverse events (SAEs) to the TJU IRB and the DSMC within 48 hours. Fatal adverse events which are unexpected must be reported within 24 hours to the TJU IRB and the DSMC. Fatalities not related to the study drug/device must be reported within 5 days.

Each protocol is assigned to a medical monitor (a physician or other member of the DSMC who has expertise in the therapeutic area of the protocol and is not directly involved in this trial). The medical monitor reviews all adverse events (in addition to unexpected adverse events), safety data and activity data observed in the ongoing clinical trial at each new dose level, prior to dose escalation.

The PI provides a report to the DSMC of all AE/SAEs, safety and toxicity data, and any corrective action that occurred on a quarterly basis. The medical monitor also provides a summary of their review. The summary of all discussions of adverse events are submitted to the DSMC, and these reports are reviewed during the DSMC meetings that take place quarterly. Patients are only identified by initials, and no other personal health information (PHI) is included in the reports.
The medical monitor may recommend reporting adverse events and relevant safety data not previously reported, and may recommend suspension or termination of the trial based on their review of AE/SAE data observed throughout the life of a clinical trial. In such circumstances, and “ad hoc” DSMC meeting will be called to discuss corrective action with the PI. If for any reason the PI of the trial disagrees with the conclusions of the Medical Monitor or DSMC, the issue will be referred to the Associate Director of Clinical Investigations, who will be responsible for dispute resolution.

The summary of all discussions of adverse events are included in the KCC investigator’s reports to the TJU IRBs as part of its annual progress report. The DSMC and the TJU IRBs may, based on the monitor’s recommendation suspend or terminate the trial. The quarterly safety and monitoring reports include a statement as to whether this data has invoked any stopping criteria in the clinical protocol.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10.2.1 Independent External and Internal Audits

In addition to review by the DSMC, all studies initiated by KCC investigators are audited by an independent auditor once they have achieved 10% of target accrual. However, a study can be audited at any time based on recommendations by the IRB, DSMC, CCRRC and/or the Director of Clinical Investigations, KCC. Studies are re-audited once they have achieved 50% of target accrual. Special audits may be recommended by the IRB, DSMC or CCRRC based on prior findings, allegations of scientific misconduct and where significant irregularities are found through quality control procedures. Any irregularities identified as part of this process would result in a full audit of that study.

In addition to the audits at 10 and 50%, the CRMO randomly audits at least 10 percent of all patients entered into therapeutic KCC trials and other trials as necessary, on at least a bi-annual basis, to verify that there is a signed and dated patient consent form, the patient has met the eligibility criteria, and that SAEs are documented and reported to the TJU IRB.

All audit reports are submitted to the DSMC for review and action (when appropriate). A copy of this report and recommended DSMC action is sent to the CCRRC and TJU IRB. The committee regards the scientific review process as dynamic and constructive rather than punitive. The review process is designed to assist Principal Investigators in ensuring the safety of study subjects and the adequacy and accuracy of any data generated. The TJU IRB may, based on the DSMC and auditor's recommendation, suspend or terminate the trial.

11.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

All subjects for this study will be provided a consent form that is compliant with local and federal regulations, describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12.0 STUDY FINANCES

12.1 Funding Source

This study is currently unfunded and will be supported by departmental funds.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

12.3 Subject Stipends or Payments

There is no subject stipend/payment.

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15.0 APPENDICES

Appendix I EPIC questionnaire
Appendix II AUA Index
Appendix III Karnofsky Performance Status scale
Appendix IV Study Calendar

Thomas Jefferson University

EPIC

The Expanded Prostate Cancer Index Composite

This questionnaire is designed to measure Quality of Life issues in patients with Prostate cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

Remember, as with all medical records, information contained within this survey will remain strictly confidential.

Today's Date (please enter date when survey completed): Month_____Day_____Year_____

Name (optional): _____

Date of Birth (optional): Month_____Day_____Year_____

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URINARY FUNCTION

This section is about your urinary habits. Please consider **ONLY THE LAST 4 WEEKS**.

1. Over the **past 4 weeks**, how often have you leaked urine?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 23/
   About once a week.....4
   Rarely or never..... 5

2. Over the **past 4 weeks**, how often have you urinated blood?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 24/
   About once a week.....4
   Rarely or never..... 5

3. Over the **past 4 weeks**, how often have you had pain or burning with urination?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 25/
   About once a week.....4
   Rarely or never..... 5

4. Which of the following best describes your urinary control **during the last 4 weeks**?

   No urinary control whatsoever..... 1
   Frequent dribbling..... 2 (Circle one number) 26/
   Occasional dribbling..... 3
   Total control..... 4

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5. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks**?

None	0	
1 pad per day	1	
2 pads per day	2	(Circle one number)
3 or more pads per day	3	

27/

6. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?

(Circle one number on each line)

		No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a.	Dripping or leaking urine	0	1	2	3	4	28/
b.	Pain or burning on urination	0	1	2	3	4	29/
c.	Bleeding with urination	0	1	2	3	4	30/
d.	Weak urine stream or incomplete emptying	0	1	2	3	4	31/
e.	Waking up to urinate	0	1	2	3	4	32/
f.	Need to urinate frequently during the day	0	1	2	3	4	33/

7. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

No problem	1	
Very small problem	2	
Small problem	3	(Circle one number)
Moderate problem	4	
Big problem	5	

34/

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BOWEL HABITS

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

8. How often have you had rectal urgency (felt like I had to pass stool, but did not) **during the last 4 weeks**?

More than once a day..... 1		
About once a day..... 2		
More than once a week..... 3	(Circle one number)	42/
About once a week.....4		
Rarely or never..... 5		

9. How often have you had uncontrolled leakage of stool or feces?

More than once a day..... 1		
About once a day..... 2		
More than once a week..... 3	(Circle one number)	43/
About once a week.....4		
Rarely or never..... 5		

10. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) **during the last 4 weeks**?

Never..... 1		
Rarely..... 2		
About half the time..... 3	(Circle one number)	44/
Usually..... 4		
Always.....5		

11. How often have you had bloody stools **during the last 4 weeks**?

Never.....1		
Rarely..... 2		
About half the time..... 3	(Circle one number)	45/
Usually..... 4		
Always.....5		

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12. How often have your bowel movements been painful **during the last 4 weeks**?

Never..... 1
Rarely..... 2
About half the time..... 3 (Circle one number) 46/
Usually..... 4
Always.....5

13. How many bowel movements have you had on a typical day **during the last 4 weeks**?

Two or less..... 1
Three to four.....2 (Circle one number) 47/
Five or more.....3

14. How often have you had crampy pain in your abdomen, pelvis or rectum **during the last 4 weeks**?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 48/
About once a week.....4
Rarely or never..... 5

15. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Urgency to have a bowel movement	0	1	2	3	4	49/
b. Increased frequency of bowel movements.....	0	1	2	3	4	50/
c. Watery bowel movements.....	0	1	2	3	4	51/
d. Losing control of your stools.....	0	1	2	3	4	52/
e. Bloody stools	0	1	2	3	4	53/
f. Abdominal/ Pelvic/Rectal pain...	0	1	2	3	4	54/

16. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem..... 1
Very small problem..... 2
Small problem.....3 (Circle one number) 55/
Moderate problem..... 4
Big problem..... 5

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SEXUAL FUNCTION

The next section is about your **current** sexual function and sexual satisfaction. Many of the questions are very personal, but they will help us understand the important issues that you face every day. Remember, THIS SURVEY INFORMATION IS COMPLETELY **CONFIDENTIAL**. Please answer honestly about **THE LAST 4 WEEKS ONLY**.

17. How would you rate each of the following during the last 4 weeks? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good	
a. Your level of sexual desire?	1	2	3	4	5	56/
b. Your ability to have an erection?	1	2	3	4	5	57/
c. Your ability to reach orgasm (climax)?	1	2	3	4	5	58/

18. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?

None at all..... 1
Not firm enough for any sexual activity..... 2
Firm enough for masturbation and foreplay only..... 3 (Circle one number) 59/
Firm enough for intercourse..... 4

19. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?

I NEVER had an erection when I wanted one..... 1
I had an erection LESS THAN HALF the time I wanted one..... 2
I had an erection ABOUT HALF the time I wanted one ..... 3 (Circle one number) 60/
I had an erection MORE THAN HALF the time I wanted one..... 4
I had an erection WHENEVER I wanted one..... 5

20. How often have you awakened in the morning or night with an erection **during the last 4 weeks**?

Never 1
Less than once a week..... 2
About once a week..... 3 (Circle one number) 61/
Several times a week..... 4
Daily..... 5

Do Not Mark in This Space

21. **During the last 4 weeks**, how often did you have <u>any</u> sexual activity?

Not at all	1		
Less than once a week	2		
About once a week	3	(Circle one number)	62/
Several times a week	4		
Daily	5		

22. **During the last 4 weeks**, how often did you have sexual intercourse?

Not at all	1		
Less than once a week	2		
About once a week	3	(Circle one number)	63/
Several times a week	4		
Daily	5		

23. Overall, how would you rate your ability to function sexually **during the last 4 weeks**?

Very poor	1		
Poor	2		
Fair	3	(Circle one number)	64/
Good	4		
Very good	5		

24. How big a problem **during the last 4 weeks**, if any, has each of the following been for you?
(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Your level of sexual desire	0	1	2	3	4	65/
b. Your ability to have an erection	0	1	2	3	4	66/
c. Your ability to reach an orgasm	0	1	2	3	4	67/

25. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?

No problem	1		
Very small problem	2		
Small problem	3	(Circle one number)	68/
Moderate problem	4		
Big problem	5		

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Overall Satisfaction

32. Overall, how satisfied are you with the treatment you received for your prostate cancer?

Extremely dissatisfied..... 1
Dissatisfied..... 2
Uncertain..... 3 (Circle one number)
Satisfied..... 4
Extremely satisfied..... 5

80/

THANK YOU VERY MUCH!!

Thomas Jefferson University

Appendix II

AUA Index

American Urological Association BPH Symptom Score Index Questionnaire

Having to urinate more frequently, as well as more urgently, can definitely interrupt the flow of your day. You should know that frequent urination is often a symptom of benign prostatic hyperplasia (BPH), a noncancerous enlargement of the prostate gland. BPH is a common condition among men over the age of 50. Waking up several times a night to urinate and having a weaker, slower, or delayed urine stream are other common symptoms.

_____ Circle the number that best applies to you

Patient Name **Date**

	not at all	less than 1 time in 5	less than _ the time	about _ the time	more than _ the time	almost always
1. Incomplete Emptying Over the last month how, often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5
2. Frequency During the last 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 During the last month, how often have you stopped and started again several times when you urinate?	0	1	2	3	4	5
4. Urgency During the last month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Weak Stream During the last month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Straining During the last 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 Or More Times
7. Nocturia During the last month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5

Add the score for each number above, and write the total in the space to the right
SYMPTOM SCORE = 1-7 MILD 8-19 MODERATE 20-35 SEVERE TOTAL_____

0=Delighted 1=Pleased 2=Mostly Satisfied 3=Mixed 4=Mostly Not Satisfied 5=Unhappy

8. Quality of life How would you feel if you had to live with your urinary condition the way it is now, no better, no worse, for the rest of your life.	0	1	2	3	4	5

Appendix III

Karnofsky Performance Status scale

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Appendix IV

Study Calendar

Assessments	Pre-Treatment	During RT	Follow Up				
		Weekly	1 Month	3 Month	6 month	9 month	1 year, then q3 mos X 1 year, q6 months X 2 years, then annually
General H&P	X	X	X	X	X	X	X
Biopsy	X						
PSA	X			X	X	X	X
Performance Status	X	X	X	X	X	X	X
CBC	X			X			
Adverse Event Evaluation		X	X	X	X	X	X
QOL: AUA, EPIC	X			X	X	X	X

See Sections 4.1 and 6.0 for additional details.