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

PROTOCOL NUMBER: ACCP002.0

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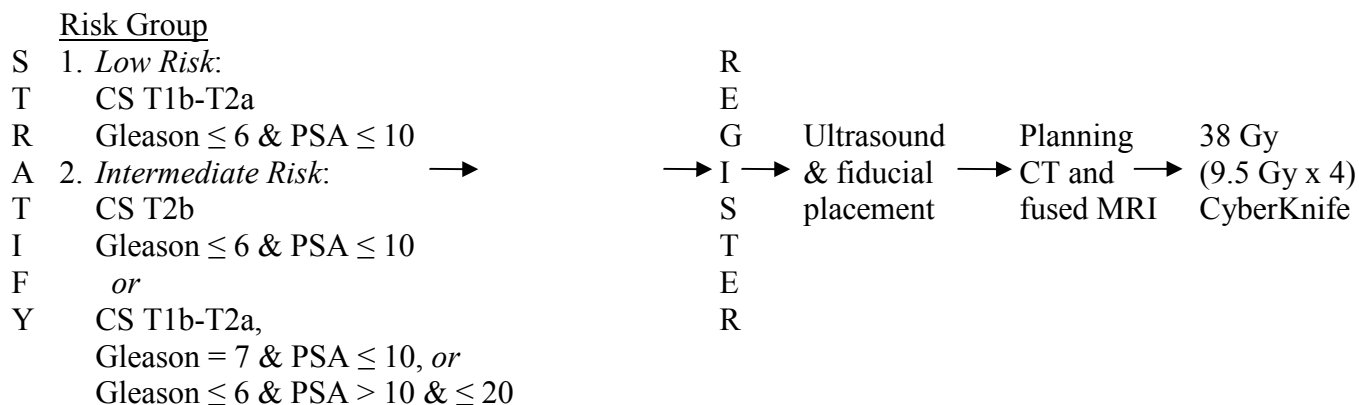
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SCHEMA



PATIENT POPULATION (see section 4.0 for complete eligibility)

Histologically-confirmed, adenocarcinoma of the prostate

Clinical Stage T1b, T1c, T2a, 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 \leq 10
- Intermediate: CS T2b, Gleason 2-6, PSA \leq 10, or
CS T1b-T2b, and Gleason 2-6, PSA \leq 20 ng/ml, or Gleason 7, PSA \leq 10 ng/ml
- _____ (Y) Is the prostate volume \leq 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, 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 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 Tables⁹, 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 ≤ 6 and PSA ≤ 10 ng/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 ≤ 10 ng/ml, T-stage $\leq T2a$ and Gleason score ≤ 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/m¹⁴.
- 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 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). The expected bDFS 5-year rate of CyberKnife monotherapy of 94% is based on a case mix of about 70% favorable / 30% intermediate prognosis cases. 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

HDR Details	Institution	# pts	Median f/u	>= Gd 3 toxicity		
				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 questionnaires¹⁶ 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 Section 1.1.5. The bDFS rate will be compared with published HDR monotherapy bDFS rates to test the hypothesis that they are identical. 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.

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.

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