PROSPECTIVE EVALUATION OF CYBERKNIFE STEREOTACTIC RADIOSURGERY FOR LOW AND INTERMEDIATE RISK PROSTATE CANCER: HOMOGENOUS DOSE DISTRIBUTION

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Protocol Signature Page

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I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the conduct of the study according to the protocol and in strict accordance with all applicable U.S. Food and Drug Administration (*"FDA"*) regulations and guidelines applicable to the Study, including without limitation the regulations set forth in Parts 50, 54, 56 and 812 of 21 C.F.R., and all other applicable federal, state, or local laws, guidelines, rules, and regulations of any type.

_____
Clinical Site

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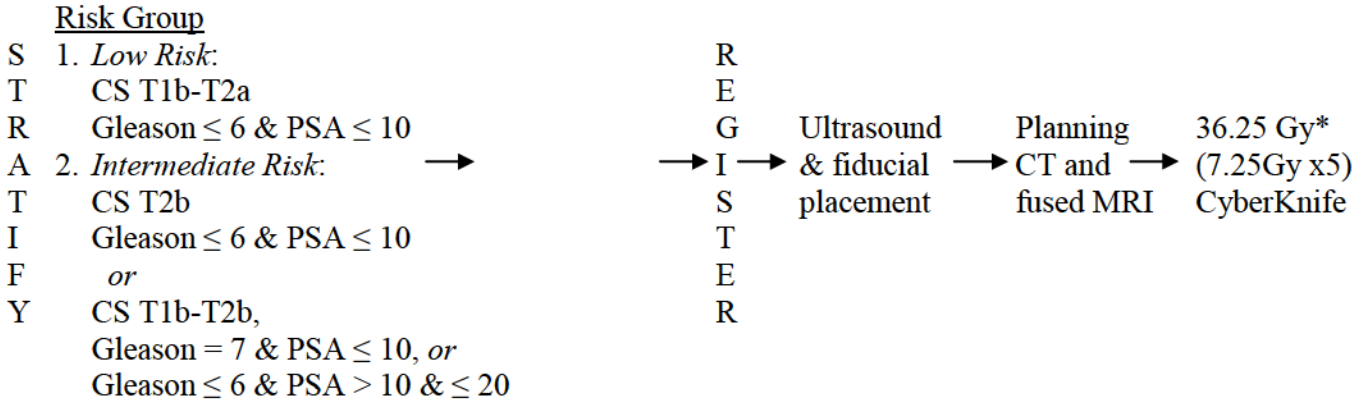
SCHEMA



*Prescribed dose to PTV; prostate receives 8 Gy x 5

PATIENT POPULATION (see section 4.0 for complete eligibility)
Histologically-confirmed, adenocarcinoma of the prostate
Clinical Stage T1b – T2b, NX-0, MX-0
One of the following combinations:
- Gleason score 2-6 and PSA ≤ 20
- Gleason score 7 and PSA ≤ 10

ECOG Performance Status 0-1
No prior prostate radiation or other definitive therapy

Required sample size: 319 patients.

ELIGIBILITY CHECKLIST

_____ (Y)	Is there histologically proven prostate adenocarcinoma, biopsy within one year of enrollment?
_____ (2-6)	What is the Gleason Score?
_____ (T1b – T2b)	What is the clinical T-stage? (AJCC 6th Edition)
_____ (Y)	Is the patient clinical Nx or N0, and Mx or M0?
_____ (0-20)	What is the patient's PSA?
_____ (L, I)	Does the patient fall into one of these risk groups (AJCC 6th Edition): - Low: CS T1b-T2a, Gleason 2-6, PSA ≤ 10 - Intermediate: CS T2b, Gleason 2-6, PSA ≤ 10, or CS T1b-T2b, and Gleason 2-6, PSA ≤ 20 ng/ml, or Gleason 7, PSA ≤ 10 ng/ml
_____ (Y)	Is the prostate volume ≤ 100 cc?
_____ (0-1)	What is the ECOG performance status?
_____ (N)	Has the patient undergone prostatectomy or cryotherapy of the prostate?
_____ (N)	Has the patient had radiotherapy to the prostate or lower pelvis?
_____ (N)	Has the patient implanted hardware near that would prohibit appropriate treatment planning or treatment delivery, in the investigator's opinion?
_____ (N)	Has the patient had chemotherapy for a malignancy in the last 5 years?
_____ (N)	Has the patient had an invasive malignancy (other than this prostate cancer, or basal or squamous skin cancers) in the last 5 years?
_____ (N)	Has the patient's androgen function been ablated during the past 2 months? See Section 5.12

1.0 BACKGROUND

1.1 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 that should be discussed with each patient in this category include radical prostatectomy, external beam radiation therapy (RT), interstitial brachytherapy and watchful waiting.

1.2 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, 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.

1.3 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.

1.4 In the past 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].

1.5 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

Rx	Details	Institution	# pts	Median f/u yrs	5-yr bDFS: Definition		
					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.

1.6 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.

1.7 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].

1.8 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 columnated 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.

1.9 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.

1.10 The CyberKnife should be an ideal device 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.

1.11 The feasibility of CyberKnife for treating localized prostate cancer was first described by King at Stanford University[61]. Their phase I protocol delivered 36.25Gy in 5 fractions of 7.25Gy. In a recent report[62] of acute and 18-month late toxicity in 26 "low-risk" patients, no patient experienced grade 3 or 4 acute or late toxicity, and only one patient experienced a grade 2 late morbidity (urethral stricture). Toxicity was less than that reported in MD Anderson's external beam dose escalation trial. Mean PSA 18 months after treatment was 0.22ng/ml. Naples Community Hospital reported[63] a series of more than 70 low and intermediate risk patients treated with the CyberKnife. The prostate received 35Gy in 5 fractions of 7Gy each; acute toxicity was minimal.

Table 2: **Hypofractionated RT Schedules** (All doses expressed in Gy)

Institution/protocol	Dose/fx	#fxs	Total dose	2Gy/fx Equivalent Dose Assuming α/β ratio of: 1.5Gy	3Gy	10Gy
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.

1.12 Calculation of Equivalent 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).

1.13 Dose Selection. 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 one year after treatment was 1.2ng/ml, somewhat greater than that reported in brachytherapy series, suggesting dose escalation beyond 7Gy x 5 would be beneficial. The Stanford CK 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 CyberKnife 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.

2.0 OBJECTIVES

PRIMARY OBJECTIVES: The primary safety goal of this study is to estimate, in both low-risk and intermediate-risk cohorts, the rates of acute and late grade 3-5 gastrointestinal and genitourinary toxicity observed during the five years following CyberKnife SRS for prostate cancer. The primary efficacy goal is to document the rate of biochemical Disease-Free Survival (bDFS), Phoenix and ASTRO definitions, at 5years.

SECONDARY OBJECTIVES: 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; work effort required in treatment planning and delivery of CyberKnife SRS.

Patients will be followed annually to 10 years, to collect additional data for descriptive analysis.

3.0 DEVICE

Accuray, Inc. (Sunnyvale, CA), received FDA clearance in July 1999 to provide treatment planning and image guided stereotactic radiosurgery and precision radiotherapy for lesions, tumors and conditions of the brain, base of skull and cervico-thoracic spine, head and neck using the CyberKnife. On August 10, 2001, Accuray, Inc. received 510(k) FDA clearance (510(k) number K011024) to provide treatment planning and image-guided stereotactic radiosurgery and precision radiotherapy for lesions, tumors, and conditions anywhere in the body when radiation treatment is indicated.

4.0 PRETREATMENT EVALUATION

Evaluations Required for Eligibility:

4.1 Complete history & physical examination

4.2 Assessment of performance status

4.3 Pathologic confirmation of adenocarcinoma of the prostate
4.4 Serum PSA, < 90 days prior to registration, or < 60 days prior to hormone therapy, and 30 or 90 days after discontinuing finasteride or dutasteride, respectively, See section 5.3.
4.5 CBC, platelets, serum BUN and creatinine and testosterone; may be drawn after registration
4.6 Ultrasound of prostate, or CT of pelvis or digital rectal exam (DRE)
  4.6.1 To determine prostate size by imaging: volume = $\pi/6$ x length x height x width; if volume determined by DRE estimate, must be confirmed on CT planning; if volume is > 100 cc then patient is ineligible
  4.6.2 Measurement from CT or ultrasound ≤ 6 months prior to registration or ≤ 14 days prior to registration if hormone therapy is given; it patient had taken finasteride or dutasteride, volume determined > 30 or > 90 days respectively after discontinuation
4.7 Patient should be able to complete questionnaires (see appendix VI); baseline questionnaires may be completed before or after enrollment, but before treatment.
  4.7.1 SF-12 questionnaire
  4.7.2 AUA questionnaire
  4.7.3 EPIC-26 questionnaire
  4.7.4 SHIM questionnaire
  4.7.5 Utilization of Sexual Medications/Devices questionnaire

5.0 PATIENT SELECTION & ELIGIBILITY

5.1 Histologically proven prostate adenocarcinoma
  5.1.1 Gleason score 2-7 (reviewed by reference lab, see also section 5.4; if initial pathology differs from that of reference lab, the reference lab's interpretation will be used for eligibility and risk group assignment (see also section 7.2.1)
  5.1.2 Biopsy within one year of date of registration
5.2 Clinical stage T1b-T2b, N0-Nx, M0-Mx (AJCC 6th Edition)
  5.2.1 T-stage and N-stage determined by physical exam and available imaging studies (ultrasound, CT, and/or MRI; see section 4.5)
  5.2.2 M-stage determined by physical exam, CT or MRI. Bone scan not required unless clinical findings suggest possible osseous metastases.
5.3 PSA ≤ 20 ng/ml (see section 5.4; if pre-enrollment PSA was drawn > 60 days prior to CyberKnife treatment, another PSA obtained ≤ 60 days prior to treatment, will become the pre-treatment PSA and will determine eligibility and risk group; pre-treatment PSA must be drawn 30 or 90 days after discontinuing finasteride or dutasteride respectively)
5.4 Patients belonging in one of the following risk groups:
  5.4.1 Low: CS T1b-T2a and Gleason 2-6 and PSA ≤ 10, *or*
  5.4.2 Intermediate: CS T2b and Gleason 2-6 and PSA ≤ 10, or CS T1b-T2b, and Gleason 2-6 and PSA ≤ 20 ng/ml, or Gleason 7 and PSA ≤ 10 ng/ml
5.5 Prostate volume: ≤ 100 cc
  5.5.1 Determined using: volume = $\pi/6$ x length x height x width
  5.5.2 Measurement from CT or ultrasound ≤ 6 months prior to registration.
5.6 ECOG performance status 0-1
5.7 No prior prostatectomy or cryotherapy of the prostate
5.8 No prior radiotherapy to the prostate or lower pelvis
5.9 No implanted hardware or other material that would prohibit appropriate treatment planning or treatment delivery, in the investigator's opinion.
5.10 No chemotherapy for a malignancy in the last 5 years.

5.11 No history of an invasive malignancy (other than this prostate cancer, or basal or squamous skin cancers) in the last 5 years.

5.12 No hormone ablation for two months prior to enrollment, or during treatment. This includes LHRH agonists (e.g. leuprolide, goserelin, triptorelin), antagonists (e.g. degarelix), peripheral blockers (e.g. flutamide, bicalutamide, nilutamide), estrogens (e.g. DES), bilateral orchiectomy and 5-alpha reductase inhibitors (finesteride or dutasteride).

5.13 Completion of patient questionnaires in section 4.7.

5.14 Consent signed.

6.0 REGISTRATION PROCEDURES

6.1 PRE-REGISTRATION REQUIREMENTS: Prior to enrolling patients into the study, facilities must complete the Facility Questionnaire, the Benchmark (Dry Run) Treatment Plan (see section 8.3.2.1), and the Physics QA requirements specified below. After review by the Principal Investigator and Physics Chair confirms satisfactory completion, sites are eligible for study participation.

6.1.1 PHYSICS QUALITY ASSURANCE shall at a minimum include:

6.1.1.1 ABSOLUTE DOSIMETRY: Each site must document CyberKnife absolute calibration in water according to AAPM TG51. Site must also document that, within the last year, photon beam output has been verified by the Radiological Physics Center (RPC), using their TLD mini-phantom procedure.

6.1.1.2 DAILY QA: participating sites must provide documentation that, for the prior month, the following has been performed daily:

6.1.1.2.1 At least 3000 MUs delivered daily for machine warm-up (per Accuray)

6.1.1.2.2 Temperature and atmospheric pressure recorded, output calibration performed, and new output factor recorded.

6.1.1.2.3 Position of laser at perch position verified to be within 1mm of floor reference point.

6.1.1.3 MONTHLY QA: sites must provide documentation that the following monthly QA is being performed:

6.1.1.3.1 Beam output in phantom verified as +/- 1% of specified output

6.1.1.3.2 Beam energy constancy verified by ion chamber measurements at 10cm and 20cm in phantom, using 60mm collimator and 80cm SAD. Ratio should be within +/- 2% of the TPR20,10 ratio determined from TPR tables.

6.1.1.3.3 Beam symmetry measured by water scanning system or by radiographic (XV) or gafchromic (EBT or MD55) film. Beam symmetry should not exceed +/- 2% using area method.

6.1.1.3.4 Fiducial tracking end-to-end tests using ball-cube phantom. Maximum tracking radial error should be <0.95mm, with left-right, ant-post, and inf-sup errors not exceeding 0.8mm.

6.1.1.3.5 Laser – radiation field congruence measured using XV or EBT film in phantom under standard conditions (SAD = 80cm, 5mm build-up material and 60mm collimator), with laser center marked by a pin. Displacement, evaluated using imaging software or graph paper, should not exceed 1mm.

6.1.1.4 Daily and monthly QA as described above may be recorded in the CyberKnife Robotic Radiosurgery System QA Log Book, or in other documents, and should continue throughout the enrollment period.

6.2 PATIENT REGISTRATION: Patients may be registered only after all eligibility criteria are met: see Eligibility Checklist above, and Inclusion Criteria and Exclusion Criteria CRFs (Case Report Forms). After the patient signs the Consent Form the patient is enrolled in the study, and scheduled for treatment. The pre-treatment CRFs are then filled out by the investigator and/or research assistant. This data is retained in the patient's chart and in research office. The date of registration shall be the date the consent was signed. Fiducials must be placed within 60 days, and the first fraction of radiosurgery must be administered within 90 days of registrations.

7.0 PATHOLOGY

7.1 Pathology Evaluation: Slides/blocks from the pre-treatment diagnostic prostatic biopsy will be reviewed to confirm the diagnosis and Gleason score. Other histopathologic features, including extent of tumor in the biopsies, the number of biopsies positive and perineural invasion, shall be recorded.

7.2 Central Review: All consenting patients must have a complete representative set of biopsy slides or tissue block submitted to the Central Pathology Laboratory in order for the case to be evaluated for central pathology review. The following must be provided:

7.2.1 A complete representative set of biopsy slides or tissue block; if initial pathology differs from that of reference lab, the reference lab's interpretation will be used for eligibility and risk group assignment

7.2.2 A Pathology report documenting the submitted blocks, core or slides contain tumor; the report must include the Accuray protocol number and the patient's case number. The patient's name and/or other identifying information should be removed from the report.

7.2.3 Submit materials for central review to Bostwick Laboratory; other central review lab may be used if approved by Sponsor and Principal Investigator.

8.0 TREATMENT: CYBERKNIFE RADIOSURGERY

8.1 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 use of linked fiducials are encouraged, since they may migrate less than individually placed fiducials. The physician will place seeds such that they are visible (and not superimposed) on CyberKnife 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.

8.2 TREATMENT PLANNING IMAGING: The treatment plan will be created based on the risk group assigned by the reference lab review.

8.2.1 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. CT scans will be taken for treatment planning. 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 CyberKnife treatment planning system to develop the radiosurgery treatment plan.

8.2.2 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 allowed.

8.2.3 URETHRAL IDENTIFICATION: To record DVH data for the prostatic and membranous urethra, visualization of these structures is recommended, but not manditory. 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:

8.2.3.1 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.

8.2.3.2 A *secondary* CT or MRI scan with an indwelling urethral catheter in place.

8.2.3.3 Urethrogram with contrast delineating the membranous and prostatic urethra.

8.2.4 Prior to treatment planning imaging, the patient will follow the bowel/urinary preparation procedures used for treatment (see section 8.4.2).

8.3 CYBERKNIFE TREATMENT PLANNING:

8.3.1 TREATMENT PLANNING PROCEDURES: Inverse planning using the CyberKnife planning system will be employed. The treatment plan used for each treatment will be based on an analysis of the volumetric dose including dose-volume histogram (DVH) analyses of the PTV and critical normal structures. The homogeneous CT model shall be used; any beams intersecting a hip prosthesis shall be turned off. Number of paths and beams used for each patient will vary and will be determined by the selected individual treatment plan. To reduce overall treatment time and total monitor units, 150-200 non-zero beams are recommended. No more than 250 beams shall be employed. Tuning structures shall be employed to minimize conformality index (CI) and new comformality index (nCI), preferably yielding values less than 1.20 and 1.25, respectively.

8.3.2 QUALITY ASSURANCE

8.3.2.1 BENCHMARK (DRY RUN) CASE REVIEW: all potential sites shall receive, prior to patient enrollment, an anonymous electronic patient data set. A treatment plan shall be developed, and the plan reviewed by the PI and Physics Chair; completion of a satisfactory plan is required prior to patient enrollment.

8.3.2.2 FIRST PATIENT PRE-TREATMENT REVIEW: the treatment plan of the first patient enrolled at each site must be reviewed prior to beginning radiosurgery. The Principal Investigator (PI) shall be notified at the time of

enrollment of this first patient, and of the proposed first treatment date, to assure PI's availability for review. After planning is complete, the treating site will send via overnight delivery to the PI site: 1) De-identified copy of the treatment planning data sets (including fused primary and secondary imaging studies, contour sets, and isodose distributions/DVHs), 2) Copies of the Pre-treatment Planning Preparation form, CyberKnife Treatment Planning form, and Treatment Plan QA form. The Principal Investigator and Physics Chair shall complete review within 3 working days of receipt; treatment will only begin after any necessary corrections are implemented and final plan is approved. The PI may require additional pre-treatment reviews as needed to insure quality. These may count toward the required reviews specificed in 8.3.2.3.1

8.3.2.3 POST-TREATMENT REVIEW: The PI site will also review treatment plans and treatment delivery records for additional protocol patients:

8.3.2.3.1 The TREATMENT PLAN of the FIRST protocol patient for all participating radiation oncologists, urologists, and physicists shall be reviewed, unless the practitioner already underwent pre-treatment review per section 8.3.2.2. Also, treatment plans and treatment delivery records of THREE additional RANDOMLY chosen cases from each site will be reviewed. If warranted by the outcomes of above QA reviews, the PI may request that additional cases be submitted for review prior to further patient treatments.

8.3.2.3.2 For patients chosen for post-treatment review, the study Monitor will notify the treating site no sooner than 1 day, but no later than 7 days, after completion of treatment. Within one week, the treating site will deliver to the PI site: 1) De-identified copy of the treatment planning data sets (including fused primary and secondary imaging studies, contour sets, and isodose distributions/DVHs), 2) Copies of the Pre-treatment Planning Preparation form, CyberKnife Treatment Planning form, and Treatment Plan QA form, 3) CyberKnife Treatment form, and screen captures documenting treatment delivery for all fractions. These will be reviewed by the PI and Physics chair within one week, with feedback given to the submitting site as needed.

8.3.3 EVALUATED STRUCTURES:

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

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

8.3.3.2.1 LOW-RISK PATIENTS: (CS T1b-T2a, PSA $\leq$ 10, Gleason score $\leq$ 6). Pathologic data from William Beaumont Hospital showed only 1% of low-risk patients had seminal vesicle (SV) involvement[64]; this eliminates the need to treat SVs in this group. Thus the CTV shall equal the GTV.

8.3.3.2.2 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.

8.3.3.3 PTV: The prescription dose shall be delivered to the Planning Tumor Volume (PTV). While the static targeting accuracy of the CyberKnife is about 1mm[65], 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.

8.3.3.4 Microscopic evaluation of prostatectomy specimens may demonstrate EXTRACAPSULAR EXTENSION: 99% of microscopic extraprostatic disease should be within 3-5mm of the prostate[66]. 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.

8.3.3.5 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.

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

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

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

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

8.3.3.5.5 TESTES, bilateral, shall be contoured.

8.3.3.6 NORMAL TISSUES: COUNTOURING REQUIRED IF VISUALIZED:

8.3.3.6.1 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.

8.3.3.6.2 MEMBRANOUS URETHRA shall be contoured, if visible.

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

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

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

8.3.4.1.1 *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).

8.3.4.1.2 Minor variations: V36.25Gy < 95%, but ≥ 90%. Prescribed dose 60-65% (72-74% if urethra not contoured), or 85-90% of Dmax

8.3.4.1.3 Major variations: V36.25Gy < 90%; prescribed dose <60% or >90% of Dmax (<72% if urethra not contoured).

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

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

8.3.4.2.2 Minor variation: V40Gy < 95%, but ≥ 90%.

8.3.4.2.3 Major variation: V40Gy < 90%.

8.3.4.2.4 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

8.3.4.3 **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.

8.3.4.3.1 Minor variation: Rectum V36Gy ≥ 1cc, but < 2cc.

8.3.4.3.2 Major variation: Rectum V36Gy ≥ 2cc

8.3.4.4 **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[67]. 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.

8.3.4.4.1 Minor variation: V37Gy ≥ 10cc, but < 20cc.

8.3.4.4.2 Major variation: V37Gy ≥ 20cc

8.3.4.5 **PENILE BULB**: *Per Protocol*: **V29.5Gy < 50%**.
Mack Roach[68] 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%.

8.3.4.5.1 Minor variation: V29.5Gy ≥ 50%, < 75%

8.3.4.5.2 Major variation: V29.5Gy ≥ 75%

8.3.4.6 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.

8.3.4.7 PROSTATIC URETHRA (when visualized): *Per Protocol*: V47Gy < 20%.
Beaumont's HDR protocol[69] 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.

8.3.4.7.1 Minor variation: V47Gy ≥20%, < 50%

8.3.4.7.2 Major variation: V47Gy ≥50%

8.3.4.7.3 If the urethra is not visualized, then the prescription (PTV) dose must be prescribed at no less than 75% of Dmax.

8.3.4.8 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.

8.3.4.8.1 Minor variation: D50 ≥ 37Gy, < 39Gy

8.3.4.8.2 Major variation: D50 ≥ 39 Gy

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

8.3.4.9.1 Minor variation: V38Gy ≥ 50%, < 75%.

8.3.4.9.2 Major variation: V38Gy ≥ 75%.

8.3.4.10 Investigators shall attempt to keep normal tissue doses and prescription coverage as close to "per protocol" specifications as possible. If all the above "Per Protocol" dose-volume criteria cannot be met on a given patient, then normal tissue constraints and target prescriptions may be relaxed to the "minor variation" range as follows. One minor variation in either the primary or secondary dose prescription coverage (e.g. PTV V36.25Gy 90-95% or GTV V40Gy 90-95%) is allowed; two minor variations or one major variation is allowed only with the consent of the site chair. One additional minor variation is allowed for constraints on the rectum, bladder, prostatic urethra, penile bulb, and for the PTV prescription isodose (i.e. percent of Dmax). Additional minor variations are allowed for the other normal tissue structures. There shall be no deliberate major variations on normal tissue constraints. All variations shall be noted.

8.3.4.11 TESTES (bilateral) shall be contoured, and no primary beams shall transverse this structure. The D50 will be recorded.

8.3.5 WORK EFFORT: for all involved disciplines (radiation oncologist, urologist and physicist), the time spent performing the various aspects of treatment planning will be recorded.

8.4 CYBERKNIFE TREATMENT DELIVERY

8.4.1 The prescribed PTV dose of 36.25Gy shall be given in 5 fractions using the CyberKnife.

8.4.2 Bowel/bladder preparation: patients will be advised to adhere to a low-gas, low-motility diet, starting at least one day prior to treatment. A fleets enema shall be administered 1-2 hours prior to treatment. If prostate movement remains significant despite these measures, a small-diameter rectal tube may be placed during treatment to vent gas. Patients shall urinate immediately prior to each treatment.

8.4.3 Treatment should be completed with 11 days; overall treatment time should be no less than 88 hours, with no less than 12 hours between any two fractions.

8.4.4 At least three fiducials should be identified for each treatment. If fewer than three fiducials can be tracked, then additional fiducials will be placed, and the patient replanned. Every effort will be made to treat using rotational corrections. The treatment system will be set to record rotations on the treatment printout. On a given treatment, if rotational corrections are not possible, treatment may continue, with rotational deltas recorded, as long as these remain below 2 degrees. For subsequent treatments, diet changes or additional bowel preparations will be made, and/or rectal tube placed, and treatment shall be attempted using rotational corrections. If treatment proceeds without rotational corrections, the therapist shall inform the attending radiation oncologist, and record the duration of treatment performed without rotations.

8.4.5 On the day of the CyberKnife treatment, the patient will be taken into the CyberKnife system treatment room, set up in their respective immobilization devices and positioned on the CyberKnife couch. X-rays will be taken with the

CyberKnife system to ensure that the tumor is aligned in a manner consistent with the position in which the treatment plan CT image was taken. Imaging should occur every 1-3 nodes, per the discretion of the attending physician. Fiducial locations in the images will be extracted and compared to the fiducial locations in the CT scans to estimate target movements. The following planning and treatment information shall be recorded for every plan and fraction delivered: set-up time required, number of nodes treated, number of nodes treated with rotational corrections, number of nodes imaged, and total treatment time. This data will be collected onto Case Report Forms.

8.4.6 All planned nodes will be treated whenever possible. If treatment must be terminated prematurely on fractions 1-4, compensate as follows. If 2/3 or more of all non-zero nodes were treated, then the untreated nodes plus the full next fraction should be treated on the next treatment day (this should introduce an error of < 5% in BED delivered). If fever than 2/3 of the non-zero nodes were treated, then the untreated portion of this fraction (only) will be made up for on the following day. The subsequent fraction shall be delivered on the next treatment day. If treatment must be terminated prematurely on the fifth fraction, and 90% of the non-zero nodes were treated, then no further treatment shall be given (this should introduce an error of < 5% for total BED delivered). If fever than 90% of the non-zero nodes were treated, then the deficit shall be delivered on the following treatment day. All such variations shall be recorded.

8.4.7 WORK EFFORT: for all member of the treatment team (therapist, physicist, radiation oncologist, and urologist), time spent actively involved with treatment shall be recorded. Also, required on-site supervisory time will be recorded.

9.0 PATIENT ASSESSMENTS AND TOXICITY

Assessment	Pre-entry	On tx day 5	Follow-up interval: months post therapy							Years post therapy
			1 wk	1	3	6	12	18	24 (every 6 mo up to 5 years)	6-10
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]	X
Prostate volume assessment	X									
CBC, platelets	X									
BUN, creatinine	X									
Testosterone	X			X	X	X	X	X	X[c]	X[c]
Toxicity evaluation	X	X	X	X	X	X	X	X	X[b]	X
AUA score	X	X	X	X	X	X	X	X	X*	X
SF-12	X			X		X	X		X*	
EPIC-26 Questionnaire	X			X		X	X		X*	X
SHIM Questionnaire	X			X		X	X		X*	X
Utilization of Sexual Rx/Devices	X			X		X	X		X*	
a. Central review of pathology; biopsy recommended at 2 yrs, & required at time of failure										

b. Continue every 6 months through to year 5 c. Testosterone levels will be monitored until the 24 month follow-up visit and will be optionally measured at follow-up visits out to 10 years. * Continue every 12 months through year 5; .	

9.1 EVALUATION DURING TREATMENT & FOLLOWING TREATMENT

9.1.1 PRE-ENTRY ASSESSMENT: see section 4.7.

9.1.2 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 CyberKnife 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.

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

9.1.4 ASSESSMENTS FOLLOWING TREATMENT: at one week after treatment, (allowed window: +/- 3 days), toxicity and AUA score will be evaluated. At 1 month (+/- 7 days) following treatment, patients will be assessed for acute toxicity, and will fill out AUA form, SF-12, EPIC-26, SHIM and Utilization of Sexual Rx/Devices. At 3, 6, 12, 18, and 24 month (+/- 2 wks) intervals (and every 6 months thereafter, through year 5, 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 annually thereafter, the SF-12, EPIC-26, SHIM and Utilization of Sexual Medications/Devices will be administered. After the 5 year follow-up patients will be seen yearly through year 10 (allowed window: +/- 1 month) and the following will be performed: PSA, toxicity evaluation, and the following questionnaires will be administered: EPIC - 26; AUA; SHIM. Examination and studies may be done at outside facility. A serum total testosterone will be measured at month 1 and every PSA through year 2.

9.1.5 PROSTATE BIOPSY will be performed at time of biochemical or local clinical failure, and is encouraged at 2 years following treatment and at time of distant failure.

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

9.2 CRITERIA FOR TOXICITY

9.2.1 ACUTE AND LATE TOXICITY

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

9.3 QUALITY OF LIFE ASSESSMENTS

9.3.1 SF-12: The SHORT FORM-12 Health Survey 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 SF-12 is self-administered, and can usually be completed in less than 3 minutes without assistance.

9.3.2 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 VI.

9.3.3 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 VI.

9.3.4 SEXUAL HEALTH INVENTORY FOR MEN (SHIM): is a widely used, internationally validated and sensitive instrument for assessing erectile dysfunction[70].

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

9.4 CRITERIA FOR DISEASE CONTROL: intervals will be measured from enrollment date.

9.4.1 BIOCHEMICIAL 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[71],[72],[73] have suggested the "nadir+2" definition is a more sensitive and specific definition of biochemical failure. Indeed, a recent expert panel met in Phoenix[74] and developed a consensus recommendation using the later definition. So that comparisons can be made with earlier literature, both definitions shall be used:

9.4.1.1 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.

9.4.1.2 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.

9.4.2 CRITERIA FOR LOCAL FAILURE: 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.

9.4.3 CRITERIA FOR NONLOCAL FAILURE

9.4.3.1 DISTANT 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.

9.4.3.2 DISEASE-FREE SURVIVAL: for any measure of disease, including PE, PSA, bone scan, CT/MRI and biopsy, or death.

9.4.3.3 DISEASE-SPECIFIC SURVIVAL: for any of the following:

9.4.3.3.1 Death due to prostate cancer.

9.4.3.3.2 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.

9.4.3.3.3 Death due to complications of treatment.

9.4.3.4 OVERALL SURVIVAL: for death from any cause

10.0 DATA COLLECTION

See appendix IV for Case Report Forms & patient questionnaires.

11.0 STATISTICAL CONSIDERATIONS

11.1 OVERVIEW: This study's primary goal is to determine the rate of acute and late grade 3-5 gastrointestinal and genitourinary toxicity following CyberKnife treatment, and to estimate efficacy, measured as 5-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 appendix V).

11.2 SAMPLE SIZE:

11.2.1 PRIMARY SAFETY OBJECTIVE: The study is designed to test the null hypothesis that the acute and late GI/GU toxicity rate 5 years following treatment is greater than 10% versus the alternative hypothesis that the toxicity rate is less than or equal to 10%. The sample size is determined such that there is 90% probability, or power, of identifying excessive toxicity if the true toxicity rate is 20% at the one-sided 5% significance level. 101 patients must then be accrued and followed for 5 years, assuming no patients excluded or lost to follow-up. Since the treatment volume for intermediate risk patients is larger than for low-risk patients, the study will be powered to assess toxicity for both subgroups. Additional enrollment for ineligible patients, or lost to follow-up: Since performing central review of pathology prior to enrollment is impractical, some patients will be upgraded, and thus made ineligible. In RTOG 77-06, central review upgraded about 8% of Gleason 2-6 patients to Gleason 7-10[75]. If we assume a similar rate of upgrading, and anticipate 8% additional ineligible/lack-of-data cases, sample size must be

increased by 1/(0.92*0.92) = 119.33. Thus 120 patients are required to establish acceptable toxicity for each risk cohort.

11.2.2 PRIMARY EFFICACY OBJECTIVE: For the low-risk cohort, the study is powered to compare 5-year bDFS rates observed with CyberKnife to 5-year bDFS rates reported with dose-escalated external beam RT. In Beaumont's monotherapy HDR series treating LR patients, 5-yr ASTRO bDFS was 98%; 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 CK delivers doses similar to HDR monotherapy, a conservative estimate of the success rate for CK is 97.5% for LR patients. In LR patients, prospective studies from Memorial Sloan Kettering[76] (203 patients, 81Gy) and MD Anderson[77] (32 patients, 78Gy) demonstrated 5-yr bDFS (Phoenix definition) of 92% and 93%, 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 93% 5-yr bDFS. Assuming the CK success rate is 97.5%, to test superiority of CK against this OPC with 80% power at the 1-sided 5% significance level will require 150 patients. Increasing the sample size by 1/(0.92*0.92) for ineligible/lack-of-data cases yields 177.22; the required sample size for low-risk patients is 178 patients.

11.2.3 TOTAL AND RELATIVE ENROLLMENT OF RISK GROUPS: Per sections 11.2.1 – 11.2.2, enrollment of 178 low-risk patients are required to compare the 5-year bDFS rate observed with CyberKnife to the 5-year OPC rate, and 120 intermediate risk patients are required to establish acceptable toxicity for each risk cohort. CaPSURE data showed a ratio of low to intermediate risk patients, using D'Amico's definition[78], of 46.8%:37.2%. This CK protocol excludes intermediate risk patients with both PSA 10-20ng/ml and Gleason 7 histology. Based on proportions of patients in these subgroups reported in Partin's[79] study, this would exclude 12% of intermediate risk patients. Combining these proportions, we would expect a ratio of low to intermediate risk patients of 1.43 : 1. Thus we would expect 172 low-risk patients enrolled by the time 120 intermediate risk patients have been enrolled. Each cohort will be closed to accrual once requisite enrollment is achieved: 178 low-risk patients, and 120 intermediate risk (298 total patients)

11.2.4 ACCRUAL RATE: the initial three months while institutions are obtaining IRB approval, therefore we do not expect to meet the targeted monthly accrual rate until after the first three months. The estimated accrual rate is 2.5 patients per study site per month. Expectations of 10 treating study sites assume an accrual period of approximately 11 months, or 14 month total

11.2.5 INTERIM ADJUSTEMENT IN ENROLLMENT: Interim analysis of the first 200 enrolled patients showed that 13 were actually ineligible because they were taking finasteride or dutasteride. Enrollment will thus be increased by 13 patients. Exclusion of patients on 5-alpha reductase inhibitors is clarified in section 5.12. We recognize that LHRH agonist/antagonist (e.g. leuprolide, goserelin, triptorelin, degarelix), hormone (e.g. DES), or peripheral blocker (e.g. flutamide, bicalutamide, nilutamide) administration given more than two months before enrollment may impact efficacy. Thus sample size (section 11.2) will be increased to insure enrollment is sufficient to achieve study objectives for the subgroup of patients naïve to such therapy. Interim analysis of the first 200 enrolled patients showed

four had received LHRH agonists or peripheral hormone blockers. We could expect four more such patients to be enrolled through completion of the study. Thus enrollment should be increased by an additional eight patients, or 21 patients total. Applying the proportion of low to intermediate risk patients described in section 11.2.3, total enrollment will be increased to 129 intermediate-risk, and 190 low-risk (319 patient total). If subsequent interim evaluations show the estimated proportion of ineligible/lack-of-data cases is inaccurate, required enrollment will be accordingly adjusted.

11.3 INTERIM ANALYIS FOR FUTILITY

When at least 50% of the Low Risk subjects have reached the 3 year time point, an interim analysis will be performed for the primary efficacy hypothesis to determine if it is futile to continue with study follow-up through 5 years. The primary efficacy study objective is to establish with 95% confidence that the 5 year bDFS rate is >93% (the OPC). For the interim analysis the 3 year bDFS rate will be used along with the same OPC of 93%.

11.3 1. Methodology:

The determination of 3 year bDFS will be made for all subjects with sufficient data through 3 years. Next, the probability of meeting the efficacy object at 3 years will be determined using simulation. Results for the subjects w/o sufficient data through 3 years will be simulated using a binomial distribution. The assumed probability of success (i.e. bDFS) will be set at the rate that was observed for the subjects w/ 3 year data. The simulation will be run 1,000 times resulting in 1,000 complete datasets. The lower confidence interval limit for 3 year bDFS rate will be calculated, using the Wilson method, for each dataset, and probability of success will be the proportion of datasets where the lower confidence limit is below 93%.

11.3.2.Rule:

If the probability of having a successful study is less than found to be less than 20% then it will be considered futile to continue with follow-up through 5 years.

11.4 STATISTICAL METHODS

11.4.1 PRIMARY ENPOINTS

11.4.1.1 SAFETY: The upper limit of a one-sided 95% confidence interval for the expected proportion of patients experiencing a Serious Adverse Event (SAE) is estimated by U, where

$$U = \frac{(2np + Z_{0.05}^2) + Z_{0.05}\sqrt{Z_{0.05}^2 + 4pn(1 \bullet p)}}{2(n + Z_{0.05}^2)}$$

Here "p" is the observed proportion of patients experiencing an SAE . The CyberKnife intervention will be considered to be safe if this study's result verifies that U is not above 20%[80].

11.4.1.2 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

$$L = \frac{(2np + Z_{0.05}^2) \bullet Z_{0.05}\sqrt{Z_{0.05}^2 + 4pn(1 \bullet p)}}{2(n + Z_{0.05}^2)}$$

Here "p" is the observed proportion of patients experiencing bDFS in either

arm of the trial . The CyberKnife intervention will be considered to be effective if this study's result verifies that L is not below 93%.

11.4.2 SECONDARY ENDPOINTS

11.4.2.1 QUALITY OF LIFE ASSESSMENTS: The SF-12 scores, AUA score, EPIC-26 scores are used to quantify quality of life (QoL) at baseline and repeatedly during the post treatment period (see Section 9.0). We will use the generalized estimating equation (GEE) method 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 patients' "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 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

11.4.2.2 ADVERSE EVENTS: All adverse events will be recorded on the case report forms. For both acute (<=90 days of treatment start) and late (>90 days of treatment start), the frequency and proportion of each type of adverse event will be presented in tabular form, on both a per-patient and a per-event basis.

11.4.2.3 SURVIVAL OUTCOMES: "Survival" analyses will be performed for the outcomes defined in Section 9.4.These include Local and Distant tumor Control, Disease-free survival for measures listed in Section 9.4.3.2, Disease-specific survival for measures including those listed in Section 9.4.3.3, and Over-all 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, 5 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.

11.4.2.4 WORK EFFORT: At each site and for each patient, time spent actively involved with planning and treatment shall be recorded for all member of the treatment team (therapist, physicist, radiation oncologist, and urologist). The required on-site supervisory time will also be recorded. Average times will be recorded. Time spent by team members will be compared and correlated with other outcomes (e.g. experience level of team member, patient enrollment, treatment planning/delivery QA outcomes,

toxicity, bDFS and QOL outcomes.

12.0 DATA SAFETY AND MONITORING

12.1 Clinical information from the subjects will be recorded onto Case Report Forms and subsequently transferred into a computer database in a secure file at a reputable Clinical Research Organization that is experienced and operates in accordance with the applicable regulatory and HIPAA guidelines.

12.2 Accuray's clinical monitor will periodically analyze data and initial outcomes from SRS treatment in order to monitor for any information of clinical concern. Additionally, as warranted, safety information will be submitted by one of the lead site's investigators and/or Accuray's clinical monitor to Accuray's medical monitor.

12.3 INDEPENDENT DATA SAFETY MONITORING BOARD: An independent Data Safety Monitoring Board (DSMB) will act as an advisory board to monitor patient safety and evaluate the efficacy of CyberKnife Stereotactic Radiosurgery for treating low and intermediate risk prostate cancer. The DSMB will conduct an independent objective review of the data to maximize the benefit to the trial participants.The DSMB will consist of 3 clinicians who are experts in or representatives of the fields of radiation oncology, stereotactic radiosurgery, urology, clinical trial methodology, and biostatistics. Membership will consist of persons completely independent of the investigators who have no financial, scientific or conflict of interest with the trial. Meetings of the DSMB will be held 4 times a year, with one annual meeting taking place face to face and the remaining meetings occurring via teleconference. The first board meeting will meet prior to initiation of the study to discuss the protocol and establish guidelines to monitor the study. The remaining quarterly meetings will be conducted via teleconference. The DSMB will monitor and evaluate all adverse events of all grades to establish relationship to the study procedures. Based on the review of toxicities summary the board will make recommendations to either continue, modify or terminate the study. After each meeting the board will provide the PI and Accuray with a written report concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial. Information on cumulative toxicities and relevant recommendations will also be provided by Accuray to the rest of the participating sites to be shared with their IRBs.

12.4 Adverse Events: An unanticipated adverse effect is defined by the FDA as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol (including a supplementary plan), or any other unanticipated serious problem with a device that relates to the rights, safety, or welfare of subjects. Should any unanticipated adverse device effects occur during the course of the study, the clinical monitor will ensure that they are documented by the investigator and reported to the sponsor and the reviewing Institutional Review Board (IRB) as soon as possible, but no later than ten working days after the investigator first learns of the effect(s). The report regarding any unanticipated adverse device effect also will be provided to all other IRBs for the sites at which this clinical evaluation is being conducted. The clinical monitor, on behalf of the sponsor, will work with one of the lead site's investigators and Accuray's medical monitor to conduct an evaluation of such effects. Following this evaluation, if the determination is made that an unanticipated adverse effect presents an unreasonable risk to subjects, the clinical evaluation will be paused, if deemed appropriate

(to enable further investigation) or terminated as soon as possible. Termination shall occur no later than five working days after the sponsor makes the determination and no later than 15 working days after the sponsor receives notice of the unanticipated adverse device effect. In the event of termination, IRB approval will be obtained prior to resuming the clinical evaluation.

12.5 Below are criteria for early termination of either arm of the trial should an excessive number of patients experience a Serious Adverse Event (SAE). This depends upon the number so far enrolled and a criterion that identifies too high a rate. The stopping criteria differ after 48, 96 and 120 patients have been enrolled in both groups with additional applications when up to144 and 178 have been enrolled in the low-risk group .Consistent with Section 11.2.1, we define an observed SAE rate of 20% as too high The statistical requirement is that for up to "m" patients enrolled, the number of observed SAEs must be few enough so that there is a 95% chance that the "true" rate does not exceed 20%.

Serious Adverse Event (SAE) Stopping Criteria	
Participants to be enrolled: 298 (178 low-risk, 120 interm-risk)	**Independently for both low- and interm-risk arms, stop an arm if the number of grade 3-5 effects for that arm equals or exceeds:** **Enrollment 1-48: 6 SAEs** **Enrollment 1-96: 14 SAEs** **Enrollment 1-120: 18 SAEs** **Enrollment 1-144: 22 SAEs** **Enrollment 1-178: 28 SAEs**

12.6 Regulatory Reporting:Any reports regarding safety issues and potential safety issues will also be provided to Accuray's Regulatory Affairs Department. Such reports will be evaluated and reported to the FDA and all applicable regulatory agencies, as deemed required.

13.0 SOURCE OF SUBJECTS AND RECRUITMENT PROCEDURES

13.1 Source of Subjects:

The subjects will be male patient with low and intermediate risk organ-confined prostate cancer. The racial, gender and ethnic characteristics of the proposed subject population will reflect the demographics of the respective clinical evaluation site's surrounding area and/or patient population. Each site will attempt to recruit subjects in respective proportion to the site's respective demographics. No exclusion criteria shall be based on race or ethnicity. Subjects will be identified and recruited from outpatient facilities affiliated with sites selected to participate in this clinical study. In addition, subjects may be recruited by referrals to the clinical study sites. In the event advertisement is used for recruitment, any such advertisement will require approval by the respective site's IRB prior to use.

13.2 Recruitment Procedures:

After evaluation by a urologist and a radiation oncologist, patients with low and intermediate risk organ-confined prostate cancer will be offered CyberKnife treatment. After the decision is made by both the patient and his physician(s) to proceed with CyberKnife treatment, they will be screened for inclusion in the clinical evaluation. Details of the evaluation will be discussed with the patient, with ample time given for questions. If they choose to participate, the patients will be asked to sign an Informed Consent Form.

13.3 Patient Confidentiality:

In the attempt to maintain patient confidentiality for all patients involved in this clinical evaluation, patient identifier information will be restricted to each respective clinical site. Subject-specific identification required to conduct this evaluation (for communication purposes between the sponsor and sites) will be restricted to the number assigned to that subject at the time of registration.

14.0 RISK TO BENEFIT RATIO

14.1 The determination of entry into the clinical evaluation will be made independent of the decision to treat with stereotactic radiosurgery. The urologist, radiation oncologist and/or medical team performing the procedure will discuss the potential risks associated with stereotactic radiosurgery and the potential benefits of control of disease progression, despite the limited clinical experience.

14.2 Risks:
Risk classifications assigned below are based on currently available literature on treating prostate cancer with radiation therapy in a manner comparable to the radiosurgery planned for this protocol. The protocol for this clinical evaluation was designed to assure that the benefits and knowledge collected for stereotactic radiosurgery of malignant prostate tumors outweigh the potential risks to the subjects.

Risks to patients in this study include all those risks currently associated with fiducial placement as well as the risks of localizing and delivering radiation to the prostate environment. The safety of the CyberKnife system in treating intracranial tumors has been well documented. Risks of the procedure for this clinical study along with the methods to minimize the risk are described below. The radiation risks presented are categorized according to version 2.0 of the National Cancer Institute's Common Toxicity Criteria. Likely effects are listed as those side effects which occur in more than 20% of patients. Less likely effects occur in 20% or less of patients treated. Rare but serious effects occur in less than 3% of patients.

14.3 Risks Associated with External Radiation Therapy:
All patients treated under this protocol will be provided with specific instructions and contact information, in the event any patient develops side effects. Many of these side effects go away shortly after radiation therapy is stopped, but in some cases side effects can be long-lasting or permanent. The following includes risks associated with external beam radiation therapy to the prostate and surrounding pelvis.

Temporary fatigue (Likely): self-limited side effect.

Temporary frequent or loose stools (likely): see notes 1 & 3. Diet changes or immodium will be prescribed if necessary.

Temporary urinary frequency, irritation, or reduced stream (Likely): see notes 1,2,3. Alpha blocker will be prescribed if necessary.

Temporary redness, tanning, or hair loss of skin in the treatment area (less likely): see note 1. Topical preparations will be prescribed, if necessary.

Permanent urinary "bother", e.g. need to urinate urgently or frequently (less likely): see notes 1,2,3. Chronic alpha blocker, or other medical therapy may be required.

Permanent bowel "bother", e.g. need to move bowels urgently or frequently (less likely): see notes 1,2,3. Addition of "bulk" (e.g. Metamucil) to diet, or immodium, may be required.

Rectal bleeding (rare, but serious): see notes 1,2,3. Hydrocortisone suppositories or enemas may be required; blood transfusions, topical anticoagulants, coagulation, or hypobaric oxygen treatments may be necessary.

Urinary obstruction which could require catheter placement (like likely): see notes 2,3. Foley, intermittent straight catheterization, or suprapubic catheter may be required.

Urethral scarring, which could impair urine stream, and could require surgery to repair (Less likely, but serious): see notes 2,3. Cystoscopy, trans-urethra incision, and/or dialation may be required.

Leakage of small amounts of urine, which could require wearing pads in underwear (less likely): see notes 2,3.

Inability to control urine, which could require a catheter, penile clamp, or surgery to repair (rare, but serious): see notes 2,3.

Urinary bleeding (rare, but serious): see notes 1,2,3: cystoscopy or electrocoagulation may be required.

Prostate, bladder, urethra, or rectal pain (rare): see notes 1,2,3. May require treatment with antibiotics, surgery (either open or cystoscopic), analgesics, or other medications placed in the bladder, urethra, or rectum.

Impotence (Less likely, but serious): see notes 1,2. May require treatment will medications (e.g. Viagra, Muse, etc…), other erectile aids (e.g. penile pump), or surgery.

Reduction in ejaculate volume (likely), which could reduce fertility: unavoidable, since the target includes structures which contribute to semen.

Pain with ejaculation, or change in the sensation of orgasm (less likely): see note 2,3. May require analgesics.

Rectal or urethral ulceration, or fistula, which could result in colostomy and/or ileostomy (rare, but serious): see notes 1,2,3. Could also require antibiotics, suprapubic or foley catheter, liquid diet, hypobaric oxygen treatments, medications or other surgeries.

Note 1: because the CyberKnife treats the prostate with over 100 beams coming from many directions, radiation dose is concentrated on the prostate. Compared with other external beam radiation devices, less radiation dose is given to the surrounding normal tissues, such as the rectum and bladder. In addition, throughout treatment, CyberKnife frequently images the prostate and corrects for movement of the patient or the prostate. This allows physicians to treat a smaller region around the prostate, compared to other radiation devices. This minimizes radiation exposure to surrounding normal structures. The design characteristics of the CyberKnife thus intrinsically minimizes the risk for side effects or adverse effects.
Note 2: the radiation tolerance of the normal tissues surrounding the target has been carefully considered, and likely acceptable tolerances have been calculated. These normal tissue constraints are listed in section 8.3.2. DVH analyses will be performed as specified, to insure adherence to these constraints, thus minimizing risk.
Note 3: the large dose per fraction delivered with CyberKnife takes advantage of the low α/β ratio of prostate cancer relative to the surrounding normal structures. The hypofractionation scheme this reduces the risk of side effects or adverse effects.

14.4 Risks Associated with Fiducial Placement:
Infection (rare): In the event that a patient experiences infection as a result of fiducial placement, antiobiotic treatment will be prescribed.

14.5 Minimization of Risk:
Stringent inclusion/exclusion criteria have been incorporated into this protocol to assure that any subject who may be at increased risk from an adverse event is not enrolled into this clinical study. Subjects will be observed post procedure to assure that any acute adverse effects are detected in a timely manner so that proper medical treatment can be initiated. Subjects also will be provided with instructions as to whom to contact along with contact telephone numbers, in the event they experience any complications.

14.6 Potential Benefits:
Although previously confined to intracranial treatment, SRS is gaining recognition in the medical community as an alternative to external beam radiation therapy in other parts of the body. Use of the CyberKnife system may provide the following benefits:

- Minimally invasive procedure performed on an out-patient basis
- Lengthen interval to tumor progression
- Improved survival
- Decreased genitourinary, rectal and gastrointestinal toxicities compared with conventional radiation therapy and radical prostatectomy
- Decreased toxicities to sexual function compared to other types of radiation therapy and radical prostatectomy

14.7 Early Termination:

Subjects may withdraw or be discontinued by the investigator from the clinical evaluation at any time, however, they may be requested to continue with their follow-up PSA tests and exams five years following their last SRS treatment.

15 COSTS AND PAYMENTS

15.1 Research Study Costs:

Screening and clinical assessment of the patient prior to the procedure will be no different than what typically occurs prior to conventional radiation therapy. Therefore, a patient's insurance will be billed for all tests and imaging associated with this evaluation. The cost of the procedure itself will be billed to the patient's insurance company under an appropriate code. This will include all operative and hospital-based charges. Follow-up assessment also is no different than what typically occurs following a conventional radiotherapy and treatment for this population of patients. Therefore, the patient's insurance will be billed for all tests and imaging associated with the follow-up visits.

15.2 Research Study Payments:

There will be no financial reimbursement to the patient for participation in this evaluation. Some data management, salary support and supplies will be provided by Accuray Inc., Sunnyvale, CA (project sponsor).

16 APPENDICES

Appendix I: Sample Patient Consent Form

Informed Consent
Prospective Evaluation of CyberKnife Stereotactic Radiosurgery for Low and Intermediate Risk Prostate Cancer: Homogenous Dose Distribution

Date: _____ / _____ / _____
MM DD YY

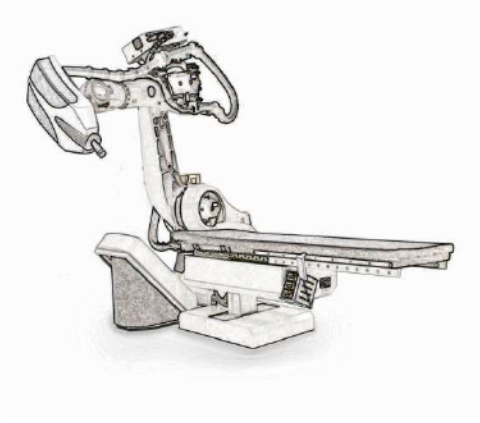
Are you participating in any other research studies? _____ yes _____ no

Why have I been asked to take part in this research study?
You are invited to participate in a clinical evaluation of a highly focused radiation treatment to prostate tumors using the CyberKnife® system (manufactured by Accuray Incorporated, Sunnyvale). The purpose of this evaluation is to look at the effect this treatment will have on the tumor and your quality of life at various timelines for 10 years after your treatment. If you decide to participate in this evaluation, you will need to meet a number of requirements before your doctors determine that this treatment is appropriate for you.

Who is conducting the study?

[PLEASE ADD INSTITUION HERE]

Why is this research study being done?
The purpose of this study is to determine the effects of CyberKnife radiosurgery in patients with prostate cancer. The CyberKnife system is a new type of radiation machine that uses a special system to precisely focus large doses of x-rays on the tumor. The device is designed to concentrate large doses of radiation onto the tumor so that injury from radiation to the nearby normal tissue will be minimal. The purpose of this evaluation is to see if this treatment will help patients with your condition and to evaluate the effect of this treatment on your quality of life over time.



The CyberKnife system previously has been used in the lung, brain, head and neck as well as other areas of the body. The results of treating tumors in the brain are similar to an operation in which the tumor is removed. The CyberKnife system has market clearance from the U.S. Food and Drug Administration to treat tumors, lesions and conditions anywhere in the body when radiation therapy is required. While the device is no longer classified as "investigational", the best treatment dose and times still are being evaluated.

The feasibility of CyberKnife for treating localized prostate cancer was first described by the group at Stanford University. They reported that the prostate tumor marker "prostate specific antigen" (PSA) decreased rapidly in 26 low risk prostate cancer patients treated with the CyberKnife with a median follow-up time of 18 months. Fewer side effects were observed compared to conventional external beam radiation. In a second study, a group from the Korea Cancer Center, Seoul, Korea, explored the advantages of CyberKnife radiosurgery as a minimally invasive treatment option for patients with prostate cancer. They demonstrated that the CyberKnife was effective for the treatment of tumors in the prostate and improved the quality of life for patients by minimizing the treatment side effects and shortening the overall treatment times. Recently, Naples Community Hospital reported a series of more than 70 low and intermediate risk prostate cancer patients treated with the CyberKnife. They reported a significant decrease in PSA values one year following CyberKnife treatment with minimal acute toxicities.

How many people will take part in the study?
Approximately 319 patients will be enrolled in this clinical evaluation.

What will happen if I take part in this research study?
Prior to entrance on this study you will have had your prostate specific antigen (PSA) and testosterone checked and your prostate biopsied within the last 12 months. The results of the biopsy showed that you have prostate cancer. In addition, you will have a digital rectal exam (DRE) to determine if the cancer can be felt. Based on the results of these tests and examination it has been determined that your prostate cancer is in an early stage and has not likely spread outside the prostate or anywhere else in your body. If you agree to be in this study, you will be asked to read and sign this consent form before having any procedure that is required for your participation in this clinical evaluation.

Preparation for CyberKnife treatment to the prostate:
You will be asked to complete some short questionnaires before your CyberKnife treatment. These questionnaires will ask you multiple choice questions about your bowel, bladder and sexual function. They will also ask you some general questions about your mood, activity and energy levels, and general health.

You will also have a physical examination and a procedure to place 4 small gold seeds into the prostate. This procedure is commonly done in patients receiving standard external beam radiation for prostate cancer and is not an experimental procedure. These gold markers will be used to determine the location of the prostate during the CyberKnife treatment. An ultrasound probe is placed into the rectum and needles containing the gold seeds are guided into the prostate and then the seeds are deposited. You will need to clean out your rectum and take antibiotics the day of the seed placement.

Within 5-10 days after placement of the gold seeds, you will be asked to return to the hospital to have a planning CT scan of the pelvis. This is a regular CT scan and is standard procedure for patients receiving external beam irradiation. The images obtained during the scan will be used to plan the CyberKnife

treatments. You will also have an MRI scan of the pelvis, unless medically contraindicated (for example if you have a pacemaker) which will be used for treatment planning purposes. You may be asked to undergo a second scan with a urethral catheter in place.

CyberKnife treatment to the prostate:

The CyberKnife treatment will usually be started a few days after the CT scan of the pelvis. Your course of radiation will consist of five separate CybeKnife treatments usually delivered over 5 consecutive week days (maximum 11 days), with no less than 12 hours between any two fractions. Each treatment session will take approximately 1.5-2.5 hours. You will lie on the treatment table and breathe normally while you receive your radiation treatment.

How long will I be in the study?

The treatment part of the study will last 5-11 days. On the last day of treatment a nurse will ask you questions about possible side effects. After your CyberKnife treatment you will need follow-up visits to determine how effective was the treatment and if you are having any treatment related side effects. At 1-2 weeks after treatment is completed, a research nurse will call you and discuss how you are doing. At 1 month after completion of the CyberKnife treatment, you will be asked to return to the hospital for a follow-up examination to check for any side effects and a blood test to measure your testosterone level. You will also be asked to complete the same questionnaires you completed prior to CyberKnife treatment. These questionnaires will ask about your bowel, bladder and sexual functioning, as well as mood, activity and energy levels, and general health..

At 3 and 6 months after completion of the CyberKnife treatment, you will be asked to return to your physician for an examination and a blood test to measure your PSA level. This is the standard procedure for follow-up visits and will occur every 6 months thereafter for 5 years, then yearly for an additional 5 years.

Testosterone levels will be monitored until the 24 month follow-up visit and will be optionally measured at follow-up visits out to 10 years.

At these visits, you also will be asked to complete questionnaires about your bowel, bladder and sexual functioning and your quality of life.

If it is suspected that your tumor is growing or if there are concerns about disease progression on your PSA exams, a prostate needle biopsy of the tumor may be performed. Two years after CyberKnife treatment, you may be asked to have a prostate biopsy.

Can I stop being in the study?

You may decide to stop and withdraw from the study at any time.

What side effects or risks can I expect from being in the study?

You may have side effects while on this study. Most of these are listed here, but there may be other side effects that we cannot predict. Side effects will vary from person to person. Everyone taking part in the study will be carefully watched for any side effects. However, doctors do not know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medications to help lessen some of the side effects. Many side effects go away soon after your radiation therapy. In some cases, side effects may be very serious, long-lasting, or may never go away. You should talk with your study doctor about any side effects that you may have while taking part in the study

The administration of radiation itself is painless and the only discomfort is expected to be from your having to lie very still during the treatment.

The biopsy and placement of the gold markers may cause some discomfort as these procedures require the use of small needles inserted into the prostate. Discomfort from these procedures will be minimized by the use of local numbing medications (anesthetics) and you may receive intravenous injection of small doses of medications to make you drowsy (sedatives). It is likely that a patient undergoing this procedure may experience discomfort from placement of the needles and minor bleeding because of injury to small blood vessels in the path of the needle. The majority of cases do not require treatment and the bleeding resolves spontaneously. Other possible side effects which are rare include infection requiring antibiotic treatment and significant bleeding requiring transfusion and/or surgery.

Possible side effects following CyberKnife treatment include irritation of the bladder or urethra (the tube that carries urine out of the bladder through the penis). This may lead to temporary symptoms including a reduced stream of urine, burning with urination, having to urinate more frequently, having to get to the bathroom quickly to urinate and/or getting up more at night to urinate. Other possible side effects include irritation to the rectum which may lead to temporary symptoms including an increase in frequency of stools, loose stools and/or more gas with bowel movements. Some patients have tempory mild fatigue, and some may develop temporary or permanent impotence (inability to have erections) or permanent accidental leakage of small amounts of urine. Other side effects which are less likely include temporary hair loss, redness or tanning of skin in the treatment area, permanent urinary urgency, permanent urinary frequency, need to move bowels urgently or frequently, and rectal or urinary bleeding. Rarely, some patients may experience the inability to control urine which could require a catheter. Extremely rare complications include rectal ulceration or fistula which could require a colostomy and/or urethral ulceration or fistula which could result in ileostomy. If the possibility of side effects make you too uncomfortable, you are encouraged to contact the study doctor as soon as possible.

Are there benefits to taking part in the study?

CyberKnife treatment to the prostate is done with the delivery of large doses of highly focused radiation instead of the more conventional approach which is done with low doses of radiation given daily over seven to nine weeks. The three important possible benefits to CyberKnife therapy are that the higher doses of radiation may be: 1) more damaging to the tumor and, therefore, lengthen the time to tumor progression 2) have a greater chance of prolonging your life, 2) less damaging to surrounding tissue 3) more convenient than treatments being given daily over seven to nine weeks 4) a minimally invasive procedure performed on an out-patient basis.

The information which is obtained from this clinical evaluation will be used to see how helpful this treatment is to patients with prostate cancer and to look at the effect this treatment has on your quality of life over time. This information also may be helpful to others with your condition.

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY BENEFITS FROM THIS CLINICAL EVALUATION.

You will be told if any new information is learned which may affect your condition or influence your willingness to continue participation in this evaluation.

While participating in this clinical evaluation, you should not take part in any other research project without approval from all of the investigators. This is to protect you from possible injury resulting from such things as extra blood drawing, extra x-rays, interaction of research drugs, or similar hazards.

What other options are there?

There are alternatives to CyberKnife radiation for treatment of your early stage cancer. These include:

- Watchful waiting: This is a program of close follow-up delaying definitive treatment of your cancer.
- Surgery: This is the surgical removal of the prostate.
- Brachytherapy: This is the placement of a radioactive source into the prostate.
- External Beam Radiation: This is the use of a machine to deliver radiation to the prostate.
- Hormonal Therapy: The use of hormones to lower or block the male hormone testosterone, to suppress prostate cancer growth.
- Cryotherapy: This is freezing the prostate.

These options may or may not be appropriate for you. You should discuss them with your physicians prior to your agreement to participate in this experimental treatment for early stage prostate cancer.

Payment

You will receive no payment for your participation in this study.
The study doctors will not be paid for your participation in this study.

What are the costs of taking part in the study?

There is no cost for participating in this evaluation. You or your insurance company will be responsible for the entire cost of treatment and subsequent evaluation. Your doctor will discuss these with you.

What are my rights if I take part in this study?

Participation in this study is entirely voluntary. You are free to withdraw your consent to participate in this treatment program at any time without prejudice to you or your medical care. Refusal to participate will involve no penalty or loss of benefits. You are free to seek care from a physician of your choice at any time. If you do not take part in or withdraw from this clinical evaluation, you will continue to receive care.

The decision may be made to take subjects out of this clinical evaluation due to unanticipated circumstances. Some possible reasons for withdrawing a subject from the evaluation are:

- failure to follow instructions
- the investigator decides that continuation could be harmful to you
- you need treatment not allowed in this clinical evaluation
- the evaluation is canceled
- other administrative reason

Who can answer my questions about the study?

If you have any questions, you will be expected to ask them of the doctor and/or his study coordinator. If you have any additional questions later, please contact:
[PLEASE ADD INSTITUTION SPECIFIC INFORMATION HERE]

What happens if I am injured because I took part in this study?
All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this evaluation. If such complications occur, the doctors will assist you in obtaining appropriate medical treatment but this evaluation does not provide financial assistance for additional medical or other costs. There will be no payment for treatment of pre-existing conditions or for any treatment of conditions arising after the evaluation. No funds have been set aside to compensate you for wages associated for lost time at your workplace.

Signatures

I have been given a copy of this form. I have read the consent form or it has been read to me. This information was explained to me and my questions were answered.

I agree to take part in this research study.

_____	_____	_____
Date	Patient's Signature	Printed Name
_____	_____	_____
Date	Signature of person conducting the informed consent discussion	Printed Name
_____	_____	_____
Date	Investigator's Signature	Printed Name

In the event that an interpreter is needed:

I have accurately and completely read the foregoing document to:_____
(patient or legal representative's name)

in _____the patient's (or legal representative's) primary language. (Identify language used)

He/She understands all terminology/conditions, acknowledges his/her agreement by signing the document in my presence.

_____	_____
Signature of Interpreter	Date

AUTHORIZATION FOR USE OF PROTECTED HEALTH INFORMATION FOR RESEARCH PURPOSES

USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION

Protected Health Information is any personal health information through which you can be identified. A decision to participate in this research means that you agree to the use of your health information for the purposes explained in this consent form. By signing this form, you are authorizing the use and disclosure of your health information collected in connection with your participation in this research study. Your information will only be used in accordance with the provisions of this consent form and applicable law.

Your health information related to this study, including, blood and other tissue samples and related records, physical examinations, past medical history, x-rays, CT scans, consulting specialist's reports, operative reports, and pathology reports may be used or disclosed in connection with this research study. Study records that identify you will be kept confidential as required by law. Except when required by law, you will not be identified by name, Social Security #, address, phone #, or any other direct personal identifier in study records disclosed outside of the [ENTER NAME OF HOSPITAL/RESEARCH FACILITY]. For records disclosed outside of [, you will be assigned a unique code number. The key to the code will be kept in a locked file in the office of the Principal Investigator, [ENTER NAME OF PRINCIPLE INVESTIGATOR].

Representatives of the following groups are authorized to use and/or disclose your health information in connection with this research study:

- The principal investigator, [ENTER NAME OF PRINICPLE INVESTIGATOR] and other researchers involved in the evaluation
- The [ENTER NAME OF HOSPITAL/RESEARCH FACILITY] Institutional Review Board,
- The research nurse, clinical research associate, and project coordinator

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

The Office of Human Research Protections in the U.S.
Department Of Health and Human Services
The U.S. Food and Drug Administration
Accuray, the vendor for CyberKnife

EXPIRATION DATE OR EVENT FOR THE RETENTION OF RECORDS

Your authorization for the use and/or disclosure of your health information expires one year after this multi-center research project is completed (subject follow-up period after treatment will be 10 years). At that time either the research information not already in your medical record will be destroyed or information identifying you will be removed from such study results at [ENTER NAME OF HOSPITAL/RESEARCH CENTER]. Any research information in your medical record will be kept indefinitely.

VOLUNTARY PARTICIPATION

Your participation is voluntary and you may choose not to participate in this research study or withdraw your consent or authorization for the use and disclosure of your health information at any time. Your choice will not at any time affect the commitment of your health care providers to administer care and there will be no penalty or loss of benefits to which you are otherwise entitled. If you decide to end your participation in the study, please notify the researcher(s) in writing.

If you have questions or concerns regarding your privacy and the use of your personal health information, please contact the Privacy Officer, at 459-2742.

Signature (Subject) Date

Signature (parent/legal guardian/conservator) Date

If signed by other than patient, indicate relationship

Witness Date

CALIFORNIA EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

California law requires that any person asked to take part as a subject in research involving a medical experiment, or any person asked to consent to such participation on behalf of another, is entitled to receive the following list of rights written in a language in which the person is fluent. This list includes the right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedure to be followed in the medical experiment and any drug or device to be utilized.
3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs, or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.
7. Be given an opportunity to ask any questions concerning the experiment or the procedures involved.
8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of the signed and dated written consent form.
10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

For questions about patient rights, contact the Chairman of the Institutional Review Board at [ENTER NAME OF HOSPITAL/RESEARCH CENTER] at [ENTER CONTACT TELEPHONE NUMBER].

I have carefully read the information contained above and I understand fully my rights as a potential subject in a medical experiment involving people as subjects.

_____ _____

Signature (patient) Date

_____ _____

Signature (parent/legal guardian/conservator) Date

_____

If signed by other than patient, indicate relationship

_____ _____

Witness Date

Appendix II: Performance Status Scales

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 III: 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)*
[illegible](s)
[illegible]

*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 IV: Data Collection Documents

Refer to: http://eventa.kikamedical.com/accuray-prostate/

Appendix V: NCI Common toxicity criteria/RTOG/EORTC:

Refer to: http://ctep.cancer.gov/forms/CTCAEv3.pdf

Appendix VI: AUA, SF-12, 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.[81] 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

Quality of Life: If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that? Delighted, Pleased, Mostly satisfied, Mixed, Mostly dissatisfied, Unhappy, Terrible

SF-12 (Short Form)

1. In general, would you say your health is excellent, very good, good, fair, or poor? Excellent ... Very Good ... Good ... Fair ... Poor ...

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

2) First, moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf. Does your health now limit you a lot, limit you a little, or not limit you at all. Limited a lot ... Limited a little ... Not limited at all ...

3. Climbing several flights of stairs. Does your health now limit you a lot, limit you a little, or not limit you at all? Limited a lot ... Limited a little ... Not limited at all ...

4. During the past four weeks, have you accomplished less than you would like as a result of your physical health? No ... Yes ...

5. During the past four weeks, were you limited in the kind of work or other regular activities you do as a result of your physical health? No ... Yes ...

6. During the past four weeks, have you accomplished less than you would like to as a result of any emotional problems, such as feeling depressed or anxious? No ... Yes ...

7. During the past four weeks, did you not do work or other regular activities as carefully as usual as a result of any emotional problems such as feeling depressed or anxious? No ... Yes ...

8. During the past four weeks, how much did pain interfere with your normal work, including both work outside the home and housework? Did it interfere not at all, slightly, moderately, quite a bit, or extremely? Not at all ... Slightly ... Moderately ... Quite a bit ... Extremely ...

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

9. How much time during the past 4 weeks have you felt calm and peaceful? All of the time ... Most of the time ... A good bit of the time ... Some of the time ... A little of the time ... None of the time ...

10. How much of the time during the past 4 weeks did you have a lot of energy? All of the time ... Most of the time ... A good bit of the time ... Some of the time ... A little of the time ... None of the time ...

11. How much time during the past 4 weeks have you felt down? All of the time ... Most of the time ... A good bit of the time ... Some of the time ... A little of the time ... None of the time ...

12 During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities like visiting with friends, relatives etc? All of the time ... Most of the time ... Some of the time ... A little of the time ... None of the time ...

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

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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

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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!!

EPIC-SF 6.2002

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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)

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