A Phase II Study of Stereotactic Body Radiotherapy (SBRT) for Prostate Cancer Using Continuous Real-time Evaluation of Prostate Motion and IMRT Plan Reoptimization based on Same Day Anatomy

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SCHEMA

Gleason Score
1. ≤6
2. 7

PSA
1. ≤ 15 ng/mL if Gleason ≤6
2. ≤ 10 ng/mL if Gleason 7

T stage
T1-2

Register on Study

Treatment Arm

7.4 Gy for 5 fractions delivered every other day; IMRT/IGRT with reoptimization for each fraction

Treatment is prescribed as a minimum to the planning target volume (PTV) to be delivered at a daily dose of 7.4 Gy/ fraction. The PTV includes with CTV (prostate only) with a nonuniform margin.

Patient Population: (See Section 3.0 for Eligibility)
- Histologically confirmed prostate adenocarcinoma within 365 days prior to registration
- Clinical stage T1-2 according to the AJCC 6th edition
- Pretreatment PSA ≤10 ng/mL if Gleason 7 or ≤ 15 ng/ml if Gleason ≤6 (within 180 days of registration)
- Gleason score must be ≤7
- No previous radical surgery or cryosurgery for prostate cancer
- No prior or planned androgen deprivation or bilateral orchiectomy

Required Sample Size: 60

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1.0 Introduction

1.1 Conventionally Fractionated External Beam Radiotherapy

The optimal radiation schedule taking into account both daily fraction size and overall duration of treatment for the curative treatment of prostate cancer using external beam radiation therapy (EBRT) is unknown. Over the last 10 years it has been typical for most patients to receive daily fractions of 1.8-2.0 Gy for a duration of 7-8 weeks to a total cumulative dose to the prostate of 70-79 Gy (1). Treatment in this fashion has been demonstrated to be safe with moderate rates of late rectal and bladder toxicity.

Four randomized trials provide evidence that doses above 74 Gy can increase the likelihood of cure but higher doses are associated with increased toxicity, especially rectal toxicity (2-5). In the MD Anderson randomized trial there was an increase in grade 2 or higher rectal toxicity from 12% to 26% between the 70 Gy and 78 Gy arms (6). In further analysis of this study it was found that both the volume of rectum treated to higher doses (70 Gy) as well as lower doses (40-60 Gy) contributed to late rectal toxicity (7).
Further dose intensification using conventional fractions of 1.8-2.0 Gy is not likely to provide significant further gains without coincident increases in late toxicity because the anterior rectal wall and prostate are in close physical proximity. Even with the most successful radiation targeting one will not be able to adequately treat the prostate without also treating a portion of the anterior rectal wall. Additionally, the delivery of radiation therapy over this protracted period of time is expensive and inconvenient for patients with some radiation schedules in excess of 9 weeks.
We propose to investigate a novel treatment regimen that will: 1) significantly reduce the duration of treatment and 2) limit the volume of normal tissue radiated while maintaining equivalent efficacy. In short, we hypothesize that hypofractionated radiation therapy using continuous real-time evaluation of prostate motion combined with reoptimization of the IMRT plan according to the anatomy of the day will improve the therapeutic ratio.

1.2 Biologic Basis of Hypofractionation

The efficacy of radiation in causing reproductive cellular death is a function of the overall radiation dose, the dose per fraction, and the overall treatment time. Classically this relationship is described according to the linear-quadratic (LQ) model. Using the LQ model the fractionation sensitivity of both tumor cells and normal tissues can be defined using the alpha-beta ratio (α/ß).

Rapidly dividing tumors or acute responding normal tissues are generally described by a high alpha-beta ratio (≥ 10 Gy) such that changes in individual fraction size would be expected to only have a modest overall impact on efficacy as compared to overall treatment dose. In contrast, slowly dividing tissues that exhibit late toxicity to radiation therapy (such as bone, connective tissues, or spinal cord) are often described by a lower alpha-beta ratio (in the range of 3-5 Gy) such that larger daily fractions would be anticipated to cause relatively greater toxicity when compared to smaller fractions when delivered to the same total dose. In most clinical scenarios cancers have alpha-beta ratios much higher than the normal tissues adjacent to them (*i.e.* 10 Gy vs. 3 Gy) and as a result

conventional radiation fractions of 1.8-2.0 Gy have the greatest likelihood of maintaining an advantageous therapeutic ratio as radiation doses are escalated.
There is accumulating evidence that prostate cancer may have a lower alpha-beta ratio than nearby normal tissues (rectum, bladder) (8). This observation has encouraged investigators to evaluate radiation fractionation schemes that use fraction sizes larger than 1.8-2.0 Gy (9). If the alpha-beta ratio of prostate cancer is lower than nearby normal tissues then treating prostate cancer with fewer, larger fractions (to a lower total dose) should result in an increase in the therapeutic ratio.

1.3 Hypofractionation in Prostate Cancer

In the last decade investigators from across the globe have examined a number of hypofractionated regimens with daily fraction sizes ranging from 2.5 to 7.25 Gy delivered in 5-28 fractions over 1-6 weeks (10). As this protocol examines a five fraction regimen, only the experience with five fraction regimens will be reviewed.
Investigators at the Virginia Mason Clinic in Seattle published the first experience with a five fraction regimen in 2006 (11). These clinicians treated a total of 40 patients with low risk prostate cancer (T2a or less, Gleason 6 or less, PSA 10.0 or less) and reported preliminary toxicity and efficacy results with a median follow-up of 41 months. The Virginia Mason clinicians delivered five fractions of 6.7 Gy (total dose 33.5 Gy) over five days.

The 5 year estimate of freedom from biochemical recurrence is 90% by RTOG-Phoenix definition. Late toxicity was defined as occurring 30 or more days after the completion of therapy. Overall, the treatment was well tolerated with no Grade 3-5 genitourinary (GU) or gastrointestinal (GI) toxicity reported at a median of 41 months of follow-up. Grade 2 genitourinary toxicity was reported in 20% (8/40) of patients and Grade 2 gastrointestinal toxicity was reported in 7.5% (3/40) of patients.
The second published experience with a five fraction regimen comes from investigators at Stanford University (12). These clinicians treated a total of 41 patients with low risk prostate cancer (T2a or less, Gleason 6 or less, PSA 10.0 or less) and reported preliminary toxicity and efficacy results with a minimum follow-up of 6 months (median 33 months). The Stanford regimen delivered 5 fractions of 7.25 Gy over 1-2 weeks.

The Stanford investigators reported no RTOG Grade 4-5 acute or late GU/GI complications. Two patients experienced RTOG Grade 3 late GU toxicity and none reported Grade 3 GI complications. A reduced rate of rectal toxicities was observed with every-other-day vs. 5 consecutive days treatment regimen (0% vs. 38%, $p = 0.0035$). At last follow-up, no patient has had a biochemical recurrence. Of 32 patients with 12 months minimum follow-up, 25 patients (78%) achieved a PSA nadir ≤ 0.4 ng/mL. A PSA decline to progressively lower nadirs up to 3 years after treatment was observed.

2.0 Objectives

2.1 Primary Objective

To evaluate the incidence of GU and GI acute and late toxicity (see Section 8.1) for patients treated with prostate stereotactic body radiotherapy (SBRT) along with prostate

localization (Calypso or ExacTrac and onboard cone-beam CT) and IMRT reoptimization for each fraction based on the anatomy of the day.

2.2 Secondary Objectives

2.2.1 Disease-free survival: Disease-free failure events include local progression, distant progression, biochemical failure as defined by the RTOG Phoenix definition, and death from any cause.

2.2.2 Evaluate patient quality of life (QOL) using the Expanded Prostate Cancer Index Composite 26 (EPIC-26) for evaluation of the QOL for up to 3 years after the completion of SBRT.

2.3 Duration of Investigation and Expected Enrollment Rate

Men will be enrolled on study after meeting eligibility criteria and signing consent. Follow-up will continue for each enrollee up to three years after enrollment. It is estimated that a subject will be involved in the study for 36 months. We anticipate that this study will begin enrolling subjects in the Fall 2009 and will enroll 2 subjects a month for 30 months for a total enrollment of 60.

3.0 Study Design and Patient Selection

3.1 Study Design

This is a Phase II single institution investigator-initiated trial where the primary end-point is the assessment of Grade 2+ late toxicity 2 years from the start of treatment. Based upon an assumed linear rate of grade 2 or greater toxicity from 18 – 36 months after the completion of treatment the primary end-point will be assessed when all patients have completed treatment, have a minimum of 3 months of follow-up, and a cumulative 120 person/years of follow-up have been recorded (an average of 2 years per patient).

3.2 Inclusion Criteria

3.2.1 Histologically confirmed diagnosis of adenocarcinoma of the prostate within 365 days of study enrollment

3.2.2 History/physical examination with digital rectal examination of the prostate within 8 weeks prior to study enrollment

3.2.3 Gleason score ≤7

3.2.4 Clinical Stage T1-T2c

3.2.5 PSA
≤ 15 ng/ml prior to start of therapy if Gleason ≤6
OR
≤ 10 ng/ml prior to start of therapy if Gleason 7

3.2.6 ECOG/Zubrod Performance Status 0-1

3.2.7 Age > 40

3.2.8 Patient signs study specific informed consent prior to study enrollment.

3.3 Exclusion Criteria

3.3.1 Prior or concurrent invasive malignancy (except non-melanomatous skin cancer) or lymphomatous/hematogenous malignancy unless continually disease free for a

minimum of 5 years. (For example, carcinoma in situ of the bladder or oral cavity is permissible)

3.3.2 Evidence of distant metastases (based on disease stage and clinical presentation)

3.3.3 Evidence of regional lymph node involvement (based on disease stage and clinical presentation)

3.3.4 Significant urinary obstruction (i.e. AUA Symptom score > 18)

3.3.5 Estimated prostate gland > 100 grams (within 8 weeks prior to study enrollment)

3.3.6 Previous radical surgery (prostatectomy) or cryosurgery for prostate cancer

3.3.7 Previous pelvic irradiation, prostate brachytherapy, or bilateral orchiectomy

3.3.8 Previous hormonal therapy, such as LHRH agonists (e.g. goserelin, leuprolide), anti-androgens (e.g., flutamide, bicalutamide), estrogens (e.g., DES), or surgical castration (bilateral orchiectomy) or planned concurrent androgen deprivation therapy

3.3.9 Previous or concurrent cytotoxic chemotherapy for prostate cancer

3.3.10 Prosthetic implants in the pelvic region that contain metal or conductive materials (e.g., an artificial hip).

3.3.11 Severe, active comorbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- Crohn's Disease or ulcerative colitis
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol. (Patients on Coumadin or other blood thinning agents are eligible for this study.)
- Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immunocompromised patients.

4.0 Pretreatment Evaluations

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Symptom Assessment and QOL Evaluation

(These may be performed prior to consent as they are routine for urology or radiation oncology clinics);

4.1.1 International Prostate Symptom Score (IPSS)/American Urological Association Symptom Score, International Index of Erectile Function (IIEF-5) and EPIC-26 QOL.

4.2 Insurance Pre-Authorization

As some private insurance carriers will not cover SBRT to the prostate it is highly recommended that pre-authorization be completed before enrolling the patient on study. Patients whose insurance carriers do not cover SBRT of the prostate need to be advised before proceeding with study enrollment.

5.0 Radiation Therapy

5.1 Dose Specifications

5.1.1 Stereotactic Targeting and Treatment

This protocol will require treatments to be performed with a stereotactic technique with the use of a 3-D coordinate system defined by implanted transponders (Calypso) or use of the ExacTrac system and/or use cone-beam CT (CBCT) with fiducial markers.

Dose Fractionation

Patients will receive 5 fractions of radiation. Each fraction size will be 7.4 Gy. The total dose will be 37 Gy. The 5 treatments will be scheduled to be delivered every other day. A minimum of 36 hours should separate each treatment. No more than 3 fractions will be delivered per week. The total duration of treatment will be no shorter than 10 days and no longer than 18 days.

5.2 Supportive Measures

5.2.1 Urinary

Symptomatic urinary medicines, (e.g. tamsulosin) are allowed at the discretion of the treating radiation oncologist or urologist.

5.2.2 Bladder

Patients will be asked to have a full urinary bladder both during simulation and treatment. This may be achieved by asking patients to drink 16-24 oz of water or other fluid 2-3 hours prior to treatment and to not urinate between this time and treatment as they are able.

5.2.3 Bowel

One tablespoon of Milk of Magnesia will be taken the night before the simulation and the night before each treatment. One Fleet's enema will be administered 2-3 hours before the simulation and each treatment.

5.3 Technical Factors

5.3.1 Radiotherapy delivery

Megavoltage radiation therapy will be utilized with 6 to 21 MV photons. Standard quality assurance measures will be taken prior and during radiation therapy.

5.4 Set-up, Localization and Tracking

5.4.1 Patient Set-up

Patients will be positioned supine in a comfortable posture. The minimum immobilization apparatus will be a pillow under the knees and the feet taped or rubber-banded together or equivalent. More complex immobilization devices are allowed, as per the discretion of the treating physician, as long as they do not

interfere with the proper functioning of the image-guidance (Calypso, ExacTrac and cone-beam CT) system.

5.4.2 Localization

The Calypso or ExacTrac or cone-beam CT system will be utilized for both localization and tracking/monitoring. The initial localization and alignment is based on the center of mass of the transponders/fiducial markers. After initial localization is performed, all effort should be made to initiate the treatment delivery as quickly as possible. Significant rotations may be corrected at initial localization stage, and intra-fractional rotations will be ignored. Further adjustment during the treatment will be translational shift of the center of mass determined via Calypso or ExacTrac, using remote couch motion.

5.5 Treatment Planning

5.5.1 Simulation

Computed Tomography (CT)

CT will be the primary image platform for treatment planning. The simulation should be performed in the supine treatment position, with the transponders/fiducial markers in place. Axial cuts of 3 mm or less will be acquired throughout the pelvis with slices of 1 mm thickness through the prostate (defined as 1 cm cranial to the cranial most point of the prostate gland or transponder/fiducial markers to 1 cm caudal to the prostate gland or inferior most transponder/fiducial marker).

MRI

MRI images are not required. However, if MR scan is planned with use of Calypso system, MR should be obtained prior to the implantation of transponders.

Contrast

Oral, IV, urethral, and bladder contrast are allowed but not required.

5.5.2 Treatment Planning/Target Volumes

1. The definition of volumes will be in accordance with the ICRU Report #50 and ICRU Report #62: Prescribing, Recording, and Reporting Photon Beam Therapy.
2. The Gross Tumor Volume **(GTV)** is defined by the physician as all known disease as defined by the planning CT and MR along with clinical information. The GTV for the purposes of this protocol is the prostate only.
3. The clinical target volume (**CTV**) will be the same as the GTV and will consist of the prostate without the seminal vesicles as defined by non-contrast axial CT scan.
4. The planning target volume (**PTV**) will be defined as the CTV plus a 3 mm margin posteriorly and 5mm in all other dimensions.

5.5.3 Dosimetry

1. Intensity Modulated Radiotherapy (IMRT) beam arrangements will be designed with a minimum of 5 non-opposed fields. Rotational IMRT is also allowed provided it demonstrates equivalent dosimetry compared to standard IMRT. If

rotational IMRT delivery is used for planning, a corresponding fixed gantry IMRT plan should also be generated.
2. Axial or non-axial beam arrangements may be utilized as per institutional preference.
3. The prescription isodose line must encompass at least 95% of the PTV with a maximal differential between the prescription isodose line and the maximum dose to the PTV of 15%. Maximal dose to the PTV is defined as to 1cc or 1% of PTV. In addition, <10% of the PTV or < 5 cc (whichever is smaller) should be treated to >112% of the prescription dose.
4. Adequate dose conformality to the PTV, defined as the ratio of prescription isodose volume to PTV volume of < 1.2, should be achieved.
5. The volume of all tissues outside the PTV receiving > 100% of the prescription dose should be < 15% of PTV volume.
6. Ideally hot spots will be manipulated to occur within the peripheral zones of the prostate itself avoiding the prostate-rectal interface as defined by the CTV.

5.6 Critical Structures

5.6.1 Critical Organ Dose-Volume Limits

1. The normal tissue volume to be contoured will include bladder, rectum, bilateral femora (to the level of ischial tuberosity), seminal vesicles, penile bulb, and skin.
2. The normal tissues will be contoured and considered as solid organs.
3. The bladder should be contoured from its base to the dome
4. The rectum should be contoured from the anus (at the level of the ischial tuberosities) for a length of 15 cm or to the rectosigmoid flexure. This generally is below the bottom of the sacroiliac joints.
5. The seminal vesicles will be contoured from the cranial most aspect of the prostate superiorly as one structure (right and left). The seminal vesicles are not a target for this trial but dosimetric data will be collected for later analysis.
7. The tissue within the skin and outside all other critical normal structures and PTVs are designated as unspecified tissue.
8. The following table lists maximum dose limits to a point or volume within several critical organs. These are absolute limits, and treatment delivery that does not abide by these limits will constitute a major protocol violation. The dose is listed as total over 5 fractions and per fraction.

Organ	Volume	Dose (Gy)
Prostate (PTV)	Maximum point dose (1cc)	≤ 43.0 Gy (8.5 Gy per fraction) 115% of prescription dose
	The smaller of 10% or 5 cc	≤41.9 Gy (8.3 Gy per fraction) 112% of prescription dose
	Minimum 95%	≥ 37 Gy (7.4 Gy per fraction) 100% of prescription dose
Rectum	Maximum point dose (1cc)	≤39.3 Gy (7.8 Gy per fraction) 105% of the prescription dose

	Less than 2 cc	> 37 Gy (7.4 Gy per fraction) 100% of prescription dose
	75% rectum	≤33 Gy (6.6 Gy per fraction) 90% of prescription dose
	60% rectum	≤28 Gy (5.6 Gy per fraction) 75% of prescription dose
	50% rectum	≤24 Gy (4.8 Gy per fraction) 65% of prescription dose
Bladder	Maximum point dose (1cc)	40.7 Gy (8.14 Gy per fraction) 110% of prescription dose
	Less than 40 cc	>24 Gy (4.8 Gy per fraction) 65% of prescription dose
Penile bulb	Maximum point dose	No more than 100% of prescription dose
	Less than 3 cc	20 Gy (4 Gy per fraction) 54% of prescription dose
Femoral heads Skin	Less than 10 cc cumulative (both sides)	20 Gy (4 Gy per fraction) 54% of prescription dose
	Maximum point dose	30 Gy (6 Gy per fraction) 81% of prescription dose
Seminal Vesicles	No dose constraint	Collect for documentation only

5.7 Image/signal-guidance for target localization

5.7.1 After patient is setup on the treatment table, either the Calypso system or ExacTrac or cone-beam CT system will be used to align the patient with the treatment machine geometry based on the treatment plan. The alignment result will be evaluated by the attending physician and attending physicist and be approved for treatment by attending physician. The alignment data will be recorded.

5.7.2 If the Calypso tracking system is used for localization of the prostate, it will be used during the treatment to track the target motion. A correction action will be performed if the target migrated more than 2 mm for more than 20 seconds in any of three orthogonal coordinates.

5.7.3 If an ExacTrac system is used for prostate localization with implanted markers, stereotactic images should be taken at least twice during the treatment (or at least every 1 minute).

5.7.4 Cone-beam CT (CBCT) images should be taken prior to radiation delivery but after image-guidance with method described either with 6.7.2 or 6.7.3 and also taken immediately after the radiation treatment. For some special cases, CBCT images may be taken more frequently during the treatment per physician's clinical judgment.

5.7.5 The initial localizations and alignment is based on the center of mass of the transponders/fiducial markers. Significant rotations may be corrected at initial localization stage, and intra-fractional rotations will be ignored. Further adjustment during the treatment will be translational shift of the center of mass determined via Calypso or ExactTrac or CBCT, using remote couch motion.

5.7.6 The physicist will be on-site for image guidance and treatment. For any image-guidance procedure, comparison with reference images or baseline data should be performed and reviewed and approved by both physician and physicist on site. The comparison can be done both manually and automatically. For any image-guidance method, if any deviation is larger than 2 mm, correction should be performed.

5.7.7 All image/signal-guidance data should be recorded for post treatment review and analysis. In some case, replanning (either offline or online) based anatomy of the day may be performed. Such request will be made by the attending physician.

5.8 Radiation Toxicity

Patients will be seen weekly by their radiation oncologist during radiation therapy. Any observations regarding radiation reactions will be recorded and should include attention toward the following potential side effects:

5.8.1 Small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, proctitis, or hematochezia

5.8.2 Bladder complications including urinary frequency/urgency, dysuria, hematuria, urinary tract infection, and incontinence

5.8.3 Radiation dermatitis

5.8.4 Clinical discretion may be exercised to treat side effects from radiation therapy. 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. Bladder irritation can be managed with phenazopyridine. Dysuria may be managed with ibuprofen. Erectile dysfunction can be treated with phosphodiesterase (PDE) inhibitors (sildenafil).

5.9 Radiation Adverse Event Reporting

Adverse events (AEs) and serious adverse events (SAEs) will be recorded in study database. Related and unexpected SAEs will be reported to the DUHS IRB per IRB policy. Sites are responsible for reporting any related and unexpected SAEs to their respective IRBs and also for notifying Dr. Lee and his Study Coordinator of such an event in order to facilitate reporting to the DUHS IRB in accordance with the required reporting timelines. Conversely, the DUHS study team is responsible for notifying all study sites of any reportable events in a timely fashion.

Adverse Event Definition

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Definition of an SAE: Any adverse experience occurring at any dose that results in any of the following outcomes:
- Death;
- A life-threatening adverse experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On study" is defined as during or within 30 days of completing protocol treatment.

Expected events - Expected events are those that have been previously identified as resulting from treatment of prostate cancer with radiation therapy. For purposes of this study, reporting requirements are determined by the assessment of the following adverse event characteristics: the type or nature of the event; the severity (grade); the relationship to the study therapy and whether the event is expected or unexpected.

Recommended assessment steps include:
Identification of adverse events using the NCI CTCAE Version 4.0 terminology. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov).
Grading the severity of the adverse event using the NCI CTCAE Version 4.0.
Determination as to whether the adverse event is related to the study therapy using the following categories: Unrelated, Possible, Probable, and Definite.
Determine whether the adverse event is expected or unexpected.

REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS THAT OCCUR WITHIN 30 DAYS OF THE DATE OF THE LAST RADIATION TREATMENT

	Grade 3 or 4	**Grade 4**	**Grade 4 & 5 Unexpected**
	With Hospitalization	**Without Hospitalization Expected**	
Unrelated, Unlikely	Not required	Not required	10 Calendar Days
Possible, Probable or	**Unexpected**	Not required	5 Calendar Days

Definite	10 Calendar Days		

Any late death (> 30 days after end of radiation) attributed to the protocol treatment should be reported within 10 calendar days of the PI learning of the event.

REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS THAT OCCUR > 30 DAYS OF THE DATE OF THE LAST RADIATION TREATMENT

	Grade 3 Unexpected with Hospitalization	**Grade 4 & 5 Unexpected**	**Grade 4 & 5 Expected**
Possible, Probable or Definite	15 Calendar Days	10 Calendar Days	15 Calendar Days

6.0 Study Visits

6.1 Study Presentation

Following the request of the patient's radiation oncologist, the patient will be given the consent form, provided time to review it and ask any questions regarding his participation in the study. After the subject has consented, the study team will collect the information required to complete eligibility. The patient will be asked to complete the AUASS, IIEF and EPIC-26 if not already available from his previous clinical visit(s).

6.2 Treatment Planning

During this period, the subject will have prostate imaging and treatment planning per standard practice.

6.3 SBRT

During SBRT visits, the subject should receive therapy according to the treatment plan based on the anatomy of the day from the CBCT accomplished prior to each treatment. At each fraction, the physicist or designee should record the following information:

- The date and number of the fraction
- Whether the patient was successfully localized and tracked using the image guidance system.
- Whether the patient required any interventions due to the information provided by the image guidance system, if so the nature of the intervention
- If reoptimization is requested by the attending physician, the physicist will perform plan reoptimization based on the anatomy of the day and previous optimization results. The minimum QA for modified plan will include MU verification using an independent software and analysis of MLC delivery information in the Dialog file from the treatment machine.

6.4 Treatment Checks

Patients will be seen and evaluated weekly during radiation with documentation of tolerance, including acute reactions.

6.5 Follow-up Visits

Patients will be seen approximately at 1, 3, 6, 12, 18, 24, 36 months following the end of radiotherapy. Follow-up visits may occur at the Department of Radiation Oncology or with referring providers. At each visit (see table) the patient will have an interval history, focused physical examination (digital rectal examination at the physician discretion), and assessment of specific GU and GI toxicity. PSA will be assessed before or at each follow-up visit.

6.6 Patient Assessments

Patient assessments are described below, some variation with respect to visit timing is permissible to allow for individual patient needs and clinic schedules.

	Baseline	SBRT Planning	During RT	1 Mo	3 Mo	6 Mo	12 Mo	18 Mo	24 Mo	36 Mo
Medical History	X									
Physical Exam	X (including DRE)			X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Planning CT/MR		X	X[2]							
Prostate Measurement	X									
Transponder or Fiducial Marker Placement		X								
AUASS, IIEF [3]	X			X	X	X	X	X	X	X
EPIC-26 QOL	X				X		X		X	X
Toxicity Assessment			X	X	X	X	X	X	X	X
PSA	X[4]				X	X	X	X	X	X

[1]Focused physical exam. Digital rectal exam (DRE) at the discretion of the physician.
[2.] CBCT to be performed prior to each treatment and reoptimization performed if needed.
[3] As per standard clinic practice.
[4] Baseline PSA must be within 180 days of study registration.

6.7 Data Collection

Data management will be performed by the study personnel under the direction of the study PI. GU and GI toxicity data will be collected at all sites using an appropriate adverse events (AE) application, such as NCI's Cancer Adverse Event Reporting System (caAERS). Demographic, pathology, PSA,IIEF, AUA and other pertinent study data will

be collected at all sites and entered into a study specific secure database. See Appendix 3 for data fields.

6.8 Adverse Events Classification

Adverse events will be recorded at each study visit. These adverse events will be classified in accordance to the CTCAE ver. 4.0.

7.0 Statistical Analysis Plan

7.1 Primary End Point

The primary end-point of the study is the safety of delivering SBRT to the prostate. The dose and fractionation of radiation is determined such that the risk of late complications should be equivalent to the BED_{3Gy} of 78 Gy in 2 Gy fractions.

A conservative estimate of grade 3 rectal toxicity for this regimen of 78 Gy in 2 Gy fractions is 1.5% at 2 years. Therefore, with a patient population of 60 patients if the true rate of grade 3 or higher rectal toxicity is 1.5% there will be a 77% power to rule out a >7.1% rate. If the true rate is 2.5%, there will be an 81% power of ruling out a >9.6% rate.

Incidence of GU and GI Acute and Late Adverse Events

Adverse events are scored according to CTCAE version 4.0. An acute adverse event will be defined as an adverse event occurring less than or equal to 90 days from the completion of RT. Both unadjusted and adjusted odds ratios and the respective 95% confidence interval will be computed.

A late adverse event will be defined as an adverse event occurring more than 90 days from the completion of RT. The time to late adverse events will be measured from the time that protocol treatment is completed (i.e., the completion of radiation) to the time of the worst late adverse event. If no such late adverse event is observed until the time of the analysis, the patient will be censored at the time of the analysis. The distribution of time to late adverse events (observed severities of adverse events over time) will be estimated.

7.2 Secondary End-Points

7.2.1 Disease-free survival: Disease-free failure events include local progression, distant progression, biochemical recurrence as defined by the RTOG Phoenix definition, and death from any cause.

7.2.2 Analysis for Endpoints Related to EPIC-26 QOL

We will use the Expanded Prostate Cancer Index Composite (EPIC-26) instrument to measure QOL. Protocol eligible patients will be included in the QOL analysis only if they have provided baseline and at least one subsequent measurement. The EPIC-26 instrument is intended to be collected on all cases participating in the trial.

The EPIC-26 will be collected at pretreatment (baseline) and at 3, 12, 24 months, and 3 years after therapy starts. Patient self-assessment of symptoms will be performed using three primary EPIC scales: urinary, bowel, and sexual symptoms.

7.3 Sample Size and Patient Accrual

We anticipate that this study will begin enrolling subjects in the Fall 2009 and will enroll 2 subjects a month for 30 months for a total enrollment of 60. This projection is based on the 250 newly diagnosed prostate cancer patients seen in the Department of Radiation Oncology each year, of which at least 75 should be eligible for this study.

7.4 Stopping Rules for Excessive Adverse Events

We estimate ≤ 7.5% of the men will experience a grade 3+ adverse event. For this study, a rate of 5% grade 3+ GU and GI adverse events (pt) according to the CTCAE version 4.0 within 24 months of the start of radiation therapy is considered acceptable. A rate of 20% is considered unacceptable. The null hypothesis (H0) is that this radiation therapy is not tolerable versus the alternative hypothesis (HA) that this radiation therapy is tolerable. With 60 patients the power to reject the null hypothesis is >90%.

The stopping and continuation rules in the Table below will be applied in two stages to the first analyzable 30 cases who received at least some treatment. Analyzable patients are defined as eligible patients who received at least some treatment. If at any stage, we show that the grade 3+ GU and GI adverse event rate may be greater than or equal to 20%, we would temporarily close the study to accrual, gather the relevant source data on the cases with grade 3+ GU and GI adverse events, prepare a statistical report summarizing the adverse event findings, and present the report to the radiation oncology and GU multidisciplinary team for review. The GU team will review all source documentation on the analyzed cases with adverse events and the statistical report summarizing the findings as soon as possible. Following the review of the data, the team will discuss the findings and make a recommendation about the study. If at the first or second stage either of the stopping rules is not met, we will continue accrual and monitoring for grade 3+ GU and GI adverse events. If we continue until the last stage, then we will either conclude "tolerability" or not.

Stopping and Continuation Rules for Grade 3+ GU/GI Adverse Events

Number of Analyzable Patients *	Reject H0 pt ≥ 0.2 and continue	Reject HA : pt ≤ 0.05 and stop
15	≤ 2	≥ 3
30	≤ 3	≥ 4

* Analyzable patients are defined as eligible patients who received at least some treatment.

8.0 References

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9.0 Appendices

Appendix 1 AJCC Staging System 6th edition
Appendix 2 The Expanded Prostate Cancer Index Composite (EPIC-26)
Appendix 3 SBRT Dosimetry Worksheet

9.1 Appendix 1 AJCC Staging System – Prostate, 6th Edition

DEFINITION OF TNM

Primary Tumor, Clinical (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Clinically inapparent tumor not palpable or visible by imaging
- T1a Tumor incidental histologic finding in 5% or less of tissue resected
- T1b Tumor incidental histologic finding in more than 5% of tissue resected
- T1c Tumor identified by needle biopsy *(e.g., because of elevated PSA)*

T2 Tumor confined with prostate*
- T2a Tumor involves less than ½ of one lobe
- T2b Tumors involves greater than ½ of one lobe but < 2 lobes
- T2c Tumor involves both lobes

T3 Tumor extends through prostate capsule**
- T3a Extracapsular extension *(unilateral or bilateral)*
- T3b Tumor involves the seminal vesicle*(s)*

T4 Tumor is fixed or invades adjacent structures other than the seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall

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

Regional Lymph Nodes (N)

Clinical
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in regional lymph node or nodes

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

Primary Tumor, Pathologic (pT)

pT2***	Organ confined
pT2a	Unilateral
pT2b	Bilateral
pT3	Extraprostatic extension
pT3a	Extraprostatic extension
pT3b	Seminal vesicle invasion
pT4	Invasion of bladder, rectum

***Note: There is no pathologic T1 classification

Appendix 1 AJCC Staging System – Prostate Continued

Distant Metastasis** (M)**

MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
- M1a Non regional lymph node*(s)*
- M1b Bone*(s)*
- M1c Other site*(s)*

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

Histopathologic Grade (G)

GX Grade cannot be assessed
G1 Well-differentiated *(slight anaplasia)*
G2 Moderately differentiated *(moderate anaplasia)*
G3-4 Poorly undifferentiated or undifferentiated *(marked anaplasia)*

Stage Grouping

Stage I	T1a	N0	M0	G1
Stage II	T1a	N0	M0	G2, G3-4
	T1b	N0	M0	Any G
	T1c	N0	M0	Any G
	T1	N0	M0	Any G
	T2	N0	M0	Any G
Stage III	T3	N0	M0	Any G
Stage IV	T4	N0	M0	Any G
	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

9.2 Appendix 2 EPIC-26

Expanded Prostate Cancer Index Composite Short Form

EPIC-26
The Expanded Prostate Cancer Index Composite

Short Form

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_____

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. 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		

3. 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)	27/
3 or more pads per day	3		

4. 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. Need to urinate frequently during the day	0	1	2	3	4	33/

5. 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)	34/
Moderate problem	4		
Big problem	5		

EPIC-SF 6.2002

Mark in This Space

6. 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. Losing control of your stools	0	1	2	3	4	52/
d. Bloody stools	0	1	2	3	4	53/
e. Abdominal/ Pelvic/Rectal pain	0	1	2	3	4	54/

7. 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

8. 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 ability to have an erection?	1	2	3	4	5	57/
b. Your ability to reach orgasm (climax)?	1	2	3	4	5	58/

9. 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

10. 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

Do Not Mark in This Space

11. 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		

12. 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		

13. 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. Hot flashes	0	1	2	3	4	74/
b. Breast tenderness/enlargement	0	1	2	3	4	75/
c. Feeling depressed	0	1	2	3	4	77/
d. Lack of energy	0	1	2	3	4	78/
e. Change in body weight	0	1	2	3	4	79/

THANK YOU VERY MUCH!!

9.3 Appendix 3 Data Collection: Dosimetry and Initial Evaluation

Patient Initials: ____ ____ ____ Subject Study ID Number: _____

1.	Prostate volume (CTV)	_____ cc	
2.	Prostate planning target volume (PTV)	_____ cc	
3.	Conformality index (Volume of prescription isodose surface / volume of PTV)	_____	
4.	Minimum dose to 1% of prostate planning target volume (P + 0.3)	_____ . _____ Gy	
5.	Maximum dose to 1% of prostate planning target volume (P + 0.3)	_____ . _____ Gy	
6.	Mean dose to the prostate planning target volume (P + 0.3)	_____ . _____ Gy	
7.	Bladder volume at time of planning CT	_____ cc	
8.	Maximal dose delivered to 2 cc or more of bladder	_____ . _____ Gy	
9.	Percent and absolute volume of bladder > 37 Gy (V100)	_____ % _____ cc	
10.	Percent and absolute volume of bladder > 33 Gy (V90)	_____ % _____ cc	
11.	Percent and absolute volume of bladder > 28 Gy (V75)	_____ % _____ cc	
12.	Percent and absolute volume of bladder >24 Gy (V65)	_____ % _____ cc	
13.	Percent and absolute volume of bladder >18.5 Gy (V50)	_____ % _____ cc	
14.	Mean dose to prostatic urethra	_____ . _____ Gy	
15.	Maximal dose to 10% of prostatic urethra	_____ . _____ Gy	
16.	Rectal volume at time of planning CT	_____ cc	
17.	Maximal dose delivered to 2 cc or more of rectum	_____ . _____ Gy	
18.	Percent and absolute volume of rectum > 37 Gy (V100)	_____ % _____ cc	
19.	Percent and absolute volume of rectum > 33 Gy (V90)	_____ % _____ cc	
20.	Percent and absolute volume of rectum > 28 Gy (V75)	_____ % _____ cc	
21.	Percent and absolute volume of rectum > 24 Gy (V65)	_____ % _____ cc	
22.	Percent and absolute volume of rectum > 18.5 Gy (V50)	_____ % _____ cc	
23.	Mean dose to right femoral head	_____ . _____ Gy	
24.	Mean dose to left femoral head	_____ . _____ Gy	
25.	Energy	_____ MV	
26.	Number of fields:	_____	
27.	Non-axial beams?	Yes or No	
28.	Date of first fraction	_____	
29.	Date of last fraction	_____	
30.	Elapsed time (days) from first fraction to last fraction:	_____	
31.	Institution Patient treated at:	_____	
32.	Mode (Calypso=1, ExacTrac=2)		

Age at time of enrollment

Month and Year of birth

Race

Zip code

Date of Prostate Biopsy

Combined Gleason Score

Primary Gleason Pattern

Secondary Gleason Pattern

Number of cores (biopsy)

Number of positive cores (biopsy)

Lobes (Right, Left or Bilateral)
Duke Pathology Review (Y or N)
Hx of Previous Biopsy (Y or N)
PSA Date
PSA level
T stage
Zubrod Baseline
AUA Score Baseline
AUA Bother score Baseline
IIEF Baseline

Follow-up Data

ID	Participant	3mo	6mo	12mo	18mo	24mo	36mo
	PSA						
	Date						
	AUA Score						