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Prostate-specific antigen kinetics after hypofractionated stereotactic body radiotherapy for localized prostate cancer

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► ***Original article***

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ABSTRACT

Background: stereotactic body radiotherapy (SBRT) has emerged as an effective treatment for localized prostate cancer. However, prostate-specific antigen (PSA) kinetics after SBRT has not been well characterized. The objective of the current study is to analyze the rate of PSA decline and PSA nadir following hypofractonated SBRT in localized prostate cancer. ***Materials and Methods***: From 2008 to 2014, thirty-nine patients newly diagnosed, localized prostate (25.6% low risk, 66.7% intermediate risk and 7.7% high risk) cancer were treated with SBRT using Cyberknife. Total dose of 36.25 Gy in 5 fractions of 7.25 Gy were administered. No one received androgen deprivation therapy (ADT). PSA nadir and rate of change in PSA (slope) were calculated and compared. ***Results:*** With a median follow-up of 52 months (range, 13-71), the median rates of decline of PSA were -0.372, -0.211 and -0.128 ng/mL/month, respectively, for durations of 1, 2 and 3 years after radiotherapy, respectively. The decline of PSA was maximal in the first year and continuously decreased for durations of 2 and 3 year. The median PSA nadir was 0.28 ng/mL after a median 33 months. There was one biochemical failure, occurring in a high risk patient. 5-year actuarial biochemical failure (BCF) free survival was 94.2%. ***Conclusion:*** In this report of localized prostate cancer, continuous decrease of PSA level for duration 1, 2 and 3 year following SBRT using Cyberknife resulted in lower PSA nadir. Also, SBRT leaded to long-term favorable BCF-free survival.

Keywords: *Stereotactic body radiotherapy, prostate cancer, Cyberknife, PSA kinetics, PSA nadir.*

INTRODUCTION

Prostate cancer is the most common cancer and the second leading cause of death from among men in the United States [1] and the incidence rate in Korea is relatively lower than those in western nations but continue to increase annually owing to the aging of society, adoption of westernized lifestyle, and adding of the prostate-specific antigen (PSA) screening test to the National Cancer Screening Program [2]. As the prevalence of prostate cancer increases, various treatment modalities are considered. External beam radiotherapy (EBRT) is conventional treatment option for localized prostate cancer [3].

The Cyberknife (Accuray, Sunnyvale, CA, USA) is one of the tools for hypofractionated SBRT and real-time image guidance to account for intrafraction prostatic motion. Advanced technique of Cyberknife allows high doses of radiation to be delivered precisely to the target while sparing the surrounding healthy tissue, thus achieving high biochemical control and low toxicity [4-6]. For localized prostate cancer, recent published literature support use of hypofractionated SBRT using Cyberknife with excellent 5-year biochemical control rates and correspondingly acceptable rates of toxicity [4-7]. According to the modern understanding of

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radiobiology, the α/β ratios of prostate cancer is maybe around 1.5 Gy and the lower than the surrounding normal tissue [8, 9]. The hypofractionated radiotherapy schema may improve the biochemical control of prostate cancer without increasing toxicities associated with late-responding tissue [8]. One phase III study trial suggested that hypofractionation regiment of 62 Gy in fractions is safe and acute and late complication were equivalent to that of the conventional fractionated regimen of 80 Gy in 40 fractions [10].

PSA is well- established biomarker for prostate cancer. In patients without androgen deprivation therapy (ADT), analysis of PSA kinetics after treatment could reveal the biologic effect of radiation on prostate cancer. The changes of PSA after EBRT and brachytherapy have been extensively researched [11]. Lower PSA nadir and rapid decline in PSA after treatment have been related to improved clinical outcome [12-15]. While recent studies have demonstrated that a lower PSA nadir (<0.5 ng/mL) has been associated with superior clinical disease-free survival [15, 16], the interpretation of the decline rate of PSA following radiotherapy is controversial. Some reports have shown a positive relationship between the increase of the decline rate and clinical outcome, while others have negative [11,17-20]. Shi *et al.* [21] reported that a rapid PSA decline in the first year after external beam radiotherapy is positively associated with prostate cancer specific mortality. Katz *et al.* [4] demonstrated that PSA declines steadily after treatment and achieves very low mean levels of 0.25 ng/mL within 4~5 years. Furthermore, kinetics of PSA decline following SBRT using Cyberknife remains poorly understood and only a few report from western countries [22]. The objective of the current study is to analyze the rate of PSA decline and PSA nadir following hypofractonated SBRT using Cyberknife in localized prostate cancer.

MATERIALS AND METHODS

We retrospectively reviewed the charts of patients treated definitively for localized prostate cancer treated with Cyberknife from 2008 to 2014. Thirty-nine patients newly diagnosed with localized prostate cancer treated SBRT using the Cyberknife robotic radiosurgery system were enrolled in this retrospective analysis. All patients had histologically confirmed primary adenocarcinoma of the prostate. None of these patients had received any other local or systemic primary treatment of prostate cancer. Prior transurethral resection of the prostate for urinary symptom relief was allowed. Patients were stratified according to 2.2014 NCCN risk stratification guidelines [23]. The study was approved by the Ethical Committee for Clinical Trials of our institution and the retrospective data was collected in our institutional database. In order to assess PSA kinetics in response to radiotherapy alone, we stopped follow up on the PSA evaluation if they failed by Phoenix definition [24]. All patients had at least 1 year of follow-up. PSA bounce was defined as an absolute increase of 0.2ng/ml from the previous PSA level, followed by a subsequent decrease [25].

SBRT treatment planning and delivery

Three to four gold fiducial markers were implanted trans-perennially into the prostate under transrectal ultrasound guidance. On one week after fiducial placement, treatment planning CT scans with contrast enhanced were performed at a slice thickness of 1.5 mm using a multi-slice scanner (Lightspeed 16, GE Medical Systems, USA). MRI scans (Signa HDxt, GE Medical System, USA) were obtained with sequences of T1-wighted, gadolinium-enhance. Fused CT and MRI were used for the treatment planning. The prostate, seminal vesicles, rectum, bladder, penile bulb, and bowel were contoured. 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 (median homogeneity index of 1.25 range, 1.23-1.41]). 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

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given over 5 consecutive days. Androgen deprivation therapy (ADT) was not applied to anyone.

Follow-up and statistical analysis

Follow-up PSA test was recommended at 1 month intervals during 3 months after treatment and 3 months interval after that. To eliminate the effect of differing follow-up durations between SBRT boost after EBRT and CF-EBRT, we calculated the rate of decline in PSA over an interval of time from the completion of radiotherapy to 1, 2, 3 and 4 years post-treatment. The slope of PSA change (ng/mL/month) was calculated as the regression coefficient in a linear regression model for each individual. The t test was performed to compare mean values and ANOVA in continuous variables and the Mann-Whiteny test was used to compare distributions of the slop of PSA. Statistical analysis was performed using the IBM SPSS software, version 19.0 (SPSS, Inc., IBM, Chicago, IL, USA).

RESULTS

All patients completed the treatment. Thirty-nine patients with a median 52 months (range, 13-71 months) follow-up were analyzed. The median age was 67 years (range, 55-77 years). Patient characteristics are summarized in table 1.

The pretreatment median PSA level was 7.25 ng/mL (3.45-18.21). Figure 1 shows PSA changes over times, with the different rate of PSA decline for each time intervals since the end of radiotherapy. To investigate the PSA kinetics after radiotherapy, the rate of PSA decline (slope) was calculated for 3 intervals following radiotherapy (0 to 1 year, 0 to 2 years and 0 to 3 years). The slope for all cohorts was maximal in the first year, but tapered off quickly in the following years, with median values of -0.372, -0.211 and -0.128 ng/mL/month for durations of 1, 2 and 3 years after radiotherapy, respectively. The distribution of the median slopes in intermediate-and high-risk patients (-0.482, -0.192 and -0.141 ng/mL/ month, respectively) for 1, 2 and 3 years following radiotherapy did not differ from those in low-risk patients (-0.288, -0.156 and -0.113 ng/mL/month, respectively) (p=0.087, p=0.432 and p=0.124, respectively) (table 2). Patients with high initial PSA (> 10 ng/mL) had greater median rate of PSA decline only during 1 year following radiotherapy than those with low initial PSA (≤10 ng/mL) (-0.725 versus -0.313 ng/mL/month, p=0.043). Similarly, high Gleason score had greater slope during 1 years (-0.528 versus -0.319 ng/mL/month, p=0.031).

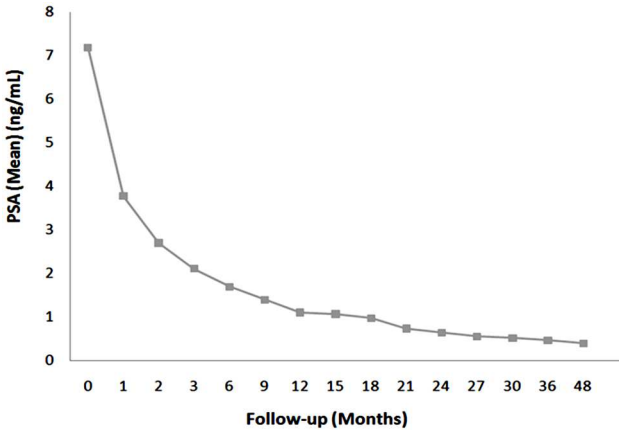


Figure 1. Prostate-specific antigen changes after stereotactic body radiotherapy using Cyberknife.

Table 1. Patient characteristics (n=39).

variables		
Median age (range)		67 (77-55)
ECOG scale		
	0	26 (%66.7)
	1	13 (%33.3)
T stage		
	T1-T2a	13 (%33.3)
	T2b-T2c	26 (%66.7)
Gleason score		
	≤6	15 (%38.5)
	7	21 (%53.8)
	≥8	3 (%7.7)
pretreatmetn PSA (ng/mL)		
	median (range)	7.25 (18.21-3.45)
	≤10	28 (%71.8)
	>10	11 (%28.2)
NCCN risk group		
	low	10 (%25.6)
	intermediate	26 (%66.7)
	high	3 (%7.7)
NCCN, National Comprehensive Cancer Network		

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The continuous PSA decline resulted in low median PSA nadir of 0.28 ng/mL (range, 0.04-1.15) with median 33 months (table 3 and figure 2). There was no statistically significant difference between low-risk patients (0.12 ng/mL) and intermediate-high risk patients (0.47 ng/mL) in median nadir (p=0.087). There were no significant difference in the comparison of the nadir by the Gleason score (≤6 versus 7) and pre-treatment PSA (≤10 versus >10). Benign PSA bounces were common with 33.3% of all patients. The median time to PSA bounce was 13 months (range, 6-18). The median height of PSA bounce was 0.34 ng/mL (range, 0.21-1.39). Patients with benign PSA bounces had lower median pre-treatment PSA (5.73 versus 8.78 ng/mL, p=0.038).

Table 2. Median rate of PSA decline following stereotactic body radiotherapy

Through year	risk group		p-value
	low	intermediate-high	
0-1	-0.288	-0.482	0.087
1-2	-0.156	-0.192	0.238
2-3	-0.113	-0.141	0.124

Table 3. Prostate-specific antigen (PSA) kinetics following stereotactic body radiosurgery using cyberknife.

Variables	
Median PSA nadir	0.28ng/mL (0.04-1.15)
PSA nadir ≤ 0.5ng/mL	28 (%71.8)
Median time to nadir	33months (9-52)
PSA bounce	13 (%33.3)
Median height of PSA bounce	0.34ng/mL (0.21-1.39)
Median time to bounce	13months (6-18)

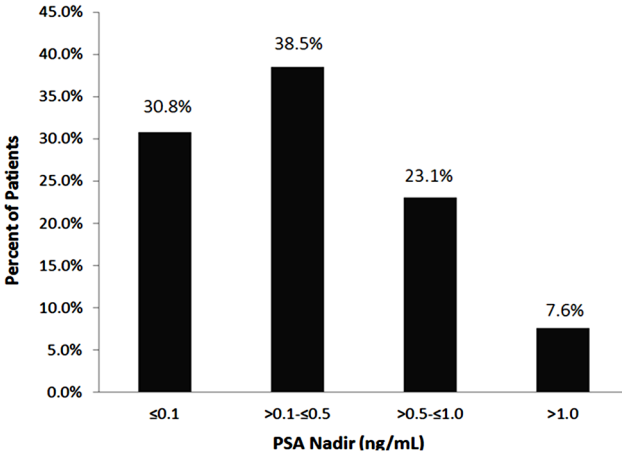


Figure 2. Prostate-specific antigen (PSA) nadir by stereotactic body radiotherapy using Cyberknife.

One biochemical failure (BCF) was observed. The actuarial 5-year BCF-free survival vas 94.2%. One patient only in high-risk group experienced BCF. BCF was not observed in patients with PSA bounce, the 5-year BCF-free survival was 100% for patients with PSA bounce versus 84.3% for the patients without PSA bounce (p=0.078)

DISCUSSION

We described the changes in the PSA levels in patients with low and intermediate risk prostate cancer treated with SBRT using Cyberknife without ADT. The majority of PSA decline occurred in the first year but tapered off quickly in the following years. Several reports have shown in PSA kinetics that significant PSA change occurs in the first year following radiotherapy [26, 27]. Consistently, in our study, the majority of the PSA decline occurred in the first year. Anward *et al.* compared the PSA kinetics between hypofractionated SBRT and conventionally fractionated EBRT for localized prostate cancer and reported that the median slopes for SBRT were -0.09, -0.06 and -0.05 ng/mL/month, respectively, for durations of 1, 2 and 3 years after radiotherapy [28]. In our study, the rate of PSA decline after SBRT was -0.372, -0.211 and -0.128 ng/mL/month for durations of 1, 2 and 3 years, respectively. Although the direct comparison of rate of PSA decline with other study is not proper, the rate of PSA decline in our study tends to be more rapid than that of Anward *et al.* [28]. Shi *et al.* described that a lower PSA at diagnosis had a lower PSA velocity following radiotherapy [21]. The pretreatment median PSA level of 7.25 ng/mL in our study was slightly higher than 6.2 ng/mL in the report of Anwar et al. Consistently. In the current study, high initial PSA had association with greater median rate of PSA decline. The high pretreatment median PSA level might influence the slope of decline of PSA. However, the difference in rate of PSA decline after radiotherapy may, due to underlying biologic differences between Asian and Western men, but any racial differences in PSA kinetics after

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hypofractionated radiotherapy, need further studies.

Recent reports show that hypofractionated schedule may provide similar excellent control as other radiation modalities. Arcangeli *et al.* 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 [29]. This is also confirmed by studies of high dose rate brachytherapy (HDR BT) [30-32]. Demanes *et al.* reported the 8 years biochemical control of 97% in low and intermediate risk prostate patients [32]. However, due to its invasive nature and technical difficulties, use of brachytherapy is less common. SBRT using Cyberknife allows the delivery of large fractions dose such as HDR BT with submillimeter accuracy to the target with excellent sparing of normal tissue.

Several clinical evidence has demonstrated that the α/β ratios of prostate cancer is maybe around 1.5 Gy [8, 9]. SBRT (5 fraction of 7.25Gy) delivered a BED of 211Gy, assuming a α/β ratio of 1.5 (e.g. BED1.5), compared with a BED1.5 of 154-166 Gy with conventionally fractionated EBRT (39-42 fractions of 1.8 Gy). Consistent with dose escalation trials which have showed a lower PSA nadir with increased total dose [9], we expect the SBRT regimen to produce a lower PSA nadir and a continuative decline of PSA. In our study, the PSA decline of SBRT was notable in the first year and constantly decreased during the period of 2 and 3 to achieve lower PSA nadir. Lamb et al. showed that the post-radiation nadir PSA is the strongest Indicator [33]. Zelefsky *et al.* demonstrated that nadir PSA values of ≤1.5 ng/mL at 2 years after radiation therapy for prostate cancer predict for long-term distant metastases and cause-specific mortality [34]. We regard the low nadir of 0.28 ng/mL in SBRT using Cyberknife as indicative of a favorable outcome despite the limited follow-up.

In this study, PSA bounce was seen in 33.3% of patients after SBRT. McBride et al. found that the mean age of those who experienced a bounce was significantly younger than those who did not [35]. Vu *et al.* reported that younger age was the only factor that predicted PSA bounce following SBRT for prostate cancer [36]. Park YH *et al.* showed that only pretreatment PSA level was associated with increased risk of PSA bounce [37]. However, in our study, only pre-treatment PSA (≤10 ng/mL) was associated with benign PSA bounce following SBRT.

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.

In this report of localized prostate cancer, continuously great rates of decline PSA for duration 1, 2 and 3 year following SBRT using Cyberknife resulted in lower PSA nadir. Also, SBRT leads to favorable BCF-free survival. Although follow-up of SBRT using Cyberknife is limited due to its recent start into the clinic, the improved PSA kinetics of SBRT is promising for control of prostate cancer.

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***Conflict of interest*: Declared none.**

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