PROSPECTIVE EVALUATION OF HYPOFRACTIONATED STEREOTACTIC BODY RADIOTHERAPY FOR LOW AND INTERMEDIATE RISK PROSTATE CANCER (HCC 09-031)

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List of Abbreviations

3D CRT	3 Dimension Conformal External Beam Radiation Therapy
ACD	ASTRO Consensus Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ASTRO	American Society for Radiation Oncologist
bDFS	biochemical Disease-Free Survival
CS	Clinical Stage
CT Scan	Computed Tomography Scan
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Treatment Volume
DRE	Digital Rectal Exam
DVH	Dose Volume Histogram
EB	External Beam
EBRT	External Beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
EQD	Equivalent Dose
GEE	Generalized Estimating Equation
GI	Gastrointestinal
GTV	Gross Tumor Volume
GU	Genitourinary
Gy	Gray
HDR	High-Dose Rate
I-125	Iodine 125
IMRT	Intensity Modulated Radiotherapy
IR	Intermediate Risk
IV	Intravenous
LDR	Low-Dose Rate
LR	Low Risk
MRI	Magnetic Resonance Imaging
MV	Mega Voltage
NCI	National Cancer Institute
OPC	Objective Performance Criteria
OPC	Objective Performance Criteria
Pa-103	Palladium – 103
PE	Physical Exam
PSA	Prostate-Specific Antigen
PTV	Planning Target Volume
PTV	Primary Tumor Volume
QOL	Quality of Life
RP	Radicular Prostatectomy
RT	Radiation Therapy
SBRT	Stereotactic Body Radiotherapy
SV	Seminal Vesicle
UCSF	University of California San Francisco

PROTOCOL SUMMARY

Title

A Prospective Evaluation of Hypofractionated Stereotactic Body Radiotherapy (SBRT) for Low and Intermediate Risk Prostate Cancer

Objectives

The *primary* objectives of this study are:

- To determine, in both low-risk and intermediate-risk cohorts, the rates of acute and late grade 3 or higher gastrointestinal and genitourinary toxicity observed during an initial 24 month follow up.
- To estimate the rate of biochemical Disease-Free Survival (bDFS), Phoenix and ASTRO definitions, at 2 years following hypofractionated SBRT for low and intermediate risk prostate cancer. Failure occurs when the PSA is ≥ 2 ng/ml more than the lowest PSA measurement before the current one, with no backdating.

The *secondary* objectives of this study are to:
To determine

1. the rate of local failure: proportion of patients with local disease progression at 2 years
2. rate of distant failure: proportion of patients with metastatic disease at 2 years
3. rate of disease-free survival: median time from start of treatment until disease progression
4. rate of disease-specific survival: death due to prostate cancer (excludes patients that relapse with inactive disease)
5. overall survival: median length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive.
6. quality of life (QOL) in generic and organ-specific domains using the FACT-G assessment tool

Patient population

In order to be eligible for this study, patients will have a histologically confirmed adenocarcinoma of the prostate which is a clinical stage T1b-T2b, Nx-0 and Mx-0. The following combinations will be allowed:
- Gleason score 2-6 and PSA ≤ 20
- Gleason score 7 and PSA ≤ 10
All patients will have an ECOG Performance Status of 0-1 and have had no prior prostate radiation or definitive therapy.

Number of patients

200

Study design and methodology

This is a phase II study.

Treatments administered

SBRT:
Patients will receive 36.25 Gy in 5 fractions (7.25 Gy/fx) delivered over a 2-week period.

Efficacy data collected

The following evaluations will be performed to assess the efficacy of stereotactic body radiation therapy (SBRT) in low and intermediate risk prostate cancer:

- the rate of local failure
- rate of distant failure
- rate of disease-free survival
- rate of disease-specific survival
- overall survival
- quality of life (QOL) in generic and organ-specific domains

Safety data collected

The following evaluations will be conducted to assess the safety of radiosurgery:

- Recording of all toxicity data per NCI CTCAE version 3.0

1.0 Background

Prostate cancer is the most common malignancy in men; an estimated 219,000 cases will be diagnosed in the United States in 2007[1]. PSA screening has led to earlier stage diagnoses; in 1998, 92% of prostate cancers were diagnosed with clinically organ-confined disease[2]. According to the NCI Consensus Conference in 1988[3], and the Prostate Cancer Panel of the American Urological Association in 1995[4], treatment options (ie standard of care options) that should be discussed with each patient in this category include radical prostatectomy, external beam radiation therapy (RT), interstitial brachytherapy and watchful waiting.

First attempts to treat organ-confined prostate cancer with radiotherapy yielded poor biochemical disease free outcomes, as insufficient doses were delivered to the target. Since the 1980's, conformal RT techniques have been developed which reduced dose to the surrounding organs, allowing the safe delivery of greater doses to the prostate. Conformal RT has been achieved either through 3-dimension conformal external beam RT (3D CRT), or through prostate brachytherapy. These techniques have yielded disease-free outcomes similar to those seen with radical prostatectomy (see table 1), although not without toxicity.

Modern external beam radiotherapy uses three-dimensional treatment planning, delivering RT to the prostate through typically 5-7 coplanar beams. With intensity modulated radiotherapy (IMRT), dose is modulated through each of these beams. Due to variations in patient positioning and internal organ motion, the position of the prostate cannot be accurately determined using exterior skin marks. Placing gold fiducials in the prostate, and imaging prior to treatment deliver reduces targeting error, but this typically does not account for movement within a given treatment session. Such intrafractional movement can be substantial: in one study[5] it was estimated at 2mm, 6mm, and 7mm in the left-right, anterior-posterior, and cranial-caudal directions, respectively. Radiation oncologists account for this uncertainty by adding a margin to the intended target. Expanding radial dimensions to create a "planning target volume" (PTV) increases the volume of surrounding normal structures in the high dose region, potentially increasing toxicity.

In the last decade, transperineal ultrasound-guided brachytherapy has gained popularity for treating organ-confined prostate cancer. Brachytherapy allows the delivery of conformal, high-dose radiotherapy to the prostate, with a rapid dose fall-off outside of the implanted region. Favorable long-term outcomes using permanent iodine-125 (I-125) and palladium-103 (Pd-103) implants have been reported in numerous studies[6 7 8 9 10,] High-dose rate (HDR) brachytherapy has been used in the treatment of prostate cancer since the 1980's[11 12 13 14 15 16 17 18 19 20 21 22 23]. Catheters are placed temporarily in the prostate, and then loaded with a high-dose Iridium-192 source, delivering a few fractions of very high-dose RT. Initial protocols employing HDR combined conventionally fractionated external beam RT with an HDR boost. More recent reports have employed HDR as monotherapy[24 25 26 27 28 29]. Adjusting for pre-treatment risk factors, these studies yield bDFS outcomes at least as favorable to those seen with LDR brachytherapy or conformal dose-escalated RT or IMRT (see table 1). Indeed, a prospective, non-randomized study from William Beaumont Hospital[30] comparing HDR monotherapy versus LDR brachytherapy (Pd-103) showed a superior 5-year event-free survival (98% vs. 85%, p=0.01) and a trend towards improved freedom from cancer failure (98% vs.

92%, p=0.1) in the HDR cohort. The same group showed acute and late toxicity, potency, and QOL following HDR brachytherapy was more favorable than either LDR brachytherapy or conformal external beam RT[31 32]. The rate of impotence three years following HDR was 16%, compared to 45% following LDR brachytherapy.

Table 1. bDFS Outcomes for Low-Risk Prostate Cancer using Current Standard of Care Treatments (brachytherapy, external beam radiation, and surgery)

				Median	5-yr bDFS: Definition		
Rx	Details	Institution	# pts	f/u yrs	Phoenix	ASTRO	Ave‡
HDR	45-50Gy + 2-4 fx boost	Seattle, Kiel, Beaumt[33]	46	5		96%	92%
	36Gy + 5.5-6Gy x 4 boost	CA Endocurie[34]	70	7.25	93%	90%	
HDR	Monotx: 6–7.25Gy x 6	CA Endocurie[35]	117#	8		96%	97%
	Monotx: 9.5Gy x 4	Beaumont[36]	95†	4.2		98%	
LDR	Monotx: 145Gy I125	RTOG 9805[37] phase II	95	5.3	99%	93%	88%
	Monotx: I125 & Pd103	11 inst meta-analysis[38]	1444	5.25	86%	88%	
EB	IMRT: 70Gy, 2.5Gy/fx	Clev Clin[39] hypofract	36	5.5	97%	97%	97%
	IMRT: 81Gy, 1.8Gy/fx	MSKCC[40]	203	7	92%	84%	83%
	3dRT/IMRT: >72Gy	9 instit meta-analysis[41]	70	5.7		79%	
	3dRT/IMRT: 70-76Gy	9 instit meta-analysis[42]	231	6.3	94%		
	3dConformal: 78Gy	MDA rand dose-esc[43]	32	>5	93%	92%	
	proton bst to 79.2Gy	MGH, Loma Linda[44]	116	5.5	96%	80.5%	
RP	Institutions	Author	#pts	f/u yrs	Definition	bDFS	Ave‡
	Baylor	Hull[45]	299	3.9	PSA≥0.4	92.5%	94%
	ClevClinic & MSKMercy	Kupelian[46]	524*	5.5	PSA≥0.2	92%	
	Univ Pennsylvania	D'Amico[47]	322	5	ASTRO	88%	
	Hopkins	Han[48]	899*	5.9	PSA≥0.2	98%	

*Number of patients, bDFS estimated based on proportions within each risk group. #75% low risk, 25% intermediate; †Included T2b in low-risk group. ‡Weighted average, using ASTRO or stated definition.

Radiation oncologists fractionate RT dose to reduce toxicity to surrounding normal tissues. For most cancers, by delivering dose over several weeks, equivalent cancer-killing effect is achieved with reduced long-term toxicity. The effect of dose fractionation on both cancer and normal tissues can be estimated using the "linear-quadratic model". In this model, the alpha-beta ratio reflects the response of normal tissues or cancers to changes in RT dose per fraction. Most cancers respond to RT as do rapidly-dividing normal tissues (e.g., skin or mucous membranes), and thus have high α/β ratios, in the 10-12 Gy range. Tissues with lower α/β ratios are more sensitive to large dose per fraction (also known as hypofractionated) RT.

The favorable control rates observed with hypofractionated RT led radiobiologists to reconsider α/β ratio of prostate carcinoma. Several researchers have concluded that prostate cancer has an unusually low α/β ratio of about 1.5Gy[49 50 51 52 53]. Another analysis[54] estimated the α/β ratio was between 3.1-3.9 Gy; a more recent study[55] of 3756

patients yielded a ratio between 2.6 and 3.7Gy. A low α/β ratio is consistent with other biologic properties of prostate cancer: an unusually long tumor doubling times[56], and a very low proportion of proliferating cells[57]. Although the actual α/β ratio for prostate cancer is debated, the accepted range of 1–4 Gy appears to be similar to, or smaller than the α/β ratios for late effects in the surrounding normal tissues (3-5 Gy). Thus a therapeutic gain could be achieved by hypofractionation. Indeed, this approach should result in equivalent or improved cancer control with reduced toxicity[58 59 60].

In 1951, Lars Leksell, a Swedish neurosurgeon, first described radiosurgery: the use of converging beams of ionizing radiation to non-surgically ablate intracranial lesions. He later developed the "GammaKnife", which focuses 201 collimated Co-60 beams at a single isocenter. A metal frame was fixed to the patient's skull, providing both a reference for treatment, and a means to rigidly fix the skull. Another method of delivering stereotactic radiotherapy uses multiple isocentric arcs from a linear accelerator equipped with a small collimator; again the patient rigidly immobilized.

In the 1990s a novel device was developed at Stanford University for delivering stereotactic radiosurgery without the need for rigid immobilization. This device, called "CyberKnife", uses a lightweight x-band linear accelerator mounted on an industrial robot. The system uses a pair of amorphous silicon detectors to gather orthogonal fluoroscopic images of the patient. Bony landmarks or implanted fiducials near the target are continuously imaged, and the system's computer automatically makes adjustments to account for variations in set-up or patient movement. The target can be treated from about 1200 different directions, using coplanar or non-coplanar beams. The CyberKnife can treat static intra- and extra-cranial sites with sub-millimeter accuracy.

Radiosurgery should be ideal for treating prostate cancer because 1) targeting accuracy for static targets is excellent, with an error of about 1mm, 2) it can adjust for intra-fractional organ motion, reducing the volume of the target PTV and therefore the dose to surrounding organs, 3) by using over one-hundred non-conplanar beams, the dose gradient between the prostate and surrounding tissues may be superior to that achieved with conventional linear accelerators, and 4) the radiobiology of prostate cancer may favor large dose per fractions.

As discussed above, the current standard of care for early localized prostate cancer include radical prostatectomy, conventional external beam radiation (IMRT), interstitial brachytherapy, and occasionally watchful waiting.[3 4] With increasing evidence of a low α/β ratio for prostate adenocarcinoma, there has been an interest in using larger radiation fractions and shorter treatment schedules (fewer fractions). Stereotactic radiosurgery was thus a logical choice to attain such goals, given its ability to deliver a highly conformal dose of radiation with rapid fall-off—allowing the sparing of nearby organs at risk. Hypofractionation and SBRT present several potential advantages. Ideally, tumor control may be increased for a given level of late complications. Conversely, late complications may be reduced for a given level of tumor control. Patient convenience would increase with fewer fractions compared with standard EBRT courses that extend between 7-9 weeks. Equipment utilization and staffing may be more efficient, which may translate to increased cost efficiency.

Given the relatively recent interest in SBRT for prostate cancer (the past 2-3 years), there are only a few institutions that have, to date, reported outcomes following SBRT for prostate cancer. This paucity of data highlights the need for trials such as the one proposed here. With the exception of Virginia Mason Medical Center and Stanford University, the majority of experiences are available in abstract form only. A Phase I/II trial of SBRT at Virginia Mason Medical Center using a linear accelerator and fiducial marker system was reported by Madsen et al. [61]. Forty low-risk patients received 33.5 Gy in 5 fractions (BED2Gy = 78 Gy; a/b = 2 Gy). Six noncoplanar fields using a linear accelerator and daily stereotactic localization of the prostate using three radio- opaque fiducial markers were used. A margin of 4 to 5 mm from block edge to the prostate was used for treatment. Patients were placed on a diet to minimize gas and took daily simethicone to reduce rectal dilatation and movement during treatment. Before each fraction, orthogonal images were obtained and analyzed for the position of the fiducial markers. An automated computer program (Isoloc 5.2; Northwest Medical Physics Equipment, Linwood, WA) was used to calculate the necessary position shifts before treatment. With a median follow-up of 41 months, 4-year PSA nadir + 2 FFBF was 90%, and ASTRO (three rises) FFBF was 70%. Acute Grade 1 or 2 toxicity RTOG toxicity was 49% (genitourinary) and 39% (gastrointestinal). There was a single incidence of Grade 3 genitourinary toxicity. Late Grade 1 or 2 toxicity was 45% (genitourinary) and 37% (gastrointestinal). No late Grade 3 or higher toxicity was reported. At Stanford University forty-one patients received 36.25 Gy in 5 fractions (BED2Gy = 90.6 Gy; a/b = 1.5 Gy) [62 63]. Patients were treated with implantable gold fiducials for daily localization, as well as intrafraction tracking performed every 30–90 s. With a median follow-up of 33 months, no patient has experienced biochemical failure (ASTRO or nadir + 2). There were 2 patients with RTOG Grade 3 late urinary toxicity and none with Grade 3 rectal toxicity. There was no Grade 4 toxicity. The first 21 patients received daily treatment; the remaining 20 patients were treated every other day. Quality of life scored according to the Expanded Prostate Cancer Index Composite suggested improved rectal complications with every-other-day dosing.

The Korean Institute of Radiological and Medical Sciences reported on forty-four patients that received 32–36 Gy in 4 fractions, with the exception of 1 patient who received 24 Gy in 3 fractions [64 65] There were 10 low-risk (PSA <10 ng/mL, Gleason score <6, Stage T1b-T2a), 9 intermediate-risk (PSA 10–20 ng/mL, Gleason score 7), and 25 high-risk patients (PSA >20 ng/mL or Gleason score >8). With a median followup of 13 months, overall survival at 3 years was 100%, with a 3-year FFBF rate of 78%. Fourteen patients experienced Grade 1 or 2 acute rectal toxicity, and 17 patients experienced Grade 1 or 2 bladder toxicity. There were no Grade 3 or greater acute toxicities. Late toxicity was not reported. Ten patients were treated by the Radiation Medical Group of San Diego and received 38 Gy in 4 fractions [66] Very preliminary results were reported; the median pretreatment PSA level was 6.9 ng/mL, and at 4 months after treatment it had decreased to 0.7 ng/mL in the first 8 patients. Toxicity was not detailed. A 21st Century Oncology Center in Fort Myers, FL reported on twenty-two patients receiving 36.25 Gy in 5 fractions[67] The Common Toxicity Criteria for Adverse Effects, version 3.0, were used to assess toxicity at intervals from 1 to 12 months after treatment. Twenty-two patients were reported, of whom 18 had been followed for at least 1 month. During treatment, 3 patients reported dysuria and 5 urinary hesitancy, all Grade 1 toxicities. At 1 month, 1 patient reported continued dysuria and hesitancy, and 4

patients reported frequency and urgency. During treatment, 5 patients reported diarrhea, and 2 reported proctitis. At 1 month, 1 patient reported continued proctitis, Grade 1.

Patients followed for more than 3 months returned to baseline urinary and rectal function. No reporting of clinical outcomes was made.

2.0 Objective

PRIMARY OBJECTIVES:

2.1 The primary safety goal of this study is to determine, in both low-risk and intermediate-risk cohorts, the rates of acute and late grade 3-5 gastrointestinal and genitourinary toxicity observed during the initial 24 months following hypofractionated SBRT for prostate cancer. Patients will be followed for at least 5 years but possibly as long as 10 years, but initially we will strive to obtain 2 year follow-up results.

2.2 The primary efficacy goal is to document the rate of biochemical Disease-Free Survival (bDFS), Phoenix and ASTRO definitions, at 2 years. As above, we will ultimately aim for at least 5 years of follow-up but possibly as long as 10 years, with a short term goal of 2 years.

SECONDARY OBJECTIVES:

2.3 To measure the following in the study population: Rates of local failure, distant failure, disease-free survival, disease-specific survival, and overall survival; quality of life (QOL) in generic and organ-specific domains.

3.0 Investigational Plan

3.1 Initial Evaluation

Prior to enrollment all patients will be evaluated with a physical exam (including DRE), review of pathology and laboratory values to confirm diagnosis, and baseline imaging studies. In addition, since there are many feasible treatment options for men with early, localized prostate cancer a detailed conversation will be had regarding all possible treatment options comprising the current standard of care. Specifically, the treating physician will discuss conventional EBRT using IMRT to doses ≥75.6 Gy using 1.8 Gy daily fractions, low dose rate brachytherapy using Cesium-131, radical prostatectomy, and watchful waiting for those men with short life expectancy. This will be an important and crucial part of the study, since long-term data is not available for SBRT as a primary treatment for prostate cancer. In other words, it is not currently accepted as standard of care, and is therefore experimental. This will be detailed in laymen's terms in the consent form as well (summarized on page 16 of consent). All participants will be made aware of the high success rates with the current standards of care (5 year disease free survivals approaching 100% as seen in Table 1) and the chance that such high rates could theoretically be compromised by participating in this trial since 5 year follow-up using SBRT is not currently available.

3.2 Accelerator

Physicians will treat with a stereotactic radiosurgery system using 6MV photons to deliver stereotactic body radiotherapy.

3.3 Doses

In this protocol, the linear quadratic formula is used to calculate equivalent doses. Three assumptions are made: 1) sublethal damage is completely repaired between fractions, 2) no repair of sublethal damage occurs during a given fraction, and 3) no repopulation occurs during the treatment course (i.e., there is no time factor). Equivalent dose at a specified dose/fx d, for an assumed α/β ratio r, is expressed as EQD_d (α/β=r). See table 2 for 2Gy/fx equivalent doses. The 5-year bDFS outcomes for HDR series and for hypofractionated EBRT are superior to those reported using conventionally fractionated 3D conformal or IMRT (see table 1). This suggests that an EQD_2 of 80 Gy or more may be required to achieve 5-year bDFS in the 96-98% range. At Stanford and Naples Community Hospital, toxicity following CyberKnife (7.25 Gy x 5 fractions, and 7 Gy x 5 fractions, respectively, both calculated 3-5mm from the prostate border) was minimal. In the Naples series, median PSA outcomes 1 year after treatment was 1.2ng/dL, somewhat greater than that reported in brachytherapy series. The protocol gave an EQ_2 74.3 to 90.6Gy (for α/β ratios of 3Gy and 1.5Gy, respectively); PSA response was excellent, falling to an average of 0.22ng/ml at 18 months. This protocol thus uses the Stanford dose and PTV: 7.25Gy x 5 fractions prescribed to the PTV, defined as the prostate expanded 3mm posteriorly, and 5mm elsewhere. The rapid dose gradient achievable with SBRT allows the simultaneous delivery of a greater dose to the prostate (GTV). To deliver a BED approaching that prescribed in the HDR monotherapy series, 8Gy x 5 is prescribed to the prostate. Thus the PTV receives an EQD_2 of 74.3Gy (if α/β=3), or an EQD_2 of 90.6Gy (α/β=1.5). The prostate receives an EQD_2 (α/β=3) of 88Gy, or 108.6Gy for α/β=1.5.

nd x (1 + d/□□ (α/β))

where n is the # of fractions and d is the dose/fraction. The “alpha-beta ratio” characterizes the radiation response of a particular tissue; a higher value is indicative of a tissue that responds acutely to the effects of radiation. Due to their highly proliferative nature, most tumors fall into this category.

SBRT treatment will be given on non-consecutive days, excluding weekends. The prescription dose will be prescribed to the isodose line best encompassing the planning target volume (PTV) depending on the volume of tumor.

Table 2: **Hypofractionated RT Schedules**

Institution/protocol	Dose/fx	#fxs	Total dose	2Gy/fx Equivalent Dose Assuming α/β ratio of: 1.5Gy	3Gy	10Gy
	(All doses expressed in Gy)					
Naples CyberKnife	7	5	35	85	70	49.6
Stanford CyberKnife	7.25	5	36.25	90.6	74.3	52.1
Beaumont HDR*	9.5	4	38	119.4	95	61.8
Demanes HDR*	7.25	6	43.5	108.8	89.2	62.5
This protocol: GTV	8	5	40	108.6	88	60
RTOG 0415	2.5	28	70	80	77	72.9

*Does not account for heterogeneity in HDR plans.

3.4 Localization, Simulation and Treatment Planning

3.4.1 FIDUCIAL PLACEMENT:

All patients will have gold fiducial seeds measuring 3-5 mm placed in the prostate prior to treatment planning. At least four fiducial seeds will be placed under transrectal ultrasound guidance, using either transperineal or transrectal approach, with local anesthesia and/or sedation as required. The physician will place seeds such that they are visible (and not superimposed) on orthogonal imaging, are not collinear, and ideally are separated by 2cm or more. Fiducials will be placed as an outpatient procedure; at least three seeds must be usable for tracking during treatment. If an interim analysis shows unacceptable fiducial migration with a specific technique or type of fiducial, further use of this technique or type of fiducial may be prohibited by the Principal Investigator. The side effects of implantation will be similar to a biopsy of the prostate. These include but are not limited to infection, bleeding, pain at local area, and dislocation of the marker. Alternatively, cone beam computed tomography (CBCT) can be used in lieu of fiducial markers at the discretion of the investigator.

3.4.2 TREATMENT PLANNING IMAGING:

To allow fiducial stabilization and resolution of swelling, planning studies will be imaged 5-10 days after fiducial placement. Alpha Cradle or a similar immobilization device will be used as needed. To avoid prostate distortion, in the primary CT used for treatment planning, no indwelling catheter shall be placed. If required to visualize the urethra, a catheter may be placed for the secondary imaging study only. All patients will be asked to empty their bladders prior to the CT to help promote a reproducible prostate position. CT scans will be taken for treatment planning. IV contrast will be given to all patients except those with an allergy or chronic renal insufficiency. CT slices will be 1 – 1.5mm, with 200-300 slices taken centered approximately at the prostate. The imaging sets will be downloaded to the appropriate treatment planning system to develop the radiosurgery treatment plan.

If not medically contraindicated, all patients will undergo MRI imaging to determine the anatomical borders of the prostate, and if possible, the urethra. This study will be fused to the treatment planning CT. No endorectal coil is allowed.

3.4.2.1 URETHRAL IDENTIFICATION: To record DVH data for the prostatic and membranous urethra, visualization of these structures is recommended, but not mandatory. If the urethra cannot be visualized and contoured, then to insure the prostatic urethra meets the dose constraint specified in 8.3.4.7, the prescription dose of 36.25Gy shall be no less than 75% of Dmax. To identify the urethra, the following may be employed:

MRI, if urethra can be identified. To verify that the MRI is capable of visualizing the urethra, on the first 3 cases an additional *secondary* scan (either MRI or CT) shall be performed with an indwelling catheter in place. This will be correlated with the MRI scan performed without a catheter; if the urethra can be reliably imaged, then subsequent catheter placement is not required.

A *secondary* CT or MRI scan with an indwelling urethral catheter in place. Urethrogram with contrast delineating the membranous and prostatic urethra.

Prior to treatment planning imaging, the patient will follow the bowel/urinary preparation procedures used for treatment. This will include emptying the bladder voluntarily or by catheterization if necessary. If the patient has moved his bowels in the past 72 hours no specific procedure is necessary. If he has been constipated without a bowel movement for greater than 72 hours an enema will be given. These measures are taken to help limit prostate motion and create a reproducible position from planning to treatment.

3.5 Treatment Delivery

The planning data containing the coordinates of tumor isocenter, the external infrared markers, and the implanted markers are transferred to the appropriate platform depending on the treating machine. The daily initial positioning during treatment delivery will be performed using lasers and skin marks and infrared optical markers as appropriate. The target isocenter will be verified using daily imaging. Depending on the platform used, the moving target will be positioned within the beam under infrared and/or image guidance. If at any at any time a patient needs IV fluids for dehydration for diarrhea, we will cancel the next scheduled fraction and resume treatment on the following fraction if the diarrhea has improved.

3.6 Supportive Care

3.6.1 Diarrhea

Patients will be instructed to begin taking loperamide after the first poorly formed or loose stool or first episode of 2 or more bowel movements in one day.

Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then, 2 mg after every episode of diarrhea until reaching the daily maximum dose.

Loperamide should not be taken prophylactically

Patients must notify the research team as to when they initiated loperamide therapy. If diarrhea persists despite loperamide therapy, then the patient should be evaluated for the need for IV fluid & electrolyte replacement.
Alternative medications

Somatostatin analog (Octreotide7) 100 - 500 mcg SC/IV tid; maximum daily dose = 1500 mcg/day; alternatively, somatostatin analog may be given at 25-50 mcg/hour as a continuous IV infusion.

Atropine/diphenoxylate which is available as either a 0.025/2.5 tab, or 0.025/2.5 per 5 mL liquid. Patients should take 1-2 tabs PO tid or qid or 5-10 mL PO tid/qid.

Atropine/difenoxin (Motofen7) 0.025/1 tab; 2 tabs PO x 1, then 1 tab PO q 2-4 hr (max 8 tabs per day)

Paregoric: (an antidiarrheal opiate): 5 - 10 mL ORALLY 1-4 times daily: maximum 40 mL/day

OTC meds: bismuth subsalicylate 262 mg tabs: 2 tabs PO q 1 hr prn; maximum 4200 mg/24 hr

4.0 Patient Selection and Eligibility

All of the following will be completed prior to enrollment in the study.

4.1 Evaluations Required for Eligibility:

4.1.2 Complete history & physical examination including a digital rectal exam

4.1.3 Assessment of performance status

4.1.4 Pathologic confirmation of adenocarcinoma of the prostate

4.1.5 Serum PSA, < 60 days prior to registration, or < 60 days prior to hormone therapy

4.1.6 CBC, platelets, serum BUN and creatinine

4.1.7 Ultrasound of prostate, or CT of pelvis to determine prostate size: volume = $\pi/6$ x length x height x width

4.1.8 Measurement from CT or ultrasound $\leq$ 90 days prior to registration, or $\leq$ 14 days prior to registration if hormone therapy given

4.2 Patient questionnaires (see appendix VI).

4.2.1 FACT-G questionnaire

4.2.2 AUA questionnaire
4.2.3 EPIC-26 questionnaire
4.2.4 SHIM questionnaire
4.2.5 Utilization of Sexual Medications/Devices questionnaire

4.3 Patient Eligibility

All patients must meet the following criteria to be considered eligible for enrollment.

1. Histologically proven prostate adenocarcinoma
   1a. Gleason score 2-7
   1b. Biopsy within one year of date of registration
2. Clinical stage T1b-T2b, N0-Nx, M0-Mx (AJCC 6th Edition)
   2a. T-stage and N-stage determined by physical exam and available imaging studies (ultrasound, CT, and/or MRI)
   2b. M-stage determined by physical exam, CT or MRI. Bone scan not required unless clinical findings suggest possible osseous metastases.
3. PSA ≤ 20 ng/dL
4. Patients belonging in one of the following risk groups:
   4a. Low: CS T1b-T2a and Gleason 2-6 and PSA ≤ 10, *or*
   4b. Intermediate: CS T2b and Gleason 2-6 and PSA ≤ 10, or CS T1b-T2b, and Gleason 2-6 and PSA ≤ 20 ng/dL, or Gleason 7 and PSA ≤ 10 ng/dL
5. Prostate volume: ≤ 100 cc
   5a. Determined using: volume = π/6 x length x height x width
   5b. Measurement from CT or ultrasound ≤ 90 days prior to registration.
6. ECOG performance status 0-1
7. No prior prostatectomy or cryotherapy of the prostate
8. No prior radiotherapy to the prostate or lower pelvis
9. No implanted hardware or other material that would prohibit appropriate treatment planning or treatment delivery, in the investigator's opinion.
10. No chemotherapy for a malignancy in the last 5 years.
11. No history of an invasive malignancy (other than this prostate cancer, or basal or squamous skin cancers) in the last 5 years.
12. No hormone ablation for two months prior to enrollment, or during treatment.
13. Completion of patient questionnaires in section 4.7.
14. Life expectancy of ≥ 10 years as determined by treating physician.
15. Consent signed.

5.0 Treatment Administration and Evaluation

5.1.1 EVALUATED STRUCTURES:

5.1.1.1 GTV: The Gross Tumor Volume (GTV) shall include the prostate; no more than 0.5cm of the immediately adjacent SV shall be included.

5.1.1.2 CTV: The Clinical Treatment Volume (CTV) shall include:

5.1.1.2.1 LOW-RISK PATIENTS: (CS T1b-T2a, PSA ≤ 10, Gleason score ≤ 6). Pathologic data from William Beaumont Hospital showed only 1% of low-risk patients had seminal vesicle (SV) involvement[68]; this eliminates the need to treat SVs in this group. Thus the CTV shall equal the GTV.

5.1.1.2.2 INTERMEDIATE RISK PATIENTS: The Beaumont study also showed only 2% of "high-risk" patients (PSA > 10, Gleason > 6, and/or CS > T2a) had SV involvement distal to 2 cm from the prostate. The intermediate risk group CTV shall therefore be the GTV plus the proximal 2cm of SVs.

5.1.1.3 PTV: The prescription dose shall be delivered to the Planning Tumor Volume (PTV). While the static targeting accuracy of the radiosurgery machines are about 1mm[69], deformation of the prostate, and target movement occurring after imaging but before dose delivery could contribute to targeting uncertainty. Although the cumulative targeting uncertainty has not been accurately quantified, the 3-5mm GTV to PTV expansion employed in the Stanford series appears more than adequate. Stanford phase I data showed safely and early clinical response rates are acceptable with this PTV. Thus the PTV shall equal the CTV expanded 3mm posteriorly, and 5mm in all other dimension.

5.1.1.4 Microscopic evaluation of prostatectomy specimens may demonstrate EXTRACAPSULAR EXTENSION: 99% of microscopic extra prostatic disease should be within 3- 5mm of the prostate[70]. Since 7.25Gy is prescribed 3-5mm outside the prostate, a dose adequate to address microscopic disease (>6Gy x 5) will easily be delivered at 5mm.

5.1.1.5 NORMAL TISSUES: CONTOURING REQUIRED: The structures listed below will be contoured and evaluated with DVH analysis. Bowel peristalsis and bladder filling change the size and location of normal structures. If the CT and MRI (or secondary CT) show normal tissues in different locations immediately adjacent (i.e., within < 2cm) the prostate, the contoured structure shall be a larger composite of both image sets. Grid size should be sufficiently large to include the entire structure.

5.1.1.5.1 RECTUM: defined as a solid structure, including the lumen and rectal wall, extending from the level of the ischial tuberosity to the sigmoid flexure.

5.1.1.5.2 BLADDER, defined as a solid structure including the bladder wall and lumen.

5.1.1.5.3 PENILE BULB: the portion of the bulbous spongiosum that lies inferior to the urogenital diaphragm.

5.1.1.5.4 SIGMOID COLON OR OTHER BOWEL lying within 2 cm of the PTV should be contoured.

5.1.1.6 NORMAL TISSUES: COUNTOURING REQUIRED IF VISUALIZED:

5.1.1.6.1 PROSTATIC URETHRA, defined as the lumen-mucosal interface, extending from bladder neck to the membranous urethra. If visible on planning studies, this shall be contoured and evaluated. If not visible, then contouring is not required, however the prescription dose (36.25Gy) should be prescribed at 75% of Dmax or greater.

5.1.1.6.2 MEMBRANOUS URETHRA shall be contoured, if visible.

5.1.1.6.3 NEUROVASCULAR BUNDLE, if visible on MRI or CT: should be contoured in transverse planes extending from the prostatic apex to the base.

5.1.2 DOSE SPECIFICATIONS: All specified doses are for the entire treatment course.

5.1.2.1 The **PRESCRIPTION DOSE** of **36.25Gy** shall be the dose to the **PTV**:

5.1.2.1.1 *Per protocol*: V36.25Gy shall be at least 95%, and the prescribed dose shall be 65-85% of Dmax (or 75-85% if urethra not contoured).

5.1.2.2 A **SECONDARY DOSE** of **40Gy** shall be the dose to the **GTV**:

5.1.2.2.1 *Per protocol*: GTV V40Gy shall be at least 95%.

5.1.2.2.2 GTV+1mm shall also be contoured for DVH analysis.

Table 3. Normal Tissue Dose Constraints for RTOG 0126, and the BEDs for Acute and Late Effects

RTOG 0126		Constraint	Acute effects: α/β = 10		Late effects: α/β = 3	
			BED	5 fx equiv	BED	5 fx equiv
Bladder	D15	80Gy	94.4	48.7	128	37.8
	D25	75Gy	88.5	46.6	120	36.4
	D50	65Gy	76.7	42.3	104	33.5
Rectum	D15	75Gy	88.5	46.6	120	36.4
	D25	70Gy	82.6	44.5	112	35.0
	D50	60Gy	70.8	40.0	96	31.9
Penile bulb	median	52.5Gy	62.0	36.4	84	29.5

5.1.2.3 **RECTUM**: *Per Protocol*: **V36Gy < 1cc.**
For the HDR component of RTOG 0321, the rectum V75%RxDose constraint was < 1cc. Assuming an α/β ratio of 3Gy for late effects, the $EQD_{1.8}$ is 30.1Gy. Adding the 45Gy of external beam prescribed in RTOG 0321 yields 75.1Gy, at 1.8Gy/fx. The 5-fraction equivalent dose is 7.12Gy x 5 = 35.6Gy (α/β=3). Thus, the 5-fraction constraint equivalent to that used in RTOG 0321 would be V35.6Gy < 1cc
Using the rectal constraint for conformal external beam RT of RTOG 0126 (see table 3), and converting to a 5 fraction equivalent dose (α/β=3) yields D15 < 36.4Gy. For a rectal volume of 50cc, this is equivalent to V36.4Gy < 7.5cc. The HDR constraint is more restrictive than that of RTOG 0126, thus this protocol adopts a constraint close to the former: rectum V36Gy < 1cc.

5.1.2.4 **BLADDER**: *Per Protocol*: **V37Gy < 10cc**.
RTOG 0321 proposed a bladder constraint for HDR delivery as: V75%Rx dose < 1 cc. Despite this restriction, for a small group of UCSF HDR plans, the *average* bladder V80%RxDose was 0.7cc[71]. An attainable HDR constraint would be V80%Rx dose < 1cc. Converting to $EQD_{1.8}$ using α/β of 3 for late effects, and adding the 45Gy external beam yields a $EQD_{1.8}$ of 78.6Gy. This is equivalent to 36.6Gy in 5 fractions. Beaumont had no bladder constraint for HDR, and reported minimal chronic bladder toxicity (most was urethral). Using the bladder constraint for conformal external beam RT of RTOG 0126 (see table 3), and converting to a 5 fraction equivalent dose (α/β=3) yields: D15 < 37.8Gy, or conservatively estimating total bladder volume at 100cc, V37.8 Gy < 15cc. While this 5 fraction dose constraint is similar to RTOG 0321's 5-fraction equivalent of 36.6 Gy, the 15cc volume constraint is far more liberal. Since bladder volumes very substantially, an absolute volume constraint may be preferable to a fractional volume constraint, especially with the rapid dose fall-off seen with CyberKnife. For this protocol, an approximate average of the two RTOG EQDs (37Gy) is used as the bladder dose constraint. A volume constraint of 10cc is approximately midway between 1cc and 15cc.

5.1.2.5 **PENILE BULB**: *Per Protocol*: **V29.5Gy < 50%**.
Mack Roach[78] found an increased incidence of impotence when the average dose to the penile bulb was greater than 52.5Gy, conventionally fractionated. This is biologically equivalent to 29.5Gy in 5 fractions, using an α/β ratio of 3Gy. Efforts should be made to minimize the penile bulb V29.5Gy to significantly less than 50%.

5.1.2.6 **SIGMOID COLON AND OTHER BOWEL**: evaluated if lying within 2cm of the PTV. No more than 1cc may receive the 2Gy/fx equivalent of 54Gy; assuming an α/β=3, the 5-fraction equivalent is 30Gy. Thus V30Gy<1cc.

5.1.2.7 **PROSTATIC URETHRA** (when visualized): *Per Protocol*: V47Gy < 20%.
Beaumont's HDR protocol[73] limited "any segment of urethra" to 125% of prescription dose, or 47.5Gy. This is equivalent to 141.3Gy at 2Gy/fx, assuming α/β ratio of 3 for late effects. The 5-fraction equivalent dose is 52.4Gy. RTOG 0321 for HDR delivery required the V125%Rx dose < 1cc. Including the 45Gy of external beam delivered, the $EQD_{1.8}$ = 118.6Gy < 1 cc; the 5 fraction equivalent is 46.4Gy. Since measured diameters of urethras will vary depending on catheter diameter or subjective MRI interpretation, a DVH constraint might best be expressed as a fraction of the total volume. Since 5cc would be a generous estimate for a urethral volume, 20% volume constraint (yielding 1cc, per RTOG 0321) is conservatively chosen. The dose constraint of 47Gy is midway between the Beaumont and RTOG requirements.

5.1.2.8 **MEMBRANOUS URETHRA** (when identified) *Per Protocol:* D50 < 37 Gy
Since urethral strictures following HDR often involve the membranous portion, this will be contoured when visualized. Dmax and D50 will be recorded; keep D50 below 37Gy.

5.1.2.9 **NEUROVASCULAR BUNDLE**: If identified, attempt to keep (for both right and left sides) V38Gy<50%.

6.0 Study Evaluations

Assessment	Pre-entry	Pre-Treatment	On tx day 5	Follow-up interval: months post therapy						
				1 wk	1	3	6	12	18	24
History	X				X	X	X	X	X	X[b]
Physical exam (DRE)	X					X	X	X	X	X[b]
ECOG Performance Scale	X					X	X	X	X	X[b]
Prostate Biopsy & Gleason score[a]	X									X
PSA	X					X	X	X	X	X[b]
Prostate volume assessment	X									
CBC, platelets	X									
BUN, creatinine	X									
Fiducial Placement		X[c]								
Bone Scan[f]										
CT Scan[f]	X[e]	X[d]								
MRI[f]		X[d]								
Ultrasound	X[e]									
Toxicity evaluation	X	X	X	X	X	X	X	X	X	X[b]
AUA score	X		X	X	X	X	X	X	X	X*
FACT-G Questionnaire	X				X		X	X		X*
EPIC-26 Questionnaire	X				X		X	X		X*
SHIM Questionnaire	X				X		X	X		X*
Utilization of Sexual Rx/Devices	X				X		X	X		X*

a. Biopsy recommended at 2 yrs if failure suspected, & required at time of documented failure
b. Continue every 6 or 12* months through year 2; upon review at 2 years, investigators may opt to continue annually through year 10.
c. Within 2 – 3 weeks after study entry
d. 5 – 10 days after fiducial placement
e. Either CT or Ultrasound ≤ 90 days prior to registration
f. To be performed for nonlocal failure as clinically indicated or deemed necessary by treating physician at any time during follow up

6.1 EVALUATION DURING TREATMENT & FOLLOWING TREATMENT

6.1.1 PRE-ENTRY ASSESSMENT: see section 4.0.

6.1.2 Stereotactic radiosurgery is an outpatient procedure. Patient management immediately after the procedure will follow routine patient care guidelines as determined by the physician. Subjects will be provided instructions on who to call with specific contact information, in the event they experience any untoward effects following treatment. In the event a subject experiences any untoward effects following treatment, information specific to the patient's condition and symptoms, treatment intervention required, and hospital stay and course will be recorded for purposes of clinical evaluation.

6.1.3 ACUTE ASSESSMENT: Patients will have toxicity evaluation and AUA score on the last day of treatment.

6.1.4 ASSESSMENTS FOLLOWING TREATMENT: at one week after treatment, toxicity and AUA score will be evaluated. At 1 month following treatment, patients will be assessed for acute toxicity, and will fill out AUA form, FACT-G, EPIC-26, SHIM and Utilization of Sexual Rx/Devices. At 3, 6, 12, 18, and 24 month intervals, patients will be seen and evaluated, including a history, physical exam, ECOG performance status, PSA, toxicity evaluation, and AUA score. In addition, at 6 months, 12 months and 24 months, the FACT-G, EPIC-26, SHIM and Utilization of Sexual Medications/Devices will be administered.

6.1.5 PROSTATE BIOPSY will be performed at time of biochemical or local clinical failure, and is encouraged at time of distant failure.

6.1.6 BONE SCAN will be performed at the time of biochemical failure, or when the patient develops signs of symptoms suggesting metastatic disease.

6.2 CRITERIA FOR TOXICITY

6.2.1 ACUTE AND LATE TOXICITY (Primary Safety Objectives)

6.2.2 Acute side effects (<=90 days of treatment start) will be assessed using the NCI Common Toxicity Criteria version 3.0 (see section 8.2.1).

6.3 QUALITY OF LIFE ASSESSMENTS (Secondary Objectives)

6.3.1 FACT-G: Functional Assessment of Cancer Therapy - General version of the scale constitutes the core of all subscales. FACT-G can be used with patients of any tumor type. It measures generic health status relevant across different age, disease, and treatment groups. It provides a comprehensive, psychometrically sound

assessment of health status from the patient's point of view by scoring responses to standard questions. The FACT-G is self-administered, and can usually be completed in less than 3 minutes without assistance.

6.3.2 EXPANDED PROSTATE CANCER INDEX COMPOSITE (EPIC)-26: is a validated comprehensive instrument developed to assess patient function and bother after prostate cancer treatment. It was developed by an expert panel of urological oncologists, radiation oncologists (including those with brachytherapy expertise), survey researchers, and prostate cancer nurses, to address symptoms related to radical prostatectomy, external beam radiotherapy, prostate brachytherapy, and hormonal symptoms. See appendix III.

6.3.3 AMERICAN UROLOGICAL ASSOCIATION (AUA) SYMPTOM INDEX: Also known as the International Prostate Symptom Score (IPSS), this widely used index assesses urinary symptom bother. See appendix III.

6.3.4 SEXUAL HEALTH INVENTORY FOR MEN (SHIM): is a widely used, internationally validated and sensitive instrument for assessing erectile dysfunction[72].

6.3.5 UTILIZATION OF SEXUAL MEDICATIONS/DEVISES: provides context for interpreting the sexual domain score of the EPIC questionnaire.

6.4 CRITERIA FOR DISEASE CONTROL: intervals will be measured from date of first treatment.

6.4.1 (Primary Efficacy Objective) ~~BIO~~CHEMICIAL DISEASE-FREE SURVIVAL (bDFS): is measured as time to PSA failure. While earlier reports of prostate cancer patients treated with radiotherapy have used the ASTRO consensus definition (ACD) of PSA failure, recent studies[75] [76] [77] have suggested the "nadir+2" definition is a more sensitive and specific definition of biochemical failure. Indeed, a recent expert panel met in Phoenix[78] and developed a consensus recommendation using the later definition. So that comparisons can be made with earlier literature, both definitions shall be used:

6.4.1.1 Phoenix definition: failure occurs when the PSA is ≥ 2 ng/ml more than the lowest PSA measurement before the current one, with no backdating. Administration of salvage therapy (hormones, surgery, etc…) will be considered failure.

6.4.1.2 Strict ASTRO Consensus Definition (ACD): failure is defined as three consecutive rises in post-treatment PSA, measured at the specified follow-up intervals. If three consecutive PSA rises occur during the first 2 years after treatment, followed by a non-hormonal induced PSA decline, this will not be considered a failure. Administration of salvage therapy (hormones, surgery, etc…) will be considered failure. Failure date is the midpoint between the dates of the last non-rising PSA and the first PSA rise.

6.4.2 CRITERIA FOR ~~LO~~CAL FAILURE (Secondary Objective): clinical evidence of local progression or recurrence. Clinical

failure includes a palpable abnormality that has increased in size, failure of regression of a palpable abnormality by 2 years after treatment, or redevelopment of a prostate abnormality after complete response. Patients with a prostate abnormality compatible with local recurrence, or a PSA failure shall undergo a prostate biopsy. Histologic criteria for local failure is a positive prostate biopsy more than 2 years after treatment. Patients with a normal exam and no evidence of PSA failure shall be considered controlled locally. Patients with clinical failure and no biopsy are

considered local failures. If a patient is locally controlled at the time of orchiectomy or androgen ablation, he is censored and considered "not evaluable" for further local control.

6.4.3 CRITERIA FOR NONLOCAL FAILURE (Secondary Objectives) If clinically indicated, a bone scan, CT or other imaging study may be performed to assess distant failure. This is conventional care and would be done if the treating physicians feels it is necessary.

6.4.3.1 ~~DIS~~TANT FAILURE (includes regional failure) documented if clinical, bone scan, CT or other imaging study shows metastatic disease. Biochemical failure with a negative prostate biopsy shall be considered distant only failure. Biopsy of metastatic site required if radiographic or clinical findings are equivocal. Type of metastatic failure (distant and/or regional) shall be recorded if known. Prostate biopsy recommended at this time.

6.4.3.2 ~~DIS~~EASE-FREE SURVIVAL: for any measure of disease, including PE, PSA, bone scan, CT/MRI and biopsy, or death.

6.4.3.3 ~~DIS~~EASE-SPECIFIC SURVIVAL: for any of the following:

6.4.3.3.1 Death due to prostate cancer.

6.4.3.3.2 Death due to other causes, with active malignancy (defined by clinical or biochemical evidence of progression). If a patient suffered a previous relapse, but has inactive disease, this is not considered a disease-specific death.

6.4.3.3.3 Death due to complications of treatment.

6.4.3.3.4 OVERALL SURVIVAL: for death from any cause

7.0 Statistical Considerations

7.1 OVERVIEW: This study's primary goal is to determine the ~~rate~~ of acute and late grade 3-5 gastrointestinal and genitourinary toxicity following SBRT treatment, and to estimate efficacy, measured as 2-year bDFS. Per RTOG/ECOG, acute toxicity will be defined as occurring within 90 days of completing treatment. Late toxicity will be defined as toxicity occurring more than 90 days after treatment. It is graded based on Common Terminology Criteria for Adverse Events (CTCAE) v3.0.(see section 8.0)

7.2 SAMPLE SIZE:

7.2.1 PRIMARY SAFETY OBJECTIVE: The study is designed to test the null hypothesis that the acute and late GI/GU toxicity rate 2 years following treatment is less than 10% versus the alternative hypothesis that the toxicity rate is greater than or equal to 10%. If we end up with 200 eligible patients, there will be 99% probability, or statistical power, of identifying excessive toxicity if the true

toxicity rate is 20%, at the one-sided significance level (α) 0.05. The intervention will be considered to be safe if the acute and late GI/GU toxicity rate 2 years following treatment is not above 10%[79]

7.2.2 PRIMARY EFFICACY OBJECTIVE: The study is powered to compare 2-year bDFS rates observed with SBRT to 2-year bDFS rates reported with dose-escalated external beam RT. In Beaumont's monotherapy HDR series treating patients, 5-yr ASTRO bDFS was 97.5%; in Demanes' series of 75% LR and 25% IR, this was 96%. We would expect Phoenix outcomes to be slightly higher than ASTRO outcomes at 5 years. Since SBRT delivers doses similar to HDR monotherapy, a conservative estimate of the success rate for SBRT is 97.5%. In LR patients, prospective studies from Memorial Sloan Kettering (203 patients, 81Gy) and MD Anderson (32 patients, 78Gy) demonstrated 5-yr bDFS (Phoenix definition) of 92% and 92%, respectively. Thames' 9-institution review of 231 dose-escalated (70-76Gy) LR patients reported 94% 5-yr Phoenix bDFS. Thus, an objective performance criteria (OPC) for low-risk patients treated with dose-escalated external beam RT is 92% 5-yr bDFS. If we assume the SBRT success rate is 97%, a sample size of 200 patients will provide 99% power to test superiority of SBRT against this OPC with 80% power at the 1-sided 5% significance level. If we assume the SBRT success rate is 96%, then the power will be 78%.

7.2.3 TOTAL AND RELATIVE ENROLLMENT: Per above sections 7.2.1–7.2.2, we plan to accrue 200 eligible patients to compare the 2-year bDFS rate observed with SBRT to the 2-year OPC rate, and to establish acceptable toxicity. The test cohort will be closed to accrual once requisite enrollment is achieved: 200 total patients.

7.2.4 ACCRUAL RATE: The accrual rate will be 5–6 patients / month over 2 years.

7.3 STATISITCAL METHODS:

The *primary* objectives of this study are:

- To determine, in both low-risk and intermediate-risk cohorts, the rates of acute and late grade 3 or higher gastrointestinal and genitourinary toxicity observed during an initial 24 month follow up.
- To estimate the rate of biochemical Disease-Free Survival (bDFS), Phoenix and ASTRO definitions, at 2 years following hypofractionated SBRT for low and intermediate risk prostate cancer. Failure occurs when the PSA is ≥ 2 ng/ml more than the lowest PSA measurement before the current one, with no backdating.

The *secondary* objectives of this study are to:

- the rate of local failure: proportion of patients with local disease progression at 2 years

- rate of distant failure: proportion of patients with metastatic disease at 2 years
- rate of disease-free survival: median time from start of treatment until disease progression
- rate of disease-specific survival: death due to prostate cancer (excludes patients that relapse with inactive disease)
- overall survival: median length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive.
- quality of life (QOL) in generic and organ-specific domains using the FACT-G assessment tool

7.3.1 PRIMARY ENDPOINTS:

Wilson score interval is used to determine the confidence intervals for the expected proportion of patients experiencing a "success" outcome.

7.3.1.1 SAFETY: The upper limit of a one-sided 95% confidence interval for the expected proportion of patients experiencing any grade 3-5 acute or late toxicity as defined above in 7.1, is estimated by U, where

$$U = \frac{(2np + Z^2_{0.95}) + Z_{0.95}\sqrt{Z^2_{0.95} + 4np(1-p)}}{2(n + Z^2_{0.95})}$$

where:
p: the observed proportion of patients experiencing any grade 3-5 acute or late toxicity as defined above in 7.1;
n: the total number of patients;
$Z_{0.95} = 1.645$.

The intervention will be considered to be safe if this study's result verifies that U is not above 10%[i].

7.3.1.2 EFFICACY: The lower limit of a one-sided 95% confidence interval for the expected proportion of patients experiencing biochemical disease-free survival (bDFS) is estimated by L, where

$$L = \frac{(2np + Z^2_{0.95}) - Z_{0.95}\sqrt{Z^2_{0.95} + 4np(1-p)}}{2(n + Z^2_{0.95})}$$

where:
p: the observed proportion of patients experiencing bDFS;
n: the total number of patients;
$Z_{0.95} = 1.645$.
The SBRT intervention will be considered to be effective if this study's result verifies that L is not below 92%.

7.3.2 SECONDARY ENDPOINTS

7.3.2.1 MEASUREMENTS OF RATE OF LOCAL FAILURE AND RATE OF DISTANT FAILURE: The PSA levels are used to quantify the rate of local and distant failures repeatedly during the post treatment period. The GEE (Generalized Estimating Equation) method will be used to

provide valid inferences. This method was originated to make inference about average behaviour, where the dependent variable depends not only on the "explanatory" variable (time measured in months) but also on the correlation of a patient's repeated measurements. The GEE approach fits the model to the observed data as closely as possible, weighting each patient's "cluster" of measurements over time inversely to its variance–covariance matrix. With this method, no imputations are required and all data recorded is use in the analysis. Other important features of GEE are that no distributional assumptions for the dependent variable are required to use the method and in most cases valid inferences are provided even when the correlation structure is miss-specified. For each PSA level, we will use GEE to fit a model to patients' longitudinal course of repeated values.

7.3.2.2 QUALITY OF LIFE ASSESSMENTS: The FACT-G scores, AUA score, EPIC-26 scores are used to quantify quality of life (QOL) at baseline and repeatedly during the post treatment period. Similarly to measurements of local and distant failure rate, we will still use the GEE method to provide valid inferences. For each score, we will use GEE to fit a model to patients' longitudinal course of repeated values. We hypothesize that immediately following treatment, the GU & GI subsections of the EPIC-26 and the AUA will demonstrate a worsening of GU and GI function, but this will return to normal with time. We further hypothesize that the sexual function subset of the EPIC-26 will show gradual worsening function relative to baseline over the five-year follow-up period. These QOL outcomes will be compared to those reported in other prospective studies using the same instruments, including RTOG 0232 and 0415.

7.3.2.3 SURVIVAL ANALYSIS: Survival analyses will be performed for the following quantities:

a. Rate of disease-free survival;

b. Rate of disease-specific survival;

c. Overall survival for death from any cause;

Periodically over the extended follow-up period, Kaplan-Meier "survival" curves will be calculated (examples: at 6 months, yearly, 2 years, at end of patient follow-up). From the Kaplan-Meier curve, descriptive statistics will be calculated including estimates of survival rates and mean and quartile survival times.

7.4 RULE FOR EARLY STOPPAGE BASED ON TOXICITY:

The NCI Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE V3.0) will be used to evaluate toxicity. We will consider a toxicity to be an adverse event that is possibly, probably or definitely related to the treatment. The maximum grade of toxicity for each category of interest will be recorded for each patient and the summary results will be tabulated by category and grade. We will describe all serious (≥ Grade 3)

AEs on a patient-by-patient basis; descriptions will include dose level and any relevant baseline data. The toxicity will be assessed every 10 patients.

For safety, we will consider that regimen to be excessively toxic and stop accrual if, at any time, the observed rate of grade 3-5 acute or late toxicity as defined above in 7.1 $\geq$ 33% and at least 4 toxicities have been observed. Thus, we will stop accrual if:

[# of participants with toxicity] / [# of participants evaluated] =
[4]/[10],
[7]/[20],
[10]/[30],
[14]/[40]
[17]/[50]
[20]/[60]
[24]/[70]
[27]/[80]
[30]/[90]
[33]/[100]
[37]/[110]

[40]/[120]
[43]/[130]
[47]/[140]
[50]/[150]
[53]/[160]
[57]/[170]
[60]/[180]
[63]/[190]
[66]/[200]

The study design has the following properties: if the true rate of grade 3-5 acute or late toxicity as defined above in 7.1 toxicity in this participant population is ≥ 42%, there is at least 90% probability that accrual will stop; if the true grade 3-5 acute or late toxicity as defined above in 7.1, toxicity rate is ≤ 8.7%, there is 90% probability that the accrual will not stop, and that the regimen will be considered safe.

8.0 Data Safety and Recording

8.1 Data safety monitoring plan

All patient data will be collected by the University of Pittsburgh Cancer Institute's Protocol Office. All data will be secured in a password protected file with observance of all applicable HIPAA regulation. A data safety monitoring board will meet monthly to evaluate toxicity for this trial. Patients/adverse events will be discussed at these monthly department meetings. Unexpected serious adverse events will be reported to the IRB and DSMC, and minutes of the monthly disease center meetings will be reviewed at the DSMC meetings. Headed by the PI, the sub-investigators of this protocol along with all radiation oncology medical staff and a study coordinator are in attendance at this meeting. There is also a quarterly meeting headed by the PI held with the collaborating surgeons trained in radiosurgery and a study coordinator. Any adverse events, changes in risk to benefit considerations for the study, and any breaches of confidentiality are discussed at these meeting as well.

8.1.1 Subject Removal Criteria

1. Disease progression
2. Development of a serious medical illness
3. Evidence of dose-limiting toxicity
4. Voluntary withdrawal
5. Protocol violation
6. Discretion of the principal investigator
7. Development of grade 4 toxicity related to experimental therapeutic

8.2 Safety Reporting

8.2.1 Acute Adverse Events

The CTCAE (described below) will be used to grade acute toxicity during this trial.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for AE reporting. All appropriate treatment areas will have access to a copy of the CTCAE version 3.0. A copy of the CTCAE version 3.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

It may include worsening or increase in severity of signs or symptoms of the illness, increase in frequency of signs and symptoms of an intermittent illness, or the appearance of a new manifestation/complication.

Exacerbation of a pre-existing illness should be considered when a subject requires new or additional concomitant drug or non-drug therapy for the treatment of that illness during the study. Lack of or insufficient clinical response, benefit, efficacy, or therapeutic effect should not be recorded as an adverse event. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

In addition, abnormal objective test findings (e.g., abnormal laboratory test results, physical evaluation) that can result in a change in study treatment dosage or in discontinuation of the treatment, or require intervention or diagnostic evaluation to assess the risk to the patient, should also be recorded as adverse events. Clinically significant changes in physical examination findings should also be recorded as adverse events. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to UPCI or its designated representative.

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to study treatment will be recorded on the adverse event page(s) of the CRF. The investigator will record all adverse events in the CRF and assess each event as to severity and causal relationship to study treatment.

'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.

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

For all adverse events, sufficient information should be obtained by the investigator to determine the causality, (i.e., study treatment or other illness). The investigator is required to assess causality and indicate that assessment on the CRF. Follow-up of the adverse event, after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator. Adverse events that continue, or emerge within 30 days, after the patient's discontinuation or completion of the study will be followed until the events resolve, are considered stable, or can be ascribed to causes other than study treatment.

All serious AE shall be reported meeting criteria for reporting can be found on the University of Pittsburgh Institutional Review Board's website at http://www.irb.pitt.edu. In the event of such adverse event, the investigator must report the event(s) via phone within 24 hours and a written report filed within 24 hours to the Principal Investigator, or the UPCI's Clinical Research Office.

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Appendix I: ECOG PERFORMANCE SCALE

0 Fully active, able to carry on all predisease activities without restriction *(Karnofsky 90-100)*.
1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work *(Karnofsky 70-80)*.
2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours *(Karnofsky 50-60)*.
3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours *(Karnofsky 30-40)*.
4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair *(Karnofsky 10-20)*.

Appendix II: AJCC STAGING SYSTEM, 6TH EDITION, PROSTATE

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)

Distant Metastasis (M)*

MX Presence of distant metastasis cannot be assessed (not evaluated by any modality)
M0 No distant metastasis
M1 Distant metastasis
  M1a Nonregional lymph node(s)
  M1b Bone(s)
  M1c Other site(s) with or without bone disease
*Note: When more than one site of metastasis is present, the most advanced category is used; pM1c is most advanced.

Appendix III: AUA, FACT-G, EPIC, SHIM, USMD Questionnaires:

American Urological Association (AUA) symptom index: was develeoped to help men determine how bothersome their urinary symptoms are and to check the effectiveness of treatment.[i] This questionnaire has also been adopted worldwide and is known as the International Prostate Symptom Score (IPSS). It is sometimes seen with a Quality of Life Scale at the end of the questionnaire.

Name: _____ Today's date: _____

(Circle one number on each line)	Almost never	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	**0**	**1**	**2**	**3**	**4**	**5**
Over the past month or so, how often have you had to urinate again less than two hours after you finished urinating?	**0**	**1**	**2**	**3**	**4**	**5**
Over the past month or so, how often have you found you stopped and started again several times when you urinated?	**0**	**1**	**2**	**3**	**4**	**5**
Over the past month or so, how often have you found it difficult to postpone urination?	**0**	**1**	**2**	**3**	**4**	**5**
Over the past month or so, how often have you had a weak urinary stream?	**0**	**1**	**2**	**3**	**4**	**5**
Over the past month or so, 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**

Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	**0**	**1**	**2**	**3**	**4**	**5**

FACT-G (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-G (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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_____

Do Not Mark in This Space

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

Do Not 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!!

SEXUAL HEALTH INVENTORY FOR MEN (SHIM)

PATIENT NAME:_____TODAY'S DATE:_____

PATIENT INSTRUCTIONS

Sexual health is an important part of an individual's overall physical and emotional well-being. Erectile dysfunction, also known as impotence, is one type of very common medical condition affecting sexual health. Fortunately, there are many different treatment options for erectile dysfunction. This questionnaire is designed to help you and your doctor identify if you may be experiencing erectile dysfunction. If you are, you may choose to discuss treatment options with your doctor.

Each question has several possible responses. Circle the number of the response that **best describes** your own situation. Please be sure that you select one and only one response for **each question**.

OVER THE PAST 6 MONTHS:

1. How do you rate your confidence that you could get and keep an erection?		VERY LOW	LOW	MODERATE	HIGH	VERY HIGH
		1	**2**	**3**	**4**	**5**
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	NO SEXUAL ACTIVITY	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	**1**	**2**	**3**	**4**	**5**
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	DID NOT ATTEMPT INTERCOURSE	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	**1**	**2**	**3**	**4**	**5**
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	DID NOT ATTEMPT INTERCOURSE	EXTREMELY DIFFICULT	VERY DIFFICULT	DIFFICULT	SLIGHTLY DIFFICULT	NOT DIFFICULT
	0	**1**	**2**	**3**	**4**	**5**
5. When you attempted sexual intercourse, how often was it satisfactory for you?	DID NOT ATTEMPT INTERCOURSE	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	**1**	**2**	**3**	**4**	**5**

Add the numbers corresponding to questions 1-5. **TOTAL:** _____

The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints:

1-7 Severe ED 8-11 Moderate ED 12-16 Mild to Moderate ED 17-21 Mild ED

UTILIZATION OF SEXUAL MEDICATIONS/DEVICES

This questionnaire is designed to assess the use of erectile aids among patients treated for prostate cancer. To help us get the most accurate measurement, please answer all questions honestly and completely. You may refuse to answer any questions for any reason. All information contained within this survey will remain strictly confidential. Thank you for participating and for helping us improve the quality of care for prostate cancer patients.

TODAY'S DATE (please enter data when survey completed) Month_____ Day_____
Year_____

The following questions relate to any treatments you may have received to assist with your erections.

1 DO YOU HAVE A PENILE PROSTHESIS?
1 No
2 Yes (Skip Questions 2-4)

2 HAVE YOU USED ANY MEDICATIONS OR DEVICES TO AID OR IMPROVE ERECTIONS?
1 No (Skip Question 3, answer Question 4)
2 Yes

3 FOR EACH OF THE FOLLOWING MEDICINES OR DEVICES, PLEASE INDICATE WHETHER OR NOT YOU HAVE TRIED IT OR CURRENTLY USE IT TO IMPROVE YOUR ERECTIONS (BY CIRCLING YOUR RESPONSE):

A VIAGRA OR OTHER PILL (NAME PILL IF NOT VIAGRA):_____
1 Have NOT tried it
2 Tried it, but was NOT HELPFUL
3 It HELPED, but I am NOT using it NOW
4 It HELPED, and I use it SOMETIMES
5 It HELPED, and I use it ALWAYS

B MUSE (INTRA-URETHRAL ALPROSTADIL SUPPOSITORY)
1 Have NOT tried it
2 Tried it, but was NOT HELPFUL
3 It HELPED, but I am NOT using it NOW
4 It HELPED, and I use it SOMETIMES
5 It HELPED, and I use it ALWAYS

C PENILE INJECTION THERAPY (SUCH AS CAVERJECT)
1 Have NOT tried it
2 Tried it, but was NOT HELPFUL
3 It HELPED, but I am NOT using it NOW
4 It HELPED, and I use it SOMETIMES
5 It HELPED, and I use it ALWAYS

D VACUUM ERECTION DEVICE (SUCH AS ERECT-AID)
1 Have NOT tried it
2 Tried it, but was NOT HELPFUL
3 It HELPED, but I am NOT using it NOW
4 It HELPED, and I use it SOMETIMES
5 It HELPED, and I use it ALWAYS

E OTHER (NAME MEDICATION/DEVICE IF NOT LISTED)_____
1 Have NOT tried it
2 Tried it, but was NOT HELPFUL
3 It HELPED, but I am NOT using it NOW
4 It HELPED, and I use it SOMETIMES
5 It HELPED, and I use it ALWAYS

4 HOW WOULD YOU DESCRIBE THE USUAL QUALITY OF YOUR ERECTIONS WITHOUT THE ASSISTANCE OF MEDICINES OR DEVICES DURING THE LAST 4 WEEKS?
1 None at all
2 Not firm enough for any sexual activity
3 Firm enough for masturbation and foreplay only
4 Firm enough for intercourse

Patient's signature_____
(Utilization of Sexual Medications/Devices, courtesy of M Sanda, D Miller, and J Wei)

Appendix IV: Study Flowchart

Study Flowchart