

Stereotactic Body Radiotherapy Using Cyberknife for Localized Prostate Cancer

Hunjung Kim,^{1,*} Hoonjung Phak,¹ and Woochul Kim¹

¹Department of Radiation Oncology, Inha University Hospital, Inha University of Medicine, Incheon, Korea

*Corresponding author: Hunjung Kim, Department of Radiation Oncology, Inha University Hospital, Inha University of Medicine, Incheon, Korea. Tel: +82-32890-3070, Fax: +82-328903082, E-mail: cancerovercome@gmail.com

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Abstract

Background: Stereotactic body radiation therapy (SBRT) using Cyberknife delivers high-dose fraction of radiation without increasing toxicity.

Objectives: We present the follow-up outcomes and toxicities of patients with localized prostate cancer treated by use of Cyberknife as a monotherapy.

Patients and Methods: This study was based on a retrospective analysis of the 34 patients treated with SBRT using Cyberknife for localized prostate cancer (26.5% low risk, 67.6% intermediate risk, and 5.9% high risk). Total dose of 36.25 Gy in 5 fractions of 7.25Gy were administered without use of androgen deprivation therapy (ADT). The acute and late toxicities were recorded using the radiation therapy oncology group scale. Prostate-specific antigen (PSA) response was monitored.

Results: Thirty-four patients with a median 52 months (range 12 - 71 month) follow-up were analyzed. The biochemical relapse-free survival was 93.3%. PSA fell to a median of 0.39 ng/mL at 4 years and PSA bounce occurred in 28.1% of patients. Acute side effects resolved within 1 - 2 months of treatment completion. There was no grade 3 and 4 late toxicity observed.

Conclusions: In this study, SBRT using Cyberknife without ADT has provided promising outcomes in localized prostate cancer with good PSA response and minimal toxicity. Hypofractionated SBRT using Cyberknife leads to long-term favorable 5-year biochemical relapse-free survival and minimal toxicity in localized prostate cancer as a monotherapy.

Keywords: Prostate Cancer, Stereotactic Body Radiotherapy, Cyberknife

1. Background

Prostate cancer is the most common cancer and the second leading cause of death from cancer among men in the United States (1). As an alternative to surgery, various radiation treatment techniques have been developed. The use of stereotactic body radiation therapy (SBRT) has recently emerged as a technique to deliver hypofractionated radiation therapy to the prostate (2-5). The alpha/beta (α/β) ratio of prostate cancer has been thought to be around 1.5 Gy and lower than the surrounding normal tissue (6, 7). Therefore, the use of a hypofractionated dose scheme should lead to a more advantageous therapeutic ratio (8, 9). Treatment with high dose-rate (HDR) brachytherapy is well established as a hypofractionated radiation therapy (10). Advanced techniques using SBRT allows high doses of radiation to be delivered precisely to the target tissue while sparing the surrounding healthy tissue, thus achieving high biochemical control and low toxicity (2-4). SBRT using Cyberknife (Accuray, Sunnyvale, CA, USA) delivers hypofractionated treatment regimens with using real-time image guidance to account for intrafraction pro-

static motion. Several recent Cyberknife publications report promising clinical efficacy with minimal toxicity (2, 11).

2. Objectives

In this report, we present the follow-up outcomes and toxicities of patients with localized prostate cancer treated by use of Cyberknife as a monotherapy.

3. Patients and Methods

3.1. Patient Characteristics

A prospective protocol-based study for the treatment of localized prostate cancer with CyberKnife robotic radiosurgery system began from March 2008 at Inha university hospital in Incheon. Since then, thirty-four patients have been treated (Table 1). Eligible patients had newly diagnosed, biopsy-proven localized prostate cancer. Exclusion criteria included clinical stage T3, involved lymph nodes or

distant metastases on imaging and/or prior pelvic radiotherapy. The study was approved by the ethical committee for clinical trials of our institution and the retrospective data was prospectively collected in our institutional database.

3.2. SBRT Treatment Planning and Delivery

Four or more gold fiducial markers were implanted transperineally into the prostate. After seven days, patients underwent MR imaging and thin-cut CT scan. Fused CT and MR images were used for the treatment planning. The clinical target volume (CTV) included the prostate and proximal seminal vesicles. The planning target volume (PTV) equaled the CTV expanded 3mm posteriorly and 5 mm in all other dimensions. The prescription dose was 36.25 Gy, delivered in five fractions, was prescribed to the PTV. The prescription dose covered at least 95% of the planning target volume, normalized to the 75 - 85% isodose line (mean homogeneity index of 1.28 [range, 1.24 - 1.43]). The rectal dose-volume goals were < 50% of the rectal volume receiving 50% of the prescribed dose, < 20% receiving 80% of the dose, < 10% receiving 90% dose, and < 5% receiving 100% of the dose. Treatments were given over 5 consecutive days. Androgen deprivation therapy (ADT) was not applied to anyone.

3.3. Follow-up and Toxicity Scoring

Patients were followed every 3 months during the first year and every 6 - 12 months thereafter. Prostate-specific antigen (PSA) levels were obtained at each follow-up. Biochemical failure was defined as an increase of at least 2ng/mL from the nadir PSA according to the Phoenix definition (12). We calculate the decline velocity of PSA over an interval of time from the completion of radiotherapy to 1, 2, 3 and 4 years following treatment. The velocity (ng/mL/year) was calculated as the regression coefficient in a linear regression model for each individual. PSA values taken after the start of ADT were excluded. PSA bounce was defined as an absolute increase of 0.2ng/mL from the previous PSA level, followed by a subsequent decrease (13). The t test was performed to compare mean values and ANOV in continuous variables. Statistical analysis was performed using the IBM SPSS software, version 19.0 (SPSS, Inc., IBM, Chicago, IL, USA). Toxicity was documented at follow-up visits using the radiation therapy oncology groups scale.

4. Results

All patients completed the treatment. Thirty-four patients with a median 52 month (range 12 - 71 month) follow-up were analyzed (Table 1). The mean age was 68.3 years (56 - 77 years).

4.1. PSA Changes and Biochemical Relapse

The median pretreatment serum PSA of 7.62 ng/mL (range 3.45 - 14.90 ng/mL) declined to a median of 0.39 ng/mL (range < 0.04 - 1.62 ng/mL) at four years post-treatment (Figure 1). The velocity of PSA declining was maximal in the first year (median -4.184 ng/mL/year), then velocity of PSA declining was gradually falling off with median values of -2.084, -1.548 and 1.032 ng/mL/month for duration of 2, 3 and 40 years after Cyberknife, respectively. The median PSA nadir was 0.31 ng/mL (range, 0.04 - 1.02 ng/mL) with median 33 months. Benign PSA bounces occurred in nine patients (28.1%) with a median PSA bounce of 0.29 ng/mL (range, 0.22 - 1.36 ng/mL) and the median time following treatment to the PSA bounce was 10.5 months (range, 6 - 12 months). There was one biochemical failure, occurring in a high risk patient. Prostate biopsy confirmed local recurrence and ADT was initiated. The five-year actuarial biochemical relapse free survival was 93.3% (Figure 2). Univariate analysis revealed no statistical significance for biochemical failure for the following prognostic factors: age, NCCN risk groups, Gleason score, T stage, pretreatment PSA.

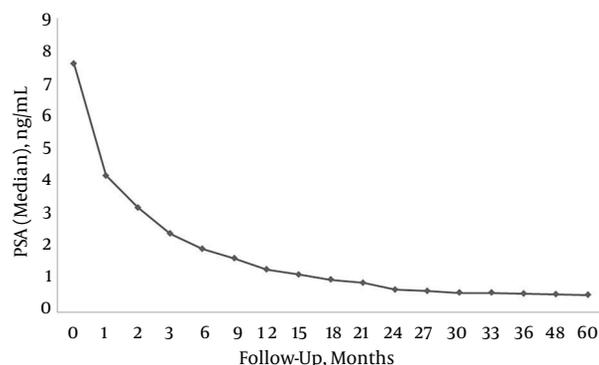


Figure 1. Prostate-Specific Antigen Changes After Stereotactic Body Radiation Therapy

4.2. Toxicity

The prevalent acute complain were urinary frequency and rectal pain, usually during the first and second weeks after treatment. Acute grade 2 genitourinary (GU) toxicities were seen in 17.6% (n = 6) and acute 2 gastrointestinal (GI) toxicities in 23.5% (n = 8) (Table 2). No grade 3 or 4 acute GU and GI toxicities occurred. Acute toxicity was usually resolved within 1 - 2 month on basic symptomatic therapy. Late toxicity rate were acceptable without grade 3 and 4 late toxicity. Late grade 2 GU toxicities were observed in 5.9% (n = 2) and grade 2 GI toxicities in 8.8% (n = 3).

Table 1. Patient and Tumor Characteristics (n = 34)^a

Variables	Value
Mean age, y	68.3 (56 - 77)
ECOG	
0	23 (67.6)
1	11 (32.4)
T stage	
T1c	2 (5.9)
T2a-b	14 (41.2)
T2c	18 (52.9)
Gleason score	
≤ 6	14 (41.2)
7	18 (52.9)
> 7	2 (5.9)
Pretreatment PSA (ng/mL)	7.62 (3.45 - 14.90)
NCCN risk group	
Low	9 (26.5)
Intermediate	
High	2 (5.9)
Overall treatment days	
5 days	20 (58.8)
> 5 days	14 (52.9)

Abbreviation: NCCN, national comprehensive cancer network.

^aValues are expressed as No. (%) unless otherwise indicated.

Table 2. Toxicity^a

Toxicity	Grade			
	I	II	III	IV
Acute				
Urinary	35.3	17.6		
Rectal	26.4	23.5		
Late				
Urinary	8.8	5.9		
Rectal	11.8	8.8	2.9	

^aValues are expressed as %.

5. Discussion

In this report, with long-term follow-up, demonstrates that SBRT using Cyberknife can achieve excellent biochemical control rates and low levels of bladder and rectal toxicity. The rapid decline of PSA level occurred in the first year and PSA fell steadily to achieve very low levels (mean

of 0.55 mg/mL) within 4 years. Anwar et al. (14) compared the PSA slope between the hypofractionated SBRT and conventionally fractionated external beam radiation therapy (EBRT) for localized prostate cancer and reported that the PSA slope for SBRT was greater than conventionally fractionated EBRT at 2 and 3 years and PSA nadir was significantly lower for SBRT.

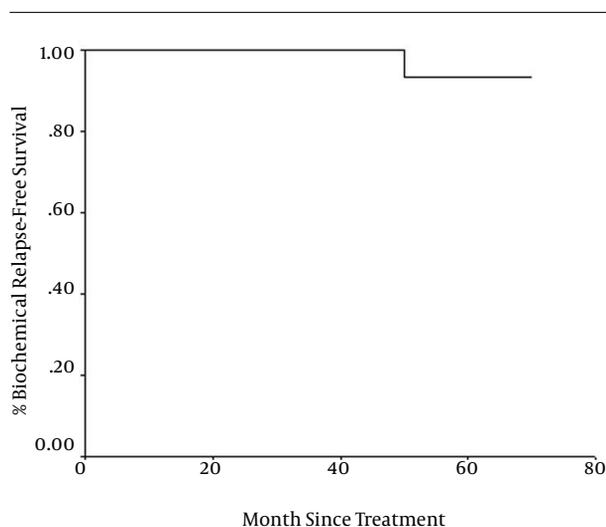


Figure 2. Biochemical Failure-Free Survival Rate After Stereotactic Body Radiation Therapy

Katz et al. (2) demonstrated that PSA decline steadily after treatment and achieve very low mean levels of 0.25 ng/mL within 4 - 5 years. In this study, PSA declined rapidly first year and velocity of decline was gradually falling off with follow up times and low PSA nadir of 0.31 mg/mL. These findings support the predictions of estimated α/β ratio of 1.5 Gy. Using the linear-quadratic radiobiologic model, 36.25 Gy of Cyberknife yields an equivalent dose (EQD) at 2 Gy fraction of 91 Gy for this α/β ratio (15).

Recent reports recommended that hypofractionated schedule may provide similar excellent control as other radiation modalities. Arcangeli et al. (16) published a report comparing 80 Gy (2 Gy/fraction) versus 62 Gy (3.1 Gy/fraction) and showed that the hypofractionated schedule is superior to the conventional fractionation in terms of freedom from biochemical failure rate with equivalent toxicity. This is also confirmed by studies of high dose rate brachytherapy (HDR BT) (17-19). Our outcomes are consistent with those that have resulted from HDR BT. Demanes et al. (19) reported the 8 year biochemical control of 97% in low and intermediate risk prostate patients. However, due to its invasive nature and technical difficulties, use of brachytherapy is less common. Cyberknife allows the delivery of large fractions dose such as HDR BT with sub-millimeter accuracy to the target with excellent sparing of normal tissue. But there is still a matter of debate about the efficacy and toxicity of hypofractionation with Cyberknife.

Toxicity following SBRT was similar to that following EBRT or brachytherapy. Zelefsky et al. (20) reported result on late toxicity using 81 Gy dose with IMRT in conventional fractionation. The 8-year actuarial likelihood of

grade 2 GI toxicity was 1.6% and 0.1% of patients experienced grade 3 rectal toxicity. The 8-year likelihood of late grade 2 and 3 GU toxicities were 9% and 3%, respectively. Katz et al. reported that, among 477 patients with low- and intermediate-risk prostate cancer treated using Cyberknife, only 1.7% of grade 3 late toxicity event occurred in patients who received 36.25 Gy in 5 fractions (21). Our current study shows the similar proportion of toxicity.

In this study, PSA bounce was seen in 28.1% of patients after SBRT. McBride et al. (5) found that the mean age of those who experienced a bounce was significantly younger than those who did not. Vu et al. (22) reported that Younger age was the only factor that predicted PSA bounce following SBRT for prostate cancer. However, age was not associated with PSA bounce in our study.

Our study should be examined in the context of study design. Our study is limited by retrospective nature of the analysis and the small number of patients. There were no strict protocols for the clinical decision-making process. Future studies should employ more comprehensive instruments to assess the effect of prostate SBRT.

SBRT using Cyberknife was well tolerated for these patients with localized prostate cancer. Rate of late GI and GU toxicity are comparable to conventional fractionated radiation therapy and brachytherapy. Our 5-year biochemical relapse free survival rate of 93.3% seems to be favorable.

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Footnote

Conflict of Interest: The authors have no conflicts of interest or financial ties to disclose.

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