PROSPECTIVE EVALUATION OF CYBERKNIFE® AS MONOTHERAPY OR BOOST STEREOTACTIC BODY RADIOTHERAPY FOR INTERMEDIATE OR HIGH RISK LOCALIZED PROSTATE CANCER: AN OBSERVATIONAL STUDY

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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

_____ _____

Signature, Principal Investigator Date

_____

Printed Name, Principal Investigator

CONTACT INFORMATION

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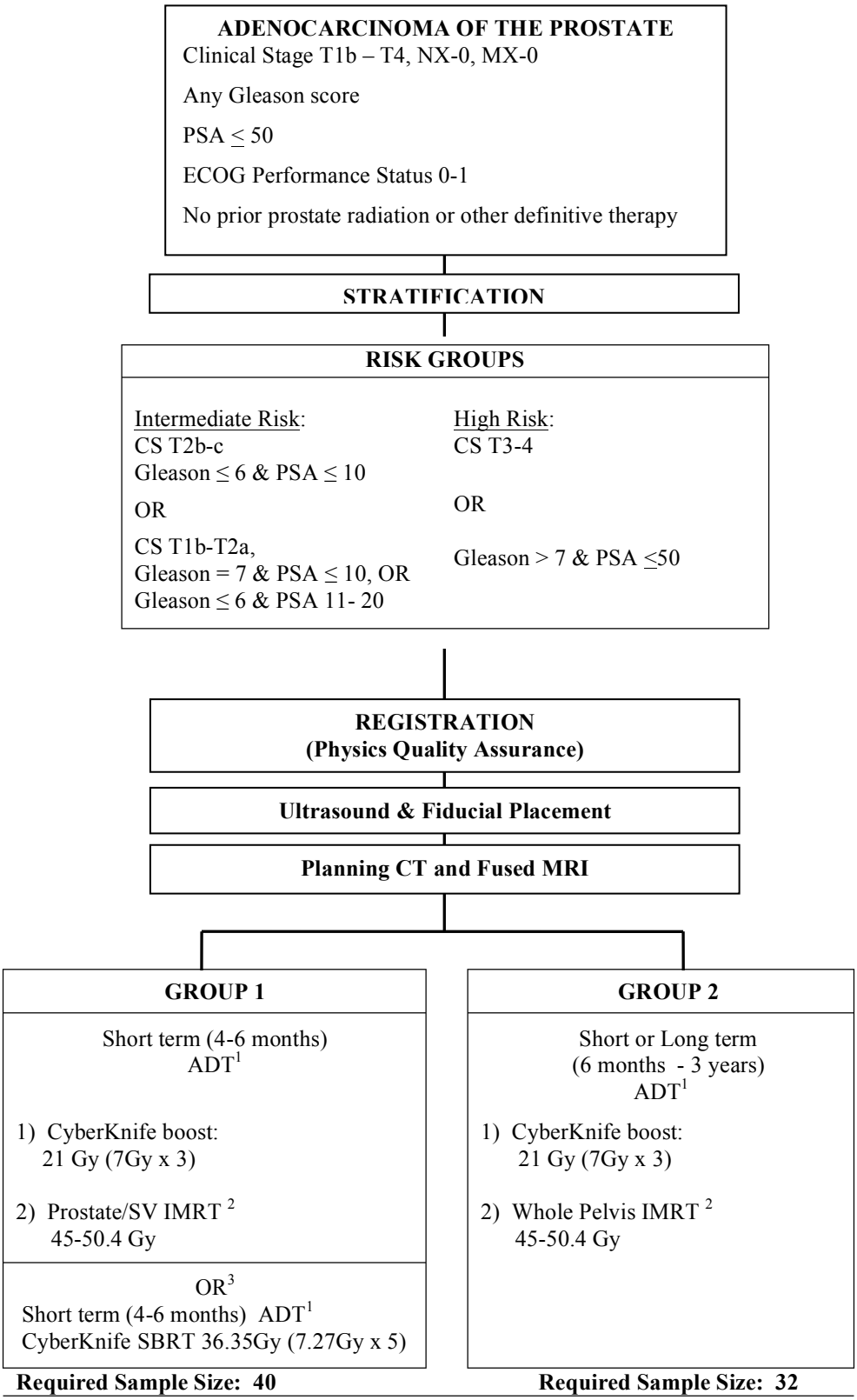
SCHEMA



1) Androgen Deprivation Therapy is strongly recommended
2) Intensity Modulated Radiation Therapy
3) Per investigator decision and patient discussion, with consideration of age, performance status, medical co-morbidities, Gleason score and other disease features (Gleason score 4+3 vs. 3+4). Strong recommendation is made for consideration of combined modality therapy in intermediate risk and certainly "high intermediate" risk disease as defined by Gleason score 4+3 disease, more than 50% positive cores, and/or PSA velocity of more than 2ng/ml in the year preceding tissue diagnosis, given survival benefit of short term ADT per randomized data in intermediate risk disease. CK SBRT monotherapy would typically be appropriate only for low volume GS 3+4 disease with no other adverse features.

ELIGIBILITY CHECKLIST

_____ (Y)	Is there histologically proven prostate adenocarcinoma, biopsy within one year of enrollment?
_____	What is the Gleason Score?
_____ (T1b-4)	What is the clinical T-stage? (AJCC 7th Edition)
_____ (Y)	Is the patient clinical Nx or N0, and Mx or M0?
_____ (0-50)	PSA evaluated 90 days prior to treatment?
_____ (I, H)	Does the patient fall into one of these risk groups (AJCC 6th Edition): - Intermediate: CS T2b-c, Gleason ≤6, PSA ≤ 10, or CS T1b-T2a, and Gleason 7, PSA ≤ 10 ng/ml, or Gleason≤6, PSA 11-20 ng/ml -High: CS T3-4 or Gleason >7 and PSA≤50
_____ (Y)	Is the prostate volume ≤ 100 cc?
_____ (0-1)	What is the ECOG performance status?
_____ (N)	Has the patient undergone prostatectomy or cryotherapy of the prostate?
_____ (N)	Has the patient had radiotherapy to the prostate or lower pelvis?
_____ (N)	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/a,Y)	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, , 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.[2,3,4] 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 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.[5,6] 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.[7] 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.[8] These values of α/β are comparable to, if not lower, than late-responding normal tissues.[8] 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.[8, 9]

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 experience, which suggests efficacy and safety, with a long follow-up. Hypofractionation with brachytherapy using high-dose-rate (HDR)-brachytherapy has demonstrated excellent efficacy and toxicity profiles as both monotherapy and post-EBRT-boost for localized PCa[10-21]. The University of California San Francisco (UCSF) has recently reported its HDR-brachytherapy-boost experience in mostly intermediate to high risk disease, achieving five-year bNED rates of 93% with minimal toxicity. A randomized phase III trial has reported superior bNED rates with HDR-brachytherapy-boost over EBRT alone, and a recent systematic review of the world literature has concluded that the combination of EBRT and HDR-brachytherapy results in superior bNED and overall survival (OS) as compared to EBRT alone or EBRT plus permanent prostate seed implant (PPI)-boost. Others have also reported equivalent disease control and improved toxicity and quality of life (QOL) measures with HDR brachy-monotherapy as compared to PPI monotherapy.

1.9. 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.

1.10. 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.

1.11. 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.[25]

1.12. 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[25]. Similar excellent results have also been reported by Jabbari et al. from the University of California for both CyberKnife® monotherapy and boost post whole pelvic radiation therapy[3], and King and Freedman using the original Stanford fractionation of five fractions when used as monotherapy[4].

1.13. 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.[27] By comparison, CyberKnife® radiosurgery is noninvasive, and so removes this particular erectile dysfunction risk factor.

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

HDR Details	Institution	#pts	Median f/u yrs	Phoenix	ASTRO
6–7.25 Gy x 6	CA Endocurie[30]	117	3.3		97%
9.5 Gy x 4	Beaumont[31]	95	4.2		98%
7.5 Gy x 6	Texas Tech[32]	145	5		90%
6.5 Gy x 6	Gamma West – Fav. (SLC)[33]	209	1.2	96%*	99%*
	Gamma West – Int. [33]	119	1.2	89%*	89%*
6 Gy x 8-9	Osaka (Japan)[34]	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 75% intermediate, and 25% high risk prognosis cases, leading to a predicted 5 year PSA DFS rate of 85%-90% for intermediate risk patients, and 75%-80% for high risk patients based on HDR brachytherapy boost trial. **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 Endocurie30	117	3.3	3	0	3
9.5Gy x 4	Beaumont[31]	95	4.2	8	0	8
7.5Gy x 6	Texas Tech[32]	145	5	5 – 8*	1	4 – 7*
6.5Gy x 6	Gamma West (SLC)[33]	328	1.2	1	0	1
6Gy x 8-9	Osaka (Japan)[34]	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.

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. 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[28] and compared with results published in peer-reviewed literature for other prostate cancer therapeutic modalities.[29]

2. OBJECTIVES

PRIMARY OBJECTIVES:

- 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.
- Compare the CyberKnife® Stereotactic Radiosurgery System bDFS rate to published HDR monotherapy bDFS rates reported in the literature.

SECONDARY OBJECTIVES:

- Measure rates of acute and late grade 3-5 gastrointestinal and genitourinary toxicity observed during the five years following CyberKnife® Stereotactic Radiosurgery System for prostate cancer. 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).
- Measure rates of local failure, distant failure, clinical disease-free survival, disease-specific survival, and overall survival
- Examine Quality of Life (QOL) in generic and organ-specific domains

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 from urologist or radiation oncologist
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 treatment
4.7. CBC, platelets, serum BUN and creatinine
4.8. The prostate volume may be obtained by prior transrectal ultrasound. A CT or MRI-based prostate volume measurement will also be acceptable (specify which modality).
4.9. Patient questionnaires (see Appendix VI).

4.9.1. AUA questionnaire
4.9.2. EPIC-26 questionnaire
4.9.3. SHIM 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 2-10 (reviewed by reference lab)
5.2.2. Biopsy within one year of date of registration
5.3. Clinical stage T1b-T4, N0-Nx, M0-Mx (AJCC 7th 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 ≤ 50 ng/ml, CBC, platelets, BUN, creatinine prior to treatment
5.5. Patients belonging in one of the following risk groups:
5.5.1. Intermediate: CS T2b-c and Gleason ≤6 and PSA ≤ 10, or CS T1b-T2b, and Gleason 7 and PSA ≤ 10 ng/ml, or Gleason ≤6 and PSA 11-20 ng/ml
5.5.2. High: CS T3-4, Gleason score >7and PSA≤50
5.6. Prostate volume: ≤ 100 cc
5.6.1. Determined using: volume = π/6 x length x height x width
5.6.2. Measurement from MRI, CT or ultrasound prior to registration.
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. Completion of patient questionnaires in section 4.7.
5.14. Consent signed.

6. REGISTRATION PROCEDURES

6.1. PHYSICS QUALITY ASSURANCE shall at a minimum include:
6.1.1. ABSOLUTE DOSIMETRY: 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: 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: 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 associate. This data is retained in the patient's chart located in the research office. The date of registration may 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 registration.

7. PATHOLOGY

7.1. Pathology procedures will be conducted in accordance with institutional policy.

7.2. Pathology Evaluation: Slides/blocks from the pre-treatment diagnostic prostatic biopsy will be reviewed by signing pathologist 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.

7.3. Central Review: encouraged but not required**.**

8. TREATMENT: CYBERKNIFE® RADIOSURGERY

8.1. Intermediate risk patients will be treated with either: CyberKnife® SBRT boost of 21 Gy (7 Gy X 3) followed by prostate/SV IMRT 45-50.4 Gy (treatment planning and delivery per current standards of care); or CyberKnife® SBRT monotherapy 36.35Gy (7.27Gy x 5). Short term Androgen Deprivation Therapy (4-6 months per standards of care) is strongly recommended for all intermediate risk patients.

High risk patients will be treated with CyberKnife® boost of 21 Gy (7 Gy X 3) followed by whole pelvis IMRT 45-50.4 Gy (treatment planning and delivery per current standards of care). Short or long term ADT (6 months up to 3 years per current standards of care) is strongly recommended for high risk patients.

Standards of care are based on National Comprehensive Cancer Network guidelines. Per investigator decision and patient discussion, the appropriate treatment plan will be determined for each patient based on their risk group outlined by these guidelines. Patient age, performance status, medical co-morbidities, Gleason score and other disease features (Gleason score 4+3 vs. 3+4) will be taken into consideration. Strong recommendation is made for consideration of combined modality therapy for patients with : Gleason score 4+3 disease, more than 50% positive cores, and/or PSA velocity of more than 2ng/ml in the year preceding tissue diagnosis, given survival benefit of short term ADT. CyberKnife® SBRT monotherapy would typically be appropriate only for low volume GS 3+4 disease with no other adverse features.

8.2. FIDUCIAL PLACEMENT: All patients will have 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 is 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 anesthetic 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.

8.3. TREATMENT PLANNING IMAGING:

8.3.1. 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.

8.3.2. 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.

8.3.3. 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.

8.3.4. URETHRAL IDENTIFICATION:

8.3.4.1. The planning CT and MRI scans will be done with a Foley catheter in place to define the natural 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.

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

8.4. CYBERKNIFE® TREATMENT PLANNING:

8.4.1. 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.

8.4.2. QUALITY ASSURANCE

8.4.2.1.BENCHMARK (DRY RUN) CASE REVIEW: 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.

8.4.3. EVALUATED STRUCTURES:

8.4.3.1.CTV: The Clinical Treatment Volume (CTV)

8.4.3.1.1. 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, and/or intermediate or high risk disease.

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

8.4.3.2.1. The PTV is an enlargement of the CTV. The CTV should be expanded to include a 2-5 mm margin at the proximal, distal,

anterior, lateral and generally less in the posterior aspects of the CTV. Posteriorly, where the CTV abuts the rectum, there will be no margin.

8.4.3.3. 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.

8.4.3.3.1. RECTUM: defined as a solid organ (not the wall), extending from 1.5 cm superior to 1.5 cm inferior to PTV.

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

8.4.3.3.3. URETHRA: To be defined on MRI more so than planning CT. Approval by the Radiation Oncologist is required.

8.4.3.3.4. 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.

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

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

8.4.4. 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%.

8.4.4.1. The **PRESCRIPTION DOSE** of 36.35Gy in 5 fractions for montherapy or 21Gy in 3 fractions for boost will be delivered in <10 days, with > 95% of the PTV encompassed within the prescription isodose volume. Maximum PTV dose 200% prescription dose.

8.4.4.2. **RECTUM**:

8.4.4.2.1. Defined as the solid organ, extending from 1.5cm superior to 1.5cm inferior to PTV. Maximum point dose (1cc): 105% of prescription dose; <3cc .>95% prescription dose; D10%<90% prescription dose; D20%<80% prescription dose; D50%<50% prescription dose.
Minor variation: 100.1 – 110% of the prescribed dose
Major variation: > 110% prescribed dose

8.4.4.3. **BLADDER**:

8.4.4.3.1. 1cc<105% prescribed dose; D10%<90% prescribed dose; D50%<50% prescribed dose.

8.4.4.4.**URETHRA**: *To be defined by Foley MRI more so than planning CT*

8.4.4.4.1. 0.03cc<107% prescribed dose.

8.4.4.5.SIGMOID COLON AND OTHER BOWEL:

8.4.4.5.1. Sigmoid colon outer wall and other bowel outer wall within 2 cm of PTV: Dmax < 75% of prescribed

8.4.4.5.2. Minor variation: Dmax > 75 – 90% of prescribed dose; Major variation: Dmax > 90% prescription dose

8.4.4.6.**NEUROVASCULAR BUNDLE**: 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.

8.4.4.7.**PENILE BULB**: 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.<0.03cc>20Gy

8.4.4.8. **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

8.4.4.9.**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.

8.5. CYBERKNIFE® TREATMENT DELIVERY

8.5.1. The prescribed PTV dose shall be given using the CyberKnife®

8.5.2. Bowel/bladder preparation:

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

8.5.2.2.To improve comfort and minimize inconvenience to the patient, if possible, the CT and MRI planning studies will be done consecutively.

8.5.3. Treatment should be completed within 7 days.

8.5.4. 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.

8.5.5. 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.

8.5.6. 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 less 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.

9. PATIENT ASSESSMENTS AND TOXICITY

Assessment	Pre-entry			Follow-up (# of months from last radiation therapy treatment)									
				1	3	6	12	18	24	30	36	48	60
History	X				X	X	X	X	X	X	X	X	X
Physical exam (DRE)	X				X	X	X	X	X	X	X	X	X
ECOG Performance Scale	X				X	X	X	X	X	X	X	X	X
Prostate Biopsy & Gleason score	X												
PSA	X				X	X	X	X	X	X	X	X	X
Prostate volume assessment	X												
CBC, platelets	X												
BUN, creatinine	X												
Toxicity evaluation	X			X	X	X	X	X	X	X	X	X	X
AUA score	X			X	X	X	X	X	X	X	X	X	X
EPIC-26 Questionnaire	X			X	X	X	X	X	X	X	X	X	X
SHIM Questionnaire	X			X	X	X	X	X	X	X	X	X	X

Follow up evaluations may be performed +/- 30 days

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. ASSESSMENTS FOLLOWING TREATMENT: At 1 month following last radiation treatment, patients will be assessed for acute toxicity, and will fill out AUA form, EPIC-26 and SHIM. At month 3, every 6 months from year 1-3 (months 6, 12, 18 and 24, 30 and 36) and at year 4 and 5, AUA, EPIC-26 and SHIM will be administered, and an H&P with DRE and toxicity evaluation will be completed. Examination and studies may be done at outside facility.

9.1.4. Recommended: at the time of biochemical failure, or when the patient develops signs of symptoms suggesting metastatic disease, it is at the physician's discretion to perform a prostate biopsy or imaging studies.

9.2. CRITERIA FOR TOXICITY

9.2.1. ACUTE AND LATE TOXICITY

9.2.2. Side effects will be assessed using the NCI Common Toxicity Criteria version 3.0 (see appendix V).

9.3. QUALITY OF LIFE ASSESSMENTS

9.3.1. 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.

9.3.2. 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.

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

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[ii],[iii],[iv] have suggested the "nadir+2" definition is a more sensitive and specific definition of biochemical failure. Indeed, a recent expert panel met in Phoenix[v] and developed a consensus recommendation using the latter 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 $\geq$ 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. A histologic criterion 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: Survival duration will be measured from the date of study entry to the date of death from any cause

10. DATA COLLECTION

See appendix IV for Case Report Forms & patient questionnaires.

11. STATISTICAL CONSIDERATIONS

11.1. DATA ANALYSIS AND SAMPLE SIZE CALCULATION

Response rates with 95% confidence intervals and one-sample Kaplan-Meier analysis will be performed to show 5 year disease free survival and overall survival for patients treated with CyberKnife® SBRT monotherapy and patients treated with whole pelvis IMRT and ADT per current standards of care, followed by CyberKnife® SBRT boost.

In treatment groups, toxicity, 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 will be reported descriptively for the samples. In addition descriptive statistics will be provided comparing the CyberKnife® Stereotactic Radiosurgery System bDFS rate to published HDR monotherapy bDFS rates reported in the literature for each group.

Investigators expect that overall, patients treated with CyberKnife® SBRT monotherapy will have a 5 year PSA DFS rate of 80% ± 0.15 (total width = .30) using a confidence level of 95%, a required sample size of 32 subjects is necessary.

Investigators expect that overall, patients treated with whole pelvis IMRT and ADT per current standards of care, followed by CyberKnife® SBRT boost will have a 5 year PSA DFS rate of 70% ± 0.15 (total width = .30) using a confidence level of 95%, a required sample size of 40 subjects is necessary.

12. RISK TO BENEFIT RATIO

12.1 The determination of entry into the clinical evaluation will be made independent of the decision to treat with stereotactic radiosurgery. The 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.

12.1 Risks:

12.1.1. 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.

12.1.2. 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.

12.1 Risks Associated with External Radiation Therapy:

12.1.3. 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.

Reproductive Risks: No fertility issues pertinent to this patient population

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.

12.2. Risks Associated with Fiducial Placement:

Infection (rare): In the event that a patient experiences infection as a result of fiducial placement, antibiotic treatment will be prescribed.

12.2Minimization 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.

12.3Potential 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

12.4Early 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.

13. COSTS AND PAYMENTS

13.1. 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.

14. Research Study Payments:

There will be no financial reimbursement to the patient for participation in this evaluation.

15. APPENDICES

Appendix I: Sample Patient Consent Form

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, 7TH EDITION, PROSTATE

Primary Tumor, Clinical (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Clinically inapparent tumor not palpable or visible by imaging

- T1a Tumor incidental histologic finding in 5% or less of tissue resected
- T1b Tumor incidental histologic finding in more than 5% of tissue resected
- T1c Tumor identified by needle biopsy *(e.g., because of elevated PSA)*

T2 Tumor confined with prostate*

- T2a Tumor involves less than ½ of one lobe
- T2b Tumors involves greater than ½ of one lobe but < 2 lobes
- T2c Tumor involves both lobes

T3 Tumor extends through prostate capsule**

- T3a Extracapsular extension *(unilateral or bilateral)*
- T3b Tumor involves the seminal vesicle*(s)*

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

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c

**Note: Invasion into the prostatic apex or into *(but not beyond)* the prostatic capsule is not classified as T3, but as T2.

Regional Lymph Nodes (N)

Clinical	NX Regional lymph nodes cannot be assessed
	N0 No regional lymph node metastasis
	N1 Metastasis in regional lymph node or nodes
Pathologic	pNX Regional nodes not sampled
	pN0 No positive regional nodes
	pN1 Metastases in regional node(s)

Distant Metastasis (M)*

MX Presence of distant metastasis cannot be assessed (not evaluated by any modality)

M0 No distant metastasis

M1 Distant metastasis

- M1a Nonregional lymph node(s)
- M1b Bone(s)
- M1c Other site(s) with or without bone disease

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

Appendix IV: Data Collection Documents

Appendix V: NCI Common toxicity criteria/RTOG/EORTC:
Refer to:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

Appendix VI: AUA, EPIC, SHIM Questionnaires

American Urological Association (AUA) symptom index: was developed to help men determine how bothersome their urinary symptoms are and to check the effectiveness of treatment.[vi] 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**

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		

EPIC-SF 6.2002

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

EPIC-SF 6.2002

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:**

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