PROSPECTIVE EVALUATION OF CYBERKNIFE STEREOTACTIC RADIOSURGERY FOR LOW AND INTERMEDIATE RISK PROSTATE CANCER: EMULATING HDR BRACHYTHERAPY DOSIMETRY

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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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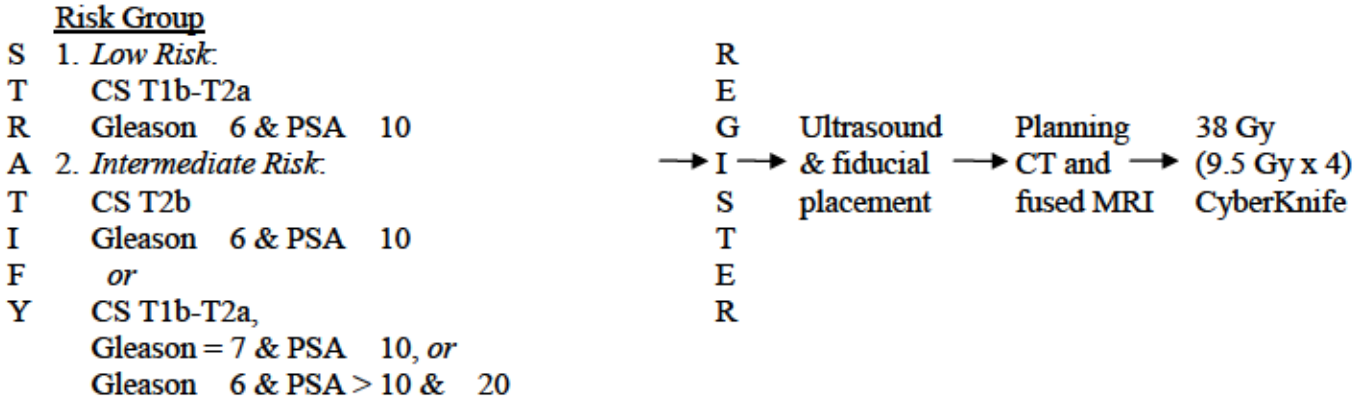
SCHEMA



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: 253

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-T2a, and Gleason 2-6, PSA 20 ng/ml, or Gleason 7, PSA 10 ng/ml
_____ (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)	Is there implanted hardware near the planning target volume 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?

1. BACKGROUND

1.1. During the prostate-specific antigen era, an ever-increasing percentage of men with prostatic adenocarcinoma have presented with clinically localized, intermediate Gleason grade, potentially curable disease. Conventional treatment options for these patients include laparoscopic or open radical prostatectomy, external beam radiation therapy, permanent source interstitial brachytherapy, and high dose rate (HDR) remote after loading brachytherapy, either as monotherapy, or in combination with external beam radiotherapy.[1]

1.2. Although each of the treatment options is potentially curative in selected patients, each treatment option also has drawbacks. The post-operative recovery period may be substantial following radical prostatectomy; the period of urologic symptoms may be protracted and occasionally severe following permanent source brachytherapy; the scheduling duration is substantial for external beam radiotherapy and the discomfort of indwelling transperineal catheters is significant for HDR brachytherapy patients. Additionally, all local treatments carry a risk of negative long-term quality of life consequences, and occasionally, serious complications.

1.3. The use of hypofractionated CyberKnife stereotactic therapeutic radiation as a modality of treatment for early-stage prostate cancer has also been described.[2] In contradistinction to traditional external beam radiotherapy, this method entails a therapeutic radiation process that uses a more precise targeting methodology, allowing a more focal treatment margin around the prostate. This more effectively limits the volume of adjacent tissue receiving high dose radiation, which in turn allows the delivery of a much shorter series of treatments, employing a much larger dose of radiation per treatment. When so applied, the radiation becomes tissue ablative within the high dose zone, and as such, may be described as a form of radiosurgery.

1.4. Although very limited experience has been gained to date, the radiosurgical approach for prostate cancer carries with it a number of potential advantages, including the possibility of lower morbidity due to the very small treatment margins, more rapid recovery from side effects due to the lack of a surgical resection or implanted radioactivity, convenience of a one week treatment course, and lack of transperineal HDR catheters with their attendant pain and hospital admission requirement.

1.5. The main technical problem that prevents the application of radiosurgery for prostate cancer is that the prostate may move substantially, both between fractions (interfraction motion) and during the treatment itself (intrafraction motion), even if rigid body immobilization is applied, due to the effect of organ motion.[3,4] This prostate motion effect necessarily leads to the application of a larger radiotherapy planning target volume to compensate, effectively rendering radiosurgery impossible by traditional radiotherapy or radiosurgical systems.

1.6. The CyberKnife® is a unique noninvasive radiosurgical system, capable of treating any part of the body from any of approximately 1600 different targeting angles, creating a highly conformal three-dimensional radiosurgical treatment volume, guided by orthogonal X-ray-based targeting feedback, and delivering radiation by a highly collimated, robotically controlled linear accelerator. The CyberKnife® system targets implanted fiducial markers with sub-millimeter initial set-up accuracy, and continuously updates the planning target volume by obtaining multiple intrafractional orthogonal X-ray-images, producing an automated robotic adjustment after each X-ray feedback step, resulting in a real-time target volume tracking process that maintains millimeter accuracy throughout the

radiosurgical treatment.[5] Thus, the CyberKnife® device allows a reproducible method of radiosurgical prostate treatment.

1.7. There are also radiobiological data that suggest hypofractionated radiosurgical treatment may be advantageous for prostate cancer, as contemporary data suggest the α/β ratio for prostate cancer tissue may be as low as 1.5Gy.[6] These values of α/β are comparable to, if not lower, than late-responding normal tissues.[6] This means that in addition to causing effective cancer cellular ablation and tissue sparing due to of its physics attributes, a course of hypofractionated CyberKnife® prostate radiosurgery may also create a favorable therapeutic ratio by virtue of the radiobiologic sensitivity of prostate cancer itself to hypofractionation, effectively resulting in radiobiologic tumor dose escalation.[6, 7]

1.8. From a dosimetry standpoint, CyberKnife® radiosurgery appears capable of producing a dose distribution comparable to that created by prostate HDR brachytherapy treatment, without the invasive transperineal catheters. As such, the CyberKnife® prostate radiosurgery dose fractionation schedule prescribed in this study is based upon prior published prostate HDR brachytherapy monotherapy experience, which suggests efficacy and safety, with a median follow-up duration of 35 months.[8] The radiosurgery volume in this study will be made to resemble prostate HDR brachytherapy therapeutic volume as closely as possible, with similar dose limitation objectives to adjacent tissues, including the rectum, bladder and urethra.

1.9. Because of the narrow treatment margin, and sharp fall off of radiation dose beyond the treatment margin, it is only appropriate to include patients with a high likelihood of localized disease for CyberKnife® monotherapy. These patients are reasonably identified by examination of the Partin Tables[9], which predict the probability of pathologic disease extension beyond the prostate, and also by examination of the long term results of permanent source brachytherapy literature[10,11], as permanent source brachytherapy produces a therapeutic margin of similar magnitude to the therapeutic margin provided by CyberKnife treatment as described in this protocol. The long-term brachytherapy literature describes biochemical disease free survival rates exceeding 80% for favorable prognosis and selected intermediate prognosis patients as described in this protocol.[10,11]

1.10. The inclusion criteria and planning target volume (PTV) margin specifications in this protocol are designed such that the risk of disease extension beyond the PTV will be less than 5% for "favorable prognosis" patients (Gleason score $\leq$6 and PSA $\leq$10ng/ml) and less than 10% for "intermediate prognosis" patients (Gleason score 7 or PSA 10.1 – 20ng/ml). Patients will be stratified according to their prognostic grouping.

1.11. Planning target volume (PTV) margins will be based upon the risk and predicted magnitude of extracapsular extension, as most recently reported by Chao, KK, et al, detailed in sections 6.1.2 – 6.1.4 of this protocol document.[12] Briefly, for classic "favorable" prognosis patients (PSA$\leq$10ng/ml, T-stage <= T2a and Gleason score $\leq$ 6), a radial margin of 2mm will be added around the prostate to create the planning target volume. The radial margin will be increased to 5 mm posterolaterally for the "intermediate prognosis" and positive perineural invasion cases, to account for their increased risk and potential radial distance of extracapsular extension from the prostate, which typically occurs along the neurovascular bundle.[12] Proximal seminal vesicle coverage will be added for intermediate risk patients or those with prostate base involvement as detailed in section 6.1.1 of this document. In

all cases, where the outer surface of the rectum abuts the posterior surface of the prostate, the PTV margin in that area will be reduced to zero.

1.12. As most patients with low and intermediate risk prostate cancers survive at least 10 years after intervention, the morbidity associated with therapy for early stage prostate cancer is a crucial factor of patient outcome. Although traditional, physician-reported toxicity data are a useful component for evaluating treatment-related morbidity, it has been shown that patient-report data (collected via standardized questionnaires) are more sensitive than physician reports to the full severity and broad range of therapy effects on patient Health-Related Quality of Life (HRQOL), particularly among men with prostate cancer.[13]

1.13. The feasibility of CyberKnife for treating localized prostate cancer was first described by King at Stanford University. Their phase I protocol delivered 36.25Gy in 5 fractions of 7.25Gy. In a recent report 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/m[14].

1.14. Another potential benefit of CyberKnife radiosurgery relative to HDR brachytherapy is better preservation of potency, even if the radiation distribution is essentially identical between these modalities. This is so because needle trauma has been identified as a potentially significant contributory factor to erectile dysfunction with brachytherapy, including HDR-based monotherapy technique, presumably due to direct physical injury to the neurovascular bundle and/or bulb of the penis, particularly when greater than 13 needle insertions are performed.[15] By comparison, CyberKnife radiosurgery is noninvasive, and so removes this particular erectile dysfunction risk factor.

1.15. To confirm our hypothesis that CyberKnife radiosurgery may be made to resemble a "noninvasive HDR dosimetry delivery system," in addition to simply creating equivalent dosimetry, it is necessary to show clinical equivalence both in terms of efficacy and toxicity.

Table 1. 5-Year bDFS Outcomes for HDR-Monotherapy for Prostate Cancer

HDR Details	Institution	# pts	Medianf/u yrs	Phoenix	ASTRO
6–7.25 Gy x 6	CA Endocurie[18]	117	3.3		97%
9.5 Gy x 4	Beaumont[19]	95	4.2		98%
7.5 Gy x 6	Texas Tech[20]	145	5		90%
6.5 Gy x 6	Gamma West – Fav. (SLC)[21]	209	1.2	96%*	99%*
	Gamma West – Int. [21]	119	1.2	89%*	89%*
6 Gy x 8-9	Osaka (Japan)[22]	111	2.25		70%†
	Totals	**796**	**2.4**		**90%**

*3 year result; Projecting constant failure rate in this series to 5 years yields 98% and 82% ASTRO-definition PSA DFS for favorable and intermediate risk cases, respectively. †Predominantly unfavorable prognosis cases in this series; 5 year local control is 97%.

Based on the data provided in the reports summarized above, and adding a PSA DFS degradation factor to the Gamma West series to compensate for their short median follow-up, the average calculated 5 year HDR monotherapy ASTRO-based PSA DFS is 98% for favorable prognosis, 82% for intermediate prognosis and 59% for unfavorable prognosis cases. There are too few Phoenix-based PSA DFS results to project a meaningful Phoenix-based HDR monotherapy PSA DFS efficacy result.

It is anticipated that the case mix in this study will be approximately 70% low risk/ 30% intermediate prognosis cases, leading to a predicted CyberKnife monotherapy 94% 5 year PSA DFS rate, with a potential range of 82% (0% favorable or low risk prognosis cases accrued) to 98% (100% favorable cases accrued). If the protocol case mix deviates from these percentages, then the protocol DFS rate required to successfully test the primary efficacy hypothesis detailed in Section **2.0** may need to be adjusted accordingly.

Table 2. Toxicity review for HDR-Monotherapy for Prostate Cancer

				>= Gd 3 toxicity		
HDR Details	Institution	# pts	Median f/u	Total (%)	GI (%)	GU (%)
6–7.25Gy x 6	CA Endocurie[18]	117	3.3	3	0	3
9.5Gy x 4	Beaumont[19]	95	4.2	8	0	8
7.5Gy x 6	Texas Tech[20]	145	5	5 – 8*	1	4 – 7*
6.5Gy x 6	Gamma West (SLC)[21]	328	1.2	1	0	1
6Gy x 8-9	Osaka (Japan)[22]	111	2.25	7	1	6
	Totals	**796**	**2.4**	**6**	**0 -1**	**5**

*3% acute and 4% chronic grade 3 GU toxicity – It is unclear to what degree acute and chronic grade 3 GU toxicity populations overlap in this study.

Due to short median follow-up, the incidence of >= grade 3 late toxicity is likely underestimated. We project that the incidence of late toxicity will increase by approximately 50% when all data reach 5 years maturity, yielding a projected cumulative 5 year HDR monotherapy grade 3 toxicity incidence of 9% (7-8% GU; 1-2% GI).In this study, biochemical disease-free survival (ASTRO and Phoenix definition), freedom from local recurrence, freedom from distant relapse, clinical disease-free survival, disease-specific survival and overall survival will be recorded. The incidence of grade 3 or higher toxicity and the effect of CyberKnife® radiosurgery on bladder, bowel, and sexual function will be followed and monitored using standardized, patient self-administered questionnaires[16] and compared with results published in peer-reviewed literature for other prostate cancer therapeutic modalities.[17]

2. OBJECTIVES

PRIMARY OBJECTIVES: The primary study goal is to document the efficacy of the CyberKnife procedure, where efficacy is defined by biochemical Disease-Free Survival (bDFS), using Phoenix and ASTRO definitions, at 5 years. This will be accomplished through testing the primary efficacy hypotheses detailed in Sections **1.1.5 and 11.2.** Additionally, descriptive statistics will be provided comparing the CyberKnife SRS bDFS rate to published HDR monotherapy bDFS rates reported in the literature. A second primary study goal is to accurately measure the rates of acute and late grade 3-5 gastrointestinal and genitourinary toxicity observed during the five years following CyberKnife SRS for prostate cancer.

SECONDARY OBJECTIVES: to measure the following in the study population: Rates of local failure, distant failure, clinical 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. 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. PRETREATMENT EVALUATION

4.1. Complete history and physical exam
4.2. DRE findings
4.3. Assessment of performance status
4.4. Histological evaluation of prostate biopsy with assignment of Gleason score
4.5. Evaluation of the pelvic lymph nodes with CT or MRI is optional
4.6. Serum PSA. Laboratory evaluation must be done within 90 days prior to registration, or <60 days prior to hormone therapy, and 30 or 90 days after discontinuing finasteride or dutasteride, respectively.
4.7. CBC, platelets, serum BUN, creatinine and testosterone; may be drawn after registration
4.8. Transrectal ultrasound volume study of the prostate or a digital rectal exam (DRE) will be performed prior to enrollment to verify the prostate volume. The prostate volume may be obtained by step section summated measurements at 5 mm intervals through the entire gland (stepping method) or the by the length-width-height method. An MRI-based prostate volume measurement will also be acceptable (specify which modality).
    4.8.1. Measurement from CT or ultrasound 6 months prior to registration, or 14 days prior to registration if hormone therapy given; if patient had taken finasteride or dutasteride, volume determined >30 or >90 days (respectively) after discontinuation.
4.9. Patient should be able to complete questionnaires (see Appendix VI), baseline questionnaires may be completed before or after enrollment, but before treatment)
    4.9.1. SF-12 questionnaire
    4.9.2. AUA questionnaire
    4.9.3. EPIC-26 questionnaire
    4.9.4. SHIM questionnaire
    4.9.5. Utilization of Sexual Medications/Devices questionnaire

5. PATIENT SELECTION & ELIGIBILITY

5.1. Patient must be 18 years of age.
5.2. Histologically proven prostate adenocarcinoma

5.2.1. Gleason score 2-7 (reviewed by reference lab) if initial pathology differs from that of reference lab, reference lab's interpretation will be used for eligibility and risk group assignment

5.2.2. Biopsy within one year of date of registration

5.3. Clinical stage T1b-T2b, N0-Nx, M0-Mx (AJCC 6th Edition)

5.3.1. T-stage and N-stage determined by physical exam and available imaging studies (ultrasound, CT, and/or MRI; see section 4.5)

5.3.2. M-stage determined by physical exam, CT or MRI. Bone scan not required unless clinical findings suggest possible osseous metastases.

5.4. PSA 20 ng/ml (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)

5.5. Patients belonging in one of the following risk groups:

5.5.1. Low: CS T1b-T2a and Gleason 2-6 and PSA 10, *or*

5.5.2. 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

5.6. Prostate volume measurement:

5.6.1. Determined using: volume = /6 x length x height x width

5.6.2. Measurement from CT or ultrasound 6 months prior to registration or 14 days prior to registration if hormone therapy given; if patient had taken finasteride or dutasteride, volume determined >30 or >90 days (respectively) after discontinuation.

5.7. ECOG performance status 0-1

5.8. No prior prostatectomy or cryotherapy of the prostate

5.9. No prior radiotherapy to the prostate or lower pelvis

5.10. No implanted hardware or other material that would prohibit appropriate treatment planning or treatment delivery, in the investigator's opinion.

5.11. No chemotherapy for a malignancy in the last 5 years.

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

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

5.14. Completion of patient questionnaires in section 4.7.

5.15. Consent signed.

6. REGISTRATION PROCEDURES

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. PHYSICS QUALITY ASSURANCE shall at a minimum include:

6.1.1. 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),.

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

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

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

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

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

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

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

6.1.3.1.3. 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.

6.1.3.1.4. 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.

6.1.3.1.5. 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.

6.1.4. 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. 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 (12 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. 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. A minimum of three 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 2 cm or more. Fiducials will be placed as an outpatient procedure. Local anesthestic injection, oral or intravenous sedating medication, oral or intravenous pain medication and prophylactic antibiotics may be given at the discretion of the investigator to maximize the safety and comfort of fiducial placement. 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 >= 7 days after fiducial placement. Alpha Cradle or a similar immobilization device will be used as needed.

8.2.2. CT scans will be taken for treatment planning. CT slices will be 1 – 1.5mm, with 250-512 slices taken centered at the prostate. The imaging sets will be downloaded to the CyberKnife treatment planning system to develop the radiosurgery treatment plan.

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

8.2.4. URETHRAL IDENTIFICATION:

8.2.4.1. The planning CT and MRI scans will be done with a Foley catheter in place to define the course of the urethra through the CTV. To improve comfort and minimize inconvenience to the patient, if possible, CT and MRI planning studies will be done consecutively. The smallest possible Foley catheter will be used.

8.2.5. 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. Any beams entering through a hip prosthesis on their way to the planning target volume 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. A priority will be placed on reducing overall treatment time, number of non-zero beams and total monitor units without compromising the dosimetric limits listed in section 8.3.4. All plans are expected to require no more than 2 hours per treatment, no more than 300 non-zero beams and no more than 95,000 monitor units for all fractions.

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 review the treatment plan with the PI and Physics Chair, either remotely through a webcast or similar technique or via overnight delivery of documents to the PI site. The treatment planning data includes the fused primary and secondary imaging studies, contour sets and isodose distributions/DVHs, as well as the pre-treatment planning preparation form, CyberKnife treatment planning form and treatment plan QA form. If the treatment plan data are sent via overnight mail, 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.

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

8.3.2.4. The TREATMENT PLANS of up to the first THREE protocol patients for all participating radiation oncologists, urologists, and physicists may be reviewed, at the discretion of the Principal Investigator and Physics Chair. 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.

8.3.2.4.1. 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. CTV: The Clinical Treatment Volume (CTV)

8.3.3.1.1. LOW-RISK PATIENTS: (CS T1b-T2a, PSA 10, Gleason score 6): The CTV is the pre-registered MRI defined prostate volume, unless MRI-based imaging is medically contraindicated or judged inaccurate by the investigator (see

section 8.3.3.1.2.), in which case the CT may be used to define the CTV. Additionally, at the discretion of the investigator, some or all of the adjacent seminal vesicle volume may be included in the CTV for any of the following reasons: prostate base involvement by any criteria, perineural invasion, or equivocal MRI evidence of seminal vesicle invasion in a patient with no other clinical or pathological evidence for seminal vesicle invasion. In the event that the planning MRI reveals evidence for direct extracapsular invasion (Stage T3a) or seminal vesicle invasion (Stage T3b) that the investigator believes to be a true positive result, the patient will be withdrawn from the protocol and treated by an alternate method off protocol.

8.3.3.1.2. INTERMEDIATE RISK PATIENTS: (PSA > 10, Gleason = 7, or CS T2b) In addition to the above, the CTV will also include not less than 1.0 cm of seminal vesicle tissue volume adjacent to the prostate volume. MRI visible fiducials, if available, are encouraged for optimal prostate volume co-registration. If MRI and CT planning is done, and image co-registration is accurate within 2 mm in the opinion of the investigator, the MRI will be used as the CTV reference imaging modality. If CT and MRI are both done for planning purposes, but in the opinion of the investigator the co-registration of these modalities is not accurate within 2 mm (The most common cause of this will likely be differing degrees of rectal contents between the studies), CT will be used as the CTV reference imaging modality. The investigator will also have the discretion to repeat the planning MRI or CT. The investigator will specify whether CT or MRI is the CTV defining modality. In the event that the planning MRI reveals evidence for direct extracapsular invasion (Stage T3a) or seminal vesicle invasion (Stage T3b) that the investigator believes to be a true positive result, the patient will be withdrawn from the protocol and treated by an alternate method off protocol.

8.3.3.2.PTV: The prescription dose shall be delivered to the Planning Tumor Volume (PTV).

8.3.3.2.1. LOW RISK PATIENTS (PSA < 10 ng/ml, T2a, Gleason Score 6): The PTV is an enlargement of the CTV. The CTV should be expanded to include a 2 mm margin at the proximal, distal, anterior, lateral and posterior aspects of the CTV. Posteriorly, where the CTV abuts the rectum, there will be no margin.

8.3.3.2.2. INTERMEDIATE RISK PATIENTS (PSA 10.1 – 20 ng/ml or Gleason Score 7 or T2b): The PTV should be expanded to include a 2mm margin at the proximal, distal, anterior, lateral and posterior aspects of the CTV. A posterior-lateral margin expansion of 5 mm will be added on the side of the positive biopsy and on the side of palpable tumor. In other words, an intermediate-risk patient will have a unilateral or bilateral CTV PTV posterior-lateral margin expansion of 5 mm. If the side of the positive biopsy is unknown, or if it conflicts with the clinical T-stage findings, the posterior-lateral margin expansion of 5 mm will be done bilaterally. Posteriorly, where the CTV abuts the rectum, there will be no margin.

8.3.3.2.3. PERINEURAL INVASION: Regardless of prognostic subset, a posterior-lateral margin expansion of 5 mm will be added on the side of the positive biopsy. If the side of the positive biopsy is unknown, or if it conflicts with the clinical T-stage findings, the posterior-lateral margin expansion of 5 mm will be done bilaterally. Posteriorly, where the CTV abuts the rectum, there will be no margin.

8.3.3.3. 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 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.

8.3.3.3.1. RECTUM: defined as the visible outer rectal wall, extending from 1.5 cm superior to 1.5 cm inferior to PTV.

8.3.3.3.2. RECTAL MUCOSA: Defined as a 3.0 mm contraction of the rectum volume.

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

8.3.3.3.4. URETHRA: To be defined by Foley catheter on planning CT. Approval by the Urologist or Radiation Oncologist is required.

8.3.3.3.5. PENILE BULB: Will be defined only if image co-registered MRI is used in the planning process. The penile bulb is defined as the portion of the bulbous spongiosum that lies inferior to the urogenital diaphragm.

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

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

8.3.3.3.8. TESTES, bilateral shall be contoured.

8.3.4. DOSE SPECIFICATIONS: All specified doses are for the entire treatment course. All volume percentages are rounded to the nearest tenth of a percent for consistency, i.e. a volume of 0.02% shall be recorded as 0.0%.

8.3.4.1. The **PRESCRIPTION DOSE** of **38 Gy** delivered in 4 fractions of 9.5 Gy per fraction will be delivered in 7 days, with > 95% of the PTV encompassed within the prescription isodose volume.

8.3.4.2. **RECTUM OUTER WALL**:

8.3.4.2.1. Defined as the visible outer rectal wall, extending from 1.5cm. superior to 1.5cm inferior to PTV. Maximum dose (D_{max}): 100% of prescribed (38Gy)

8.3.4.2.2. Minor variation: 100.1 – 110% of the prescribed dose (41.8 Gy).

8.3.4.2.3. Major variation: > 41.8 Gy

8.3.4.3. **RECTAL MUCOSA:**

8.3.4.3.1. Defined as a 3.0 mm contraction of the Rectum outer wall volume. Maximum dose (D_{max}): 75% of prescribed (28.5Gy)

8.3.4.3.2. Minor variation: Dmax > 75 – 90% of prescribed dose (34.2 Gy)

8.3.4.3.3. Major variation: Dmax > 34.2 Gy

8.3.4.4. **BLADDER**:

8.3.4.4.1. Dmax: 120% of prescribed dose. Highest 10% (D_{10}): 110% of prescribed dose.

8.3.4.5. **URETHRA**: *To be defined by Foley catheter on planning CT*

8.3.4.5.1. Maximum dose: 120% of prescribed dose; Highest 10% (D_{10}): ≤110% of prescribed dose; Highest 50% (D_{50}): ≤ 105% of prescribed dose

8.3.4.6. SIGMOID COLON AND OTHER BOWEL:

8.3.4.6.1. Sigmoid colon outer wall and other bowel outer wall within 2 cm of PTV: Dmax < 75% of prescribed (28.5Gy)

8.3.4.6.2. Minor variation: Dmax > 75 – 90% of prescribed dose (34.2 Gy)

8.3.4.6.3. Major variation: Dmax > 34.2 Gy

8.3.4.7. **NEUROVASCULAR BUNDLE**: Urologist or radiation oncologist contour approval required. D_{90}, D_{50}, D_{10}, D_{max}, V_{100} and V_{50} will be carried for possible dosimetry-morbidity correlation but no specific dosimetry constraint will be applied – neurovascular bundle anatomy will be defined only if image co-registered MRI is used in the planning process. If it is the opinion of the urologist that the neurovascular bundle is not well visualized on MRI, this will be indicated on the reporting CRFs and the neurovascular bundle dosimetry parameters will not be reported for that patient.

8.3.4.8. **PENILE BULB**: Urologist or radiation oncologist contour approval required. D_{90}, D_{50}, D_{10}, D_{max}, V_{100} and V_{50} will be carried for possible dosimetry-morbidity correlation but no specific dosimetry constraint will be applied.

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

8.3.4.10. **CONFORMALITY INDEX FOR NORMAL TISSUES**: The ratio of the prescription isodose volume to the PTV will be $\geq$1.0 and $\leq$1.5. Minor variation: $\leq$ 0.99 or $\geq$1.51 – 2.0

8.3.4.11. **DOSE INHOMOGENEITY FOR NORMAL TISSUES:** The PTV volume receiving at least 150% of prescription dose (57 Gy) will be > 1%, without a specific maximum limitation, provided other normal tissue dosimetry constraints are met. This translates to a prescription isodose line that does not exceed 66%. More typically, it is expected that the prescription isodose line will be in the range of 50-59% for patients in this protocol.

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 38Gy shall be given in 4 fractions using the CyberKnife.

8.4.2. Bowel/bladder preparation:

8.4.2.1. The rectum will be emptied of its contents by use of one or more Fleets enemas prior to the planning CT and MRI scans.

8.4.2.2. There will be no fluid intake by the patient within 4 hours prior to a planning study. If the patient takes a diuretic, that medication will not be taken that day until after the planning study(s) have been completed. The bladder will be drained completely through the use of a Foley catheter and then refilled with 100cc of sterile water prior to the planning CT and prior to the planning MRI scans. If CT and MRI scans are done consecutively, the bladder will be drained between these studies and refilled with 100 cc of sterile water immediately prior to the second study.

8.4.2.3. The planning CT and MRI scans will be done with a Foley catheter in place to define the course of the urethra through the CTV. To improve comfort and minimize inconvenience to the patient, if possible, the CT and MRI planning studies will be done consecutively.

8.4.3. Treatment should be completed within 7 days.

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. Target movement is expected to require imaging every 1-3 nodes, per the discretion of the attending physician, and in no situation should imaging occur less frequently than every 5 nodes. 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 1-3, 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 fewer 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 fourth 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 fewer 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. PATIENT ASSESSMENTS AND TOXICITY

Assessment	Pre-entry	On tx day 4	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									
Testosterone	X				X	X	X	X	X	
CBC, platelets	X									
BUN, creatinine	X									
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 year 5
* . 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 baseline and with 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.

9.1.7. Axial Imaging (CT or MRI) of the abdomen and pelvis 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[1].

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[2],[3],[4] have suggested the "nadir+2" definition is a more sensitive and specific definition of biochemical failure. Indeed, a recent expert panel met in Phoenix[5] 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. DATA COLLECTION

See appendix IV for Case Report Forms & patient questionnaires.

11. STATISTICAL CONSIDERATIONS

11.1. *OVERVIEW: The study's primary goals are to determine CyberKnife monotherapy efficacy and to evaluate the incidence of grade 3 or higher toxicity as stated in Section 2.0. Per RTOG/ECOG, acute toxicity will be defined as occurring within 90 days from completion of treatment. Late toxicity will be defined as occurring more than 90 days from completion of treatment. It is graded based upon Common Terminology Criteria for Adverse Events (CTCAE), v3.0., and RTOG/ECOG definitions (see appendix 5).*

11.2. *INTERIM ANALYSIS: An interim analysis was performed. The results below are based on an overall one-sided alpha of 0.05 and using the O'Brien-Fleming spendingfunction, and were calculated using nTerim (Statistical Solutions Ltd). The interim analysis is based on 4,512 months of follow-up, out of a total possible of 15,600 months (60 months* 260 Subjects). Hence the interim analysis is performed with approximately 29% of the total data possible for the final analysis. The final alpha must now be 0.04999. If the Z-score at the interim analysis exceeds 3.45701, then the trial could be stopped. If th Z-score doesn't exceed 3.45701, then the trial will continue through the primary assessment period of 5 years, where the P-value for success is at most .0499991.*

	Look 1	Final Analysis- Look 2
proportion of information	0.29	1.0
Z-Score Boudary	3.45701	1.64575
Nominal Alpha	0.00027	0.049991
Incremental Alpha	0.00027	0.05

11.3. SAMPLE SIZE:

Primary Efficacy Endpoint and Hypothesis: 5-Year Biochemical Disease-Free Survival(bDFS) Among CyberKnife Treated Patients

bDFS is the primary efficacy outcome for the study. The proportion of patients disease-free within 5 years of the initial procedure is the rate of interest. The null and alternative hypotheses are as follows:

$$H_0 : \pi < 90\%$$
$$H_1 : \pi \geq 90\%$$

π ▪ ▪ is the expected proportion of CyberKnife treated patients bDFS at 5 years. The CyberKnife procedure is considered to be effective if this study's result verifies that the lower limit of the one-sided 95% confidence interval for π is not below 90%.

Statistical Sample Size Derivation

Primary Efficacy Objective

We calculate the CyberKnife Treatment Group sample size, N, required to test the null hypothesis that the rate in the Treatment Group is less than 90%, against the one-sided alternative hypothesis that the rate is at least 90%..

We chose N large enough to test the null hypothesis against the alternative hypothesis with power equal to 80% at the one-sided 5% significance level.

Let Z_u denote the upper u-th percentile of the standard normal distribution. Hence $Z_{.05}$ = 1.645 corresponding to the one-sided 5% level of significance and $Z_{.20}$ = 0.84 corresponds to 80% power. Then the sample size is determined by Formula 1:

$$N = \frac{\left[z_\beta \sqrt{\pi_1(1-\pi_1)} + z_\alpha \sqrt{\pi_0(1-\pi_0)}\right]^2}{[\pi_1 - \pi_0]^2}, \text{ where}$$

π_1 is the expected proportion of CyberKnife treated patients bDFS at 5 years if the alternative hypothesis is true; the bDFS rate is then expected to equal or exceed 0.94. For purposes of sample size estimation, we require 80% power if $\pi_1 \geq 0.945$. π_0 is the expected lower limit of the 95% confidence interval for π and is set equal to 0.90. Then **N= 232**. Allowing 8% sample size degradation for lost to follow-up, the sample size must be increased to 232/.92 = **253 subjects**.

Primary Safety Objective

The primary safety objective is to establish with 95% confidence that the percentage of CyberKnife treated patients experiencing ≥ Grade 3 toxicity is not more than 5% higher than the approximately 9% 5-year rate extrapolated from Table 2, Section 1.15.

With N=232 CyberKnife treated subjects, if the observed ≥ Grade 3 toxicity rate equals 9%, then with 95% confidence the "true" rate ≤ 12.6%. Since the difference between 12.6% and 9% is less than 5%, the sample size of 232 subjects is more than large enough to meet the primary safety objective.

11.3.1 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 patients per study site per month. Expectations of 5 treating study sites assumes an accrual period of approximately 29 months total.

11.4STATISTICAL METHODS

11.4.1 PRIMARY OBJECTIVES

1. 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

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

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 90%.

2. Safety

The upper limit of a one-sided 95% confidence interval for the expected proportion of patients experiencing ≥ Grade 3 gastrointestinal and genitourinary toxicity is estimated by U, where

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

Here "p" is the observed proportion of patients experiencing ≥ Grade 3 gastrointestinal or genitourinary toxicity . The CyberKnife intervention will be considered to be safe if this study's result verifies that U is not more than 5% higher than the literature rate of 9%..

11.4.2. SECONDARY OBJECTIVES

1. Local and Distant Tumor Control

As defined in Section 9.4, the failure to achieve local and distant tumor control will be documented for each patient. These rates will be summarized and descriptive statistics (standard deviations, confidence intervals) will calculated.

2. Quality of Life Assessments

The SF-12 total score, AUA score, EPIC-26 total score and the EPIC-sexual domain sub score 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 behavior, 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 straight line 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. We hypothesize that the slope of a fitted line will not be significantly less than zero; that is, QoL will be maintained throughout the assessment period.

3. 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.

4. Survival

"Survival" is variously defined in Sections **1.1.5, 2.0**. 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.

5.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 with other outcomes (e.g. experience level of team member, patient enrollment, treatment planning/delivery QA outcomes, toxicity, bDFS and QOL outcomes) and correlations determined.

12. 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 the trial (through 25%,50% and 75% enrollment of 232 patients) should an excessive number of patients experience ≥ Grade 3 gastrointestinal and genitourinary toxicity. This depends upon the number so far enrolled and a criterion that identifies too high a rate. The stopping criteria differ after 58, 116 and 174 patients have been enrolled .Consistent with Section **1.1.5, 2.0** we define an observed ≥ Grade 3 gastrointestinal and genitourinary toxicity rate of over 14% as too high. The statistical requirement is that for up to "m" patients enrolled, the number of observed cases with ≥ Grade 3 toxicity must be few enough so that there is a 95% chance that the "true" rate does not exceed 14%.

≥ *Grade 3 toxicity* **Stopping Criteria**	
Participants to be enrolled: 253	**Stop study if the number of patients with grade 3-5 toxicity equals or exceeds:** **Enrollment 1-58: 4 Events** **Enrollment 1-116: 10 Events** **Enrollment 1-178: 17 Events**

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. SOURCE OF SUBJECTS AND RECRUITMENT PROCEDURES

13.1 Source of Subjects:

13.1.1. 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:

13.1.2. 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:

13.1.3. 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. 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:

14.1.1. 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.

14.1.2. 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:

14.1.3. 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 Imodium will be prescribed if necessary.

Temporary urinary frequency, irritation, or reduced stream (Likely): see notes 1,2,3. Alpha blocker, antispasmodic, anti-inflammatory or other appropriate symptomatic medicines 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 Imodium, may be required.

Rectal bleeding (rare, but serious): see notes 1,2,3. Hydrocortisone suppositories or enemas may be required; blood transfusions, , photocoagulation, topical chemical coagulation ,hyperbaric oxygen treatments. In extremely rare cases, colostomy may be necessary.

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

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

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

Permanent 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. In extremely rare cases major surgery such as urinary diversion could 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 (implantable penile prosthesis).

Reduction in ejaculate volume (likely), which could reduce fertility: This condition is highly likely following treatment 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 commonly used externally generated radiation methods. This minimizes radiation exposure to surrounding normal structures. The design characteristics of the CyberKnife thus intrinsically minimize 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.

14.2. 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.

14.4 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.

14.5 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 outpatient 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

14.6 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, facility-based 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

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 ten (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 253 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 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.

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 four separate CyberKnife treatments usually delivered over 4 consecutive week days (maximum 7 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 4-7 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. 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 and testosterone levels. This is the standard procedure for follow-up visits and will occur every 6 months thereafter for 5 years and yearly through year 10. At some of 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 temporary 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 INSTITUION 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 5 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.[6] 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		

Do Not Mark in This Space

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

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

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

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

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

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

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

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

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

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

Do Not Mark in This Space

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

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

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

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

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

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Hot flashes	0	1	2	3	4	74/
b. Breast tenderness/enlargement	0	1	2	3	4	75/
c. Feeling depressed	0	1	2	3	4	77/
d. Lack of energy	0	1	2	3	4	78/
e. Change in body weight	0	1	2	3	4	79/

THANK YOU VERY MUCH!!

SEXUAL HEALTH INVENTORY FOR MEN (SHIM)

PATIENT NAME:_____ **TODAY'S DATE:**_____

PATIENT INSTRUCTIONS

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

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

OVER THE PAST 6 MONTHS:

1. How do you rate your confidence that you could get and keep an erection?		Very Low	Low	Moderate	High	Very High
		1	**2**	**3**	**4**	**5**
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No Sexual Activity	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	**1**	**2**	**3**	**4**	**5**
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	**1**	**2**	**3**	**4**	**5**
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did Not Attempt Intercourse	Extremely Difficult	Very Difficult	Difficult	Slightly Difficult	Not Difficult
	0	**1**	**2**	**3**	**4**	**5**
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	**1**	**2**	**3**	**4**	**5**

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

The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints:
1-7 Severe ED 8-11 Moderate ED 12-16 Mild to Moderate ED 17-21 Mild ED

UTILIZATION OF SEXUAL MEDICATIONS/DEVICES

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

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

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

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

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

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

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

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

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

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

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

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

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

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