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Prostate-specific antigen kinetics after primary stereotactic body radiation therapy using CyberKnife for localized prostate cancer

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ABSTRACT

Purpose: To assess prostate-specific antigen (PSA) kinetics and report on the oncologic outcomes for patients with localized prostate cancer treated with stereotactic body radiation therapy (SBRT) using CyberKnife.

Methods: We extracted the list and data of 39 patients with clinically localized prostate cancer who had undergone primary SBRT using CyberKnife between January 2008 and December 2012 from the Smart Prostate Cancer database system of Seoul St. Mary's Hospital. Changes in PSA over time, PSA velocity, and PSA nadir were evaluated from the completion of SBRT using CyberKnife. Biochemical recurrence (BCR)-free survival after primary SBRT using CyberKnife was determined using Kaplan–Meier analysis.

Results: The rate of PSA decrease was maximal in the first month (median −3.34 ng/mL/mo), which then fell gradually with median values of −1.51, −0.32, −0.28, −0.20, and −0.03 ng/mL/mo for durations of 3, 6, 9, 12, and 24 months after SBRT using CyberKnife, respectively. The median PSA nadir was 0.31 ng/mL after a median 23 months. Kaplan–Meier analysis calculates an actuarial 5-year BCR-free survival after SBRT using CyberKnife as 80.8%.

Conclusions: PSA decline occurred rapidly in the first month, and then the rate of PSA decline fell off steadily over time throughout 2 years after treatment. Also, SBRT using CyberKnife leads to long-term favorable BCR-free survival in localized prostate cancer.

1. Introduction

Prostate cancer is the most common cancer of all newly diagnosed male cancers, and the second leading cause of cancer death in the United States.[1] The American Cancer Society estimates that prostate cancer will be expected to account for 28% of incident male cancer cases in 2013. The majority of prostate cancer is localized, and various curative treatment options have aimed to improve the oncologic and functional outcomes of these patients. Radical prostatectomy and external beam radiation therapy (EBRT) is the conventional treatment option for localized prostate cancer. However, these treatment modalities are limited by the need for anesthesia, several functional impairments, and long treatment duration.

Stereotactic body radiation therapy (SBRT) via CyberKnife (Accuray, Sunnyvale, CA, USA) uses real-time image guidance to account for intrafraction prostatic motion.[2] It can facilitate delivery of an optimal therapeutic dose to the prostate with a rapid dose falloff near the targeted lesion, resulting in potentially better local control. Recent studies have reported that SBRT using CyberKnife in patients with low or intermediate risk has achieved excellent biochemical recurrence (BCR) free survival.[3–5]

Prostate-specific antigen (PSA) is a well-established biomarker for prostate cancer which can be used to monitor response to treatment. Changes in PSA and its derivatives after radical prostatectomy or EBRT have been extensively researched. However, PSA kinetics in response to SBRT using CyberKnife remains poorly understood. Thus far, only a few studies from western countries

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provide the data regarding PSA kinetics after SBRT using CyberKnife.[6,7] Due to racial differences in longitudinal changes in serum PSA levels,[8] it is necessary to elucidate changes in PSA after SBRT using CyberKnife in Asian populations. The purpose of the current study is to assess PSA kinetics and report oncologic outcomes for patients with localized prostate cancer treated with SBRT using CyberKnife.

2. Methods

The protocol of this study was approved by the Institutional Review Board at the Catholic University of Korea, Seoul St. Mary's Hospital. We extracted the list and data of 46 patients with clinically localized prostate cancer who had undergone primary SBRT using CyberKnife between January 2008 and December 2012 from the Smart Prostate Cancer database system of Seoul St. Mary's Hospital.[9] Treatment was delivered using CyberKnife with doses of 35 Gy or 36.25 Gy in five fractions.[10] Included patients had at least 1 year of follow up, and four serial PSA assays. To insure a uniform population in which to evaluate PSA outcomes, patients were excluded if they received neoadjuvant or adjuvant androgen deprivation therapy (ADT, $n = 4$), or used 5-α reductase inhibitors ($n = 3$). Thus, a total of 39 patients were included in this study.

The primary endpoint was to assess PSA changes in response to SBRT using CyberKnife. The secondary endpoint was to determine the potential long-term clinical outcomes after primary SBRT using CyberKnife. Clinical outcome measures included age, body mass index (BMI), Karnofsky performance status scale, serum PSA level, biopsy Gleason score, clinical stage, and BCR. To summarize PSA measurements during the follow-up period, PSA velocity was estimated as the rate of change of PSA over time (ng/mL/y). PSA values taken after the start of ADT were excluded. PSA bounce was defined as an absolute increase of 0.2 ng/mL from the previous PSA level, followed by a subsequent decrease.[11] Biochemical recurrence was defined as an increase of at least 2 ng/mL from the nadir PSA according to the Phoenix definition.[12] Finally, patients were stratified into three risk groups (low, intermediate, and high) based on the National Comprehensive Cancer Network (NCCN) risk group.[13]

Statistical analysis was performed using the IBM SPSS software, version 19.0 (SPSS, Inc., IBM, Chicago, IL, USA). Continuous variables are presented as mean; median (interquartile range [IQR]), and categorical variables are presented as proportions. BCR-free survival was estimated using the Kaplan–Meier method.

3. Results

3.1. Baseline demographics

The baseline characteristics of the 39 patients are presented in Table 1. The mean age was 70.8 (IQR, 68–75) years, and the mean body mass index was 23.5 (IQR, 21.7–25.9) kg/m^2. The mean serum PSA level was 9.2 (IQR, 6.2–11.1) ng/mL, and NCCN risk groups were distributed as follows: low, 11 (28.2%); intermediate, 25 (64.1%); and high, 3 (7.7%).

3.2. PSA changes after SBRT using CyberKnife

The median follow-up duration was 53.0 (IQR, 26.0–68.0) months. Fig. 1 shows PSA changes declining over time, with the different PSA velocities for each time intervals since SBRT using CyberKnife. The rate of PSA decrease was maximal in the first month (median −3.34 ng/mL/mo), then gradually falling off with median values of −1.51, −0.32, −0.28, −0.20, and −0.03 ng/mL/mo for duration of 3, 6, 9, 12, and 24 months after SBRT using CyberKnife, respectively. The median PSA nadir was 0.31 (IQR, 0.12–0.67) ng/mL after a median 23 months.

Table 1
Baseline demographics of the patients.

Variables	
Age (y)[a]	70.8, 72.0 (68.0–75.0)
BMI (kg/m^2[a])*	23.5, 24.4 (21.7–26.0)
Karnofsky performance status (%)	
≥80	25 (86.2)
<80	4 (13.8)
Comorbidity (%)	
Diabetes	4 (13.8)
Hypertension	12 (41.4)
Pretreatment PSA (ng/mL)[a]	9.2, 8.4 (6.2–11.1)
Prostate volume (cm^3)[a]	34.6, 35.0 (20.5–45.7)
PSA density (ng/mL/g)[a]	0.36, 0.22 (0.14–0.53)
Biopsy Gleason score (%)	
≤6	16 (55.2)
7	10 (34.4)
≥8	3 (10.4)
No. total biopsy cores[a]	10.3, 10.0 (10.0–12.0)
No. positive cores[a]	2.6, 2.0 (2.0–3.0)
Max % core involvement[a]	35.8, 33.0 (20.0–50.0)
Clinical stage (%)	
T1c	12 (41.4)
T2a	3 (10.3)
T2b	9 (31.0)
T2c	5 (17.2)
NCCN risk group (%)	
Low	6 (20.7)
Intermediate	20 (69.0)
High	3 (10.3)

BMI, body mass index; NCCN, National Comprehensive Cancer Network.
[a] Values are expressed as mean, median (interquartile range).

Fourteen patients (35.9%) experienced a PSA bounce during the follow-up period. The median time to PSA bounce was 11 (IQR, 6.0–18.5) months; 92.8% (13/14) of PSA bounces were seen within 24 months after SBRT using Cyberknife. The median PSA level before the bounce was 1.07 (IQR, 0.34–2.54) ng/mL, and the median height of PSA bounce was 0.40 (IQR, 0.2–1.20) ng/mL. Patients with PSA bounces had lower pretreatment PSA levels (10.8 vs. 7.5 ng/mL, $P = 0.039$), and only pretreatment PSA level was associated with increased risk of PSA bounce on multivariated logistic regression analysis (odds ratio = 0.786, 95% confidence interval = 0.614–0.987, $P = 0.043$).

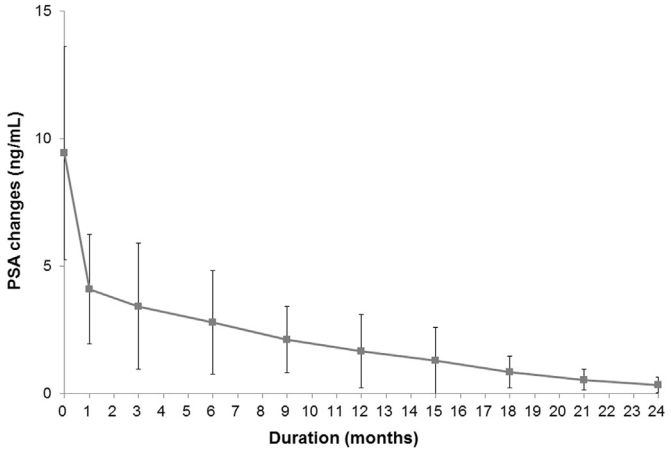

Fig. 1. Prostate-specific antigen changes after stereotactic body radiation therapy using CyberKnife.

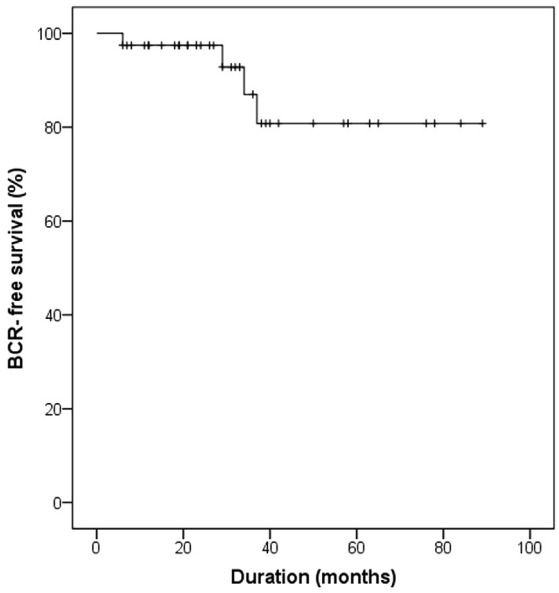

Fig. 2. Biochemical recurrence rate after stereotactic body radiation therapy using CyberKnife in the overall patient population.

3.3. Biochemical recurrence after SBRT using CyberKnife

Four BCRs (12.8%) were observed over a median follow-up duration of 42.0 (IQR 18.0–64.0) months. In univariate Kaplan–Meier analysis, the actuarial 5-year BCR-free survival was 80.8% (Fig. 2). Two patients in the intermediate-risk group and two in the high-risk group experienced BCRs. Five-year BCR-free survival was 100% for low-risk, 83.9% for intermediate-risk, and 33.3% for high-risk patients (Fig. 3A, $P = 0.033$). When categorized by PSA bounce, BCR was not observed in patients with PSA bounce, whereas four BCRs were observed in patients without PSA bounce. Although not reaching statistical significance, the 5-year BCR-free survival was 100% for patients with PSA bounce versus 68.7% for the patients without PSA bounce (Fig. 3B, $P = 0.100$).

4. Discussion

In the current study, we described the changes in the serum PSA levels in patients with localized prostate cancer treated with SBRT using CyberKnife. The majority of PSA decline occurred in the 1st month, following which the rate of PSA decline fell off steadily over time for 2 years after treatment. Several reports have shown PSA kinetics after SBRT using CyberKnife.[14–16] Bolzicco et al[15] demonstrated that the patients with SBRT monotherapy had PSA nadirs of 0.93 ng/mL, 0.87 ng/mL, and 0.62 ng/mL at 1, 2, and 3 years.[15] Katz et al[14] reported that PSA decline after SBRT gradually fell to an overall median of 0.20 ng/mL at 3 years[17] and 0.12 ng/mL at 5 years.[14] Anwar et al[6] compared the PSA kinetics between conventionally fractionated external beam radiotherapy and SBRT in localized prostate cancer, and reported that the median PSA nadirs and slopes for SBRT were 0.70, 0.40, 0.24 ng/mL and −0.09, −0.06, −0.05 ng/mL/mo at 1, 2, and 3 years, respectively.[6] In our study, PSA velocity after SBRT using CyberKnife was −3.34, −1.51, −0.32, −0.28, −0.20, and −0.03 ng/mL/mo at 1, 3, 6, 9, 12, and 24 months. In Korean men, PSA levels after SBRT tends to be decreasing more rapidly and lower compared to Western men. This may be due to underlying biologic differences between Asian and Western men, but any racial differences in PSA kinetics after SBRT or other radiation therapies need further elucidation in future studies.

In this study, PSA bounce was seen in 35.9% of patients after SBRT using CyberKnife. Incidence of PSA bounce after SBRT using CyberKnife has been reported diversely from 17% to 31% according to the varying definitions.[14,16,18] The predictors of PSA bounce in patients undergoing SBRT has been studied, and McBride et al[18] found that patients with PSA bounce were younger than those without PSA bounce. Vu et al[19] analyzed the clinical and pathologic predictors of PSA bounce in patients after SBRT, and reported that younger age was the predictive factor for PSA bounce (odds ratio = 0.937, 95% confidence interval = 0.892–0.984, $P = 0.009$) (19). However, age was not associated with increased risk of PSA bounce and only pretreatment PSA level was associated with increased risk of PSA bounce in our study. Our study suggests that further studies are necessary to elucidate the predictive factors for PSA bounce after SBRT.

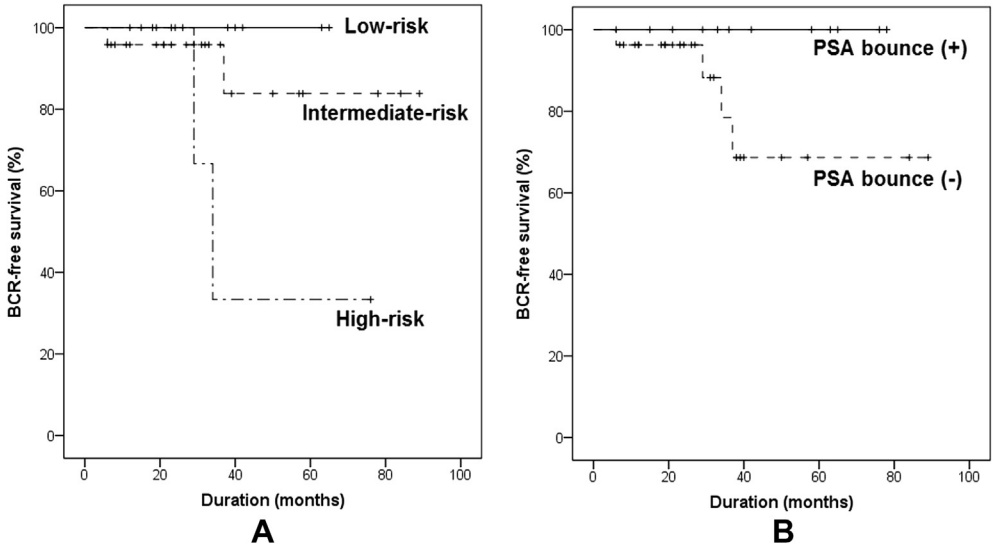

Fig. 3. Biochemical recurrence rate after stereotactic body radiation therapy using CyberKnife according to the (A) NCCN risk group and (B) PSA bounce.

We also found that SBRT using CyberKnife leads to long-term favorable BCR-free survival in localized prostate cancer. Radiobiologically, slowly growing prostate cancer cells are thought to have a low α/β ratio consistently less than 3.[6,20,21] This low α/β ratio suggests that prostate cancer cells are highly sensitive to dose per fraction, which means that a hypofractionated radiation therapy with a large radiation dose delivered in a smaller number of fractions may be advantageous. Several studies suggest that SBRT may provide similar excellent biochemical control as other radiation modalities. According to the risk group, 4- or 5-year BCR-free survival was known to be 93–97% for low-risk,[3,14,22,23] 86.2–92% for intermediate-risk,[14,23,24] and 77.7–80% for high-risk patients.[14,23] These results are consistent with ours; however, BCR-free survival in high-risk patients was poor in our study. It may result from the delayed start of ADT. Patients with high-risk prostate cancer may be considered for long-term neoadjuvant/concomitant/adjuvant ADT.[13] However, we delayed ADT after BCR because of the history of ischemic heart disease of these two patients. They commenced ADT immediately after BCR, and were still alive at follow-up duration of 47 and 64 months, respectively.

Our study has several important limitations. First, our study is limited by its retrospective nature, the small number of patients, and relatively short follow-up duration. There were no protocols for the clinical decision-making process and follow up. Furthermore, we did not perform assessments of the toxicity and quality of life among patients who received SBRT using CyberKnife. Therefore, validated questionnaires still need to be used to define the advantages and disadvantages of this treatment modality. Additionally, in order to accurately estimate the PSA kinetics, patients who received neoadjuvant or adjuvant ADT were excluded. Nonetheless, we believe that these results are still notable because few studies have been done to assess PSA kinetics after SBRT using CyberKnife in Asian patients with localized prostate cancer.

5. Conclusion

The majority of PSA decline occurred in the 1st month, and then, the rate of PSA decline fell off steadily over time with a continuing drop at 2 years after treatment. PSA bounce was seen in a significant proportion of patients after SBRT using CyberKnife. We also confirmed that SBRT using CyberKnife leads to long-term favorable BCR-free survival in localized prostate cancer.

Conflict of interest

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

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