Prostate-Specific Antigen (PSA) Bounces Following Stereotactic Body Radiotherapy for Prostate Cancer: Importance of PSA Test Frequency

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Purpose: Prostate-specific antigen (PSA) bounce is a common phenomenon that can be observed in patients of prostate cancer treated by radiotherapy. However, the clinical, pathological, or dosimetric predictors and clinical significance of PSA bounce in stereotactic body radiotherapy (SBRT) patients is still unknown.

Methods: Between August 2006 to December 2015, 74 prostate cancer patients were treated by SBRT with Cyberknife at two medical centers. The prescription dose was 35-37.5 Gy in 5 fractions. Follow-up PSA tests were more frequently performed in one hospital than the other (median 4 vs. 10 times for initial one year). PSA bounce was defined as a rise of 0.2 ng/mL followed by a decline to or below the previous nadir.

Results: A total of 74 patients, PSA bounce was observed in 41 patients (55.4%). On univariate analysis, the treated medical center ($p = 0.02$), PSA follow-up frequency ($p = 0.01$), patient age ($p < 0.01$), and total prescription dose ($p = 0.03$) were significant clinical factors in predicting the incidence of PSA bounce, while in multivariable analysis only the PSA follow-up frequency, and patient age remains significant.

Conclusion: PSA bounce was seen in a significant proportion of patients after Cyberknife SBRT. The PSA follow-up test frequency, and patient age were significant factors that were correlated with the incidence of PSA bounces in this study.

Keywords: PSA bounce; prostate cancer; radiotherapy; recurrence

INTRODUCTION

Prostate cancer is the 2nd most common type of cancer in men globally[1]. In South Korea, prevalence rate of prostate cancer is lower than the United States, but it is a growing trend due to westernized habits and active prostate-specific antigen (PSA) screening test[2]. According to nationwide Iranian cancer registry between 2008-2010, the average 3-year age standardized incidence rate of prostate cancer was 11.52 per 100000 males[3]. PSA is a well -known biomarker for prostate cancer which can be used in diagnosis or treatment response assessment[4-6]. Several studies have been published dealing the significance of PSA kinetics. Prostate cancer could be distinguished from benign hyperplasia by PSA density or velocity, and the cancer extent could be predicted through initial PSA level[7]. In addition, biochemical relapse (BCR) can be confirmed by post-treatment PSA kinetics. However, fluctuation of the follow-up PSA level can be often observed in patients treated with radiotherapy, and this often cause confusion to both clinicians and patients. This phenomenon is defined as PSA bounce, and it's significance has been largely studied[4,8-14]. However, the results were various, and therefore, the predictive factors for PSA bounce and its clinical impact is still in controversial. Furthermore, most reports were associated with brachytherapy (BT), and conventional fractionated external beam radiotherapy (EBRT). There have been limited number of reports about PSA bounce after stereotactic body radiotherapy (SBRT). Purpose of this study was to analyze the PSA bounce characteristics after SBRT, the predictive factors of PSA bounce, and the clinical impact of PSA bounce.

MATERIALS AND METHODS

Study design

We retrospectively reviewed medical records of patients treated with SBRT using Cyber-knife radiosurgical system (Accuray Inc., Sunnyvale, CA) from August 2006 to December 2015 at two medical centers (Gyeongsang National University Hospital and Seoul St. Mary's Hospital). Seventy-four patients were enrolled in this retrospective analysis. All patients had localized prostate adenocarcinoma, which was confirmed by histologic and imaging examination, and they received definitive SBRT as the sole treatment. None of the pa-

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Table 1. Patient characteristics (n = 74)

Variables		
Median age (IQR)	Median 70	IQR 65-75
T stage (%)	T1	23 (31.1)
	T2	45 (60.8)
	T3-4	6 (8.1)
Gleason score (%)	≤ 6	51 (68.9)
	7	14 (18.9)
	≥ 8	9 (12.2)
Initial PSA (%)	Median 7.3	IQR 5.4-11.4
	< 10 ng/mL	49 (66.2)
	≥ 10 ng/mL	25 (33.8)
NCCN risk group (%)	Low	13 (17.6)
	Intermediate	32 (43.2)
	High	29 (39.2)
Medical center (%)	GNUH	50 (67.6)
	CMC	24 (32.4)
Prescription dose (%)	36 Gy	23 (31.1)
	37.5 Gy	51 (68.9)
PSA test frequency (%)	< 8 times/year	29 (39.2)
	≥ 8 times/year	45 (60.8)

IQR; interquartile range, ECOG, Eastern Cooperative Oncology Group; PSA, prostate specific antigen; NCCN, National Comprehensive Cancer Network; GNUH, Gyeongsang National University Hospital; CMC, Seoul St. Mary's Hospital.

tients underwent surgery, such as radical prostatectomy. Patients who had undergone hormone therapy or chemotherapy before or after SBRT were also excluded from this study. Patient characteristics such as age, T stage, Gleason score, initial PSA, follow-up PSA, and risk stratification by National Comprehensive Cancer Network (NCCN) guidelines were recorded.

Treatment

All patients were implanted fiducial markers into the prostate for tumor tracking and scanned computed tomography images and magnetic resonance images. Gross tumor volume (GTV) was defined as prostate only in low- to intermediate-risk, while prostate with half of seminal vesicle in high-risk patients. Planning target volume (PTV) was extended 5-mm beyond the GTV in all directions, except posteriorly where a 3-mm extended. The pre-scription dose was 36-37.5 Gy in 5 fractions to PTV, which was normalized to 78-84% of maximum point dose of PTV (Dmax). (**Figure 1**). SBRT was implemented using the Cyberknife with real time fiducial tracking method. This study was approved by our institutional review board (XC14RIMI0026K), and informed consent was waived because of the retrospective nature of the study.

PSA kinetic definition

All patients had at least 14 months of follow-up and 4 times of PSA test after completed SBRT. Initial PSA was defined the most recent PSA value before SBRT. PSA bounce was defined as a rise over a cutoff of 0.2 ng/mL but less than 2.0 ng/mL above a previous PSA, followed by a spontaneous decline to below the pre-bounce nadir. Time to PSA bounce was estimated from end of SBRT to first PSA bounce measurement. The amplitude of PSA bounce was calculated as the difference between pre-bounce nadir and the highest PSA value followed by the PSA decline[13]. BCR was defined as a rise of 2 ng/mL or more above the nadir PSA by the Phoenix definition[14].

Statistical analysis

Univariate and multivariable analysis were performed using logistic regression analysis for finding the factors related to the PSA bounce. We assessed the linearity of quantitative predictors in our logistic regression model and employed a stepwise selection process for variable inclusion. Biochemical relapse free survival (BCRFS) and locoregional relapse-free survival (LRRFS) were defined as the interval between the first day of SBRT and the day of BCR date or any locoregional recurrence detected on im-aging, such as CT or MRI. None of the patients underwent Prostate-specific membrane antigen (PSMA)-positron emission tomography (PET) at that time. BCRFS and LRRFS curve were generated using the Kaplan-Meier analysis, and difference were calculated by the log-rank test. All statistical analysis was performed using the SPSS software (Version 21.0; SPSS, Inc., Chicago, IL, USA). *P* value < 0.05 was considered statistically significant.

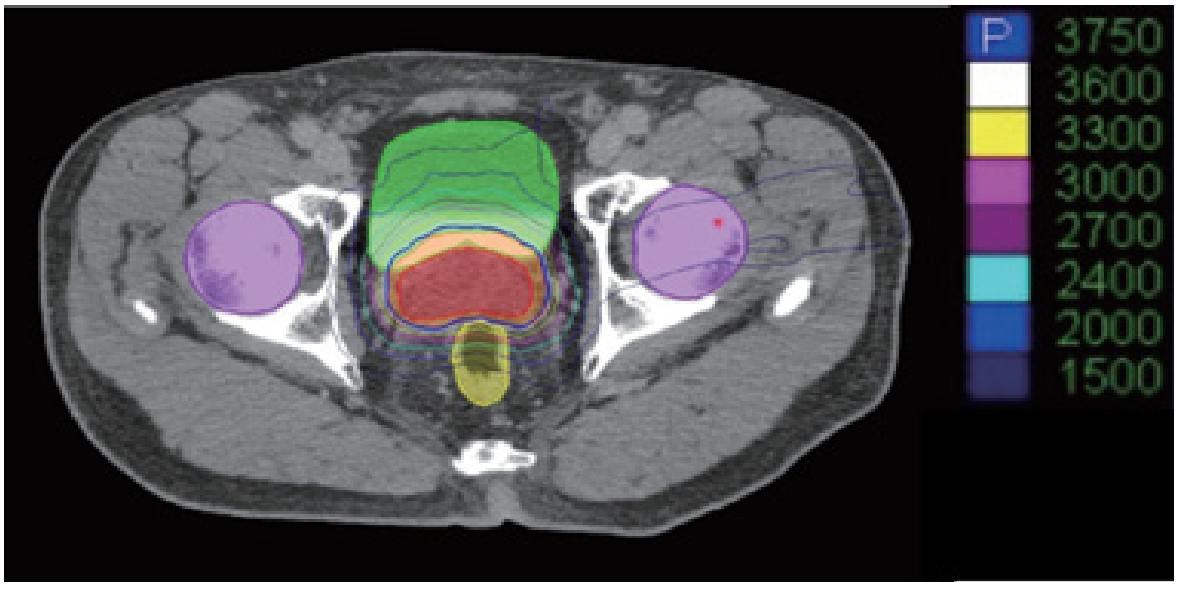

Figure 1. An example of a Cyberknife treatment plan.

Table 2. Multivariable analysis of PSA bounces

Variables	OR	95% CI	*p* value
Medical center (GNUH vs. CMC)	9.57	1.87 - 49.08	0.010
Age (<70 vs. ≥70 years)	28.33	5.84 – 137.38	0.006
Prescription dose (37.5 vs. 36 Gy)	0.36	0.06 – 2.23	0.27
PSA test frequency (≥8 vs. <8 times/year)	0.70	0.05 – 5.12	0.030
Gleason score (<7 vs. ≥7)	0.68	0.14 – 3.25	0.63
Initial PSA level (serial)	0.89	0.78 – 1.04	0.15
Risk group (Low/intermediate vs. high)	0.16	0.01 – 1.84	0.14

OR, odds ratio; CI, confidential interval; GNUH, Gyeongsang National University Hospital; CMC, Seoul St. Mary's Hospital; PSA, prostate specific antigen.

RESULTS

Seventy-four patients of prostate cancer treated at two medical centers were included in this study. Fifty (67.6%) patients were treated at Gyeongsang National University Hospital, and 24 (32.4%) patients were treated at Seoul St. Mary's Hospital. Patient characteristics are summarized in **Table 1**. Their median age was 70 years (IQR, 50-87 years). The number of patients with T1, T2, and T3-4 was 23 (31.1%), 45 (60.8%), and 6 (8.1%), respectively. Fifty-one (68.9%) patients were Gleason score 6 or less, 14 (18.9%) patients were Gleason score 7, and 9 (12.2%) patients were Gleason score 8 or higher. NCCN risk groups were distributed as follows: low, 13 (17.6%); intermediate, 32 (43.2%); and high, 29 (39.2%). Prescription dose was 36 Gy in 5 fractions for 23 (31.1%) of patients, and 37.5 Gy in 5 frac-tions for 51 (68.9%) of patients. Follow-up PSA tests were more frequently performed in one hospital than the other (median 3 (IQR 3-4) vs. 10 (IQR 8-12) times for initial 1 years).

Median follow up duration was 51 months (range, 14-92). Forty-one (55.4%) of patients had a PSA bounce. The median time to PSA bounce was 14.6 months (IQR, 6-22) after the end of SBRT and the median PSA bounce size was 0.5 ng/mL (IQR 0.3-0.7). The PSA bounce duration was median 3 months (IQR 2-5). The median time to PSA nadir was median 35 months (IQR, 5-58). In univariate analysis, the treated medical center ($p = 0.02$), PSA test frequency ($p = 0.01$), patient age ($p < 0.01$), and prescription dose ($p = 0.03$) were significant clinical factors to predict the incidence of PSA bounce. In multivariable analysis, only the age ($p < 0.01$) and PSA test frequency ($p = 0.03$) remains significant (**Table 2**). Other patient characteristics, including performance status, T stage, Gleason score, initial PSA level, risk classification did not predict PSA bounces.

Thirteen BCR were observed. The 3-year BCRFS rate was 90.6%. Nine patients who experienced PSA bounces were clinically diagnosed to have biochemical recurrences, while 4 patients with no PSA bounces were diagnosed to have recurrence and received salvage therapy. Three locoregional recurrences (LRR) were observed. One LRR was observed in patients without PSA bounce, and two recurrences were observed in patients with PSA bounce. **Figure 2** shows the BCRFS, and LR-RFS according to PSA bounce, respectively ($p > 0.05$).

DISCUSSION

After definitive RT for prostate cancer, PSA levels can transiently increase before ultimately dropping below the previous nadir, and this phenomenon is called "PSA bounce"[17]. This bounce has been observed across various RT techniques as well as in patients undergoing radical prostatectomy[18]. While various thresholds for PSA bounce exist, the most commonly used definition is a rise over a cutoff of 0.2 ng/mL but less than 2.0 ng/mL above a previous PSA, followed by a spontaneous decline to below the pre-bounce nadir[18].

There are several conflicting results of PSA bounce and its correlation with clinical prognosis. Urabe et al. report the results of a systematic review and meta-analysis evaluating the prognostic significance of PSA bounce[19]. There were 2706 of all 8881 patients (30.5%) who experienced PSA bounce, and it was associated with better BCRFS after definitive radiation therapy with a pooled hazard ratio of 0.62. However, some reports indicated no correlation between PSA bounce and prognosis, and certain studies even reported an inverse correlation (**Table 4**).

We summarized and showed several published studies which focus on the PSA bounce in patients treated by brachytherapy (BT), external beam radiotherapy (EBRT), and SBRT (**Table 4**). Ciezki et al.[10] reported 46.3% of PSA bounce incidence in 162 patients after BT. Eric et al.[11] reported the incidence of PSA bounce after EBRT as 20% with a cut-off value of 0.4 ng/mL in 4839 patients. Vu et al. (12) reported the incidence as 28% after SBRT with a cut-off value of 0.2 ng/mL. The overall reported incidence of PSA bounce was 14-46% in BT, 12-20% in EBRT, and 28-55% in SBRT studies. However, since large variations exist even in same RT techniques and same cut-off value, we could

Table 3. PSA bounce characteristics

PSA test frequency	PSA bounce characteristics	Predictive factors on multivariable analysis
Not controlled	Incidence: 41 (55.4%) Median time: 14.6 months Median amplitude: 0.5 ng/mL	Age (OR 28.33, $p = 0.006$) PSA test frequency (OR 0.70, $p = 0.030$)
Every 3 months	Incidence: 19 (25.7%) Median time: 21.9 months Median size: 0.51 ng/mL	Age (OR 0.157, $p = 0.003$)
Every 6 months	Incidence: 5 (6.8%) Median time: 30 months Median size: 0.46 ng/mL	No significant factor

Table 4. Review of previous PSA bounce studies

Study	No. of patients	Min. PSA FU time (Freq. of PSA test)	Freq. of bounce	Predictive factors	Clinical influence
Brachytherapy					
Ciezki et al. (8)	162	5 Ys (per 6 Ms)	46.3%	-Young age -Early time to initial PSA rise	Better BFFS
Richard et al. (7)	373	1 Y (per 6 Ms)	31%	-Young age -High dose -Large glands	NC
EBRT					
Eric et al. (9)	4839	5 Ys (per 3-6 Ms)	20%	-Low risk group -Young age -Low initial PSA	Increased risk of BF
Charles et al. (3)	964	1 Y (per 3-6 Ms)	12%	NC	Better BFFS
SBRT					
Vu et al. (10)	120	18 Ms (per 3 Ms)	28%	-Young age	NC
Lee et al. (19)	39	1 Y (per 3 Ms)	35.9%	-Lower pretreatment PSA level	Better BFFS
Nathan et al. (11)	91	36 Ms (per 3 Ms)	51.1%	-Large glands -Nadir >0.1 ng/mL	NC
Our study	74	14 Ms (per 1 or 6 Ms)	55.4%	-Young age -Frequently PSA test	NC

PSA, prostate specific antigen; No., number; Min., minimum; FU, follow up; Freq., frequency; Y, year; BFFS. Biochemical failure free survival; NC, no correlation; BF, biochemical failure; M, month.

assume that other factors would affect the incidence of PSA bounce.

In our study, we described the PSA bounces in patients of prostate cancer treated by SBRT with Cyberknife. Among the 74 patients, 41 (55.4%) patients experienced a PSA bounce defined by ≥ 0.2 ng/mL above the previous PSA level followed by a spontaneous decline to below the pre-bounce nadir. In multivariable analysis showed young age, frequent PSA tests were statistically significant factors to predict the PSA bounce.

The pathophysiology underlying PSA bounce remains unknown, but some data support an inflammatory or immune etiology[18,20]. In one study by Hamidi et al, they found concomitant prostatitis in 112 prostate cancer specimens[21]. The detection rate of focal prostatitis was higher in the group with PSA fluctuation of > 9.5% than the group with PSA fluctuation of < 9.5% (58% vs. 4.5%). They also suggest fluctuations can be detected in prostate cancer patients who have large prostates or concomitant prostatitis[21]. In terms of RT, some studies reported high prescription dose will increase the incidence of PSA bounce. Richard et al.[9] reported the incidence of PSA bounce as 38% vs. 24% ($p = 0.04$) in patients whose D90 was higher vs. lower than 160 Gy. Compared to the studies in Vu et al.[12] and Lee et al.[22] who reported the incidence as 28% and 35.9% treated with SBRT, our study showed much higher incidence of PSA bounce even though the prescription dose was similar.

The main reason of the higher incidence of PSA bounce in our study was frequent PSA testing. The variation in PSA testing frequency across different hospitals in our study was primarily determined by individual physician judgment. According to the definition of a PSA bounce, it may be expected, but the frequency of reaching a level more than 0.2 ng/mL higher than the previous PSA level and subsequently falling back below the previous nadir may increase as the PSA test is conducted more

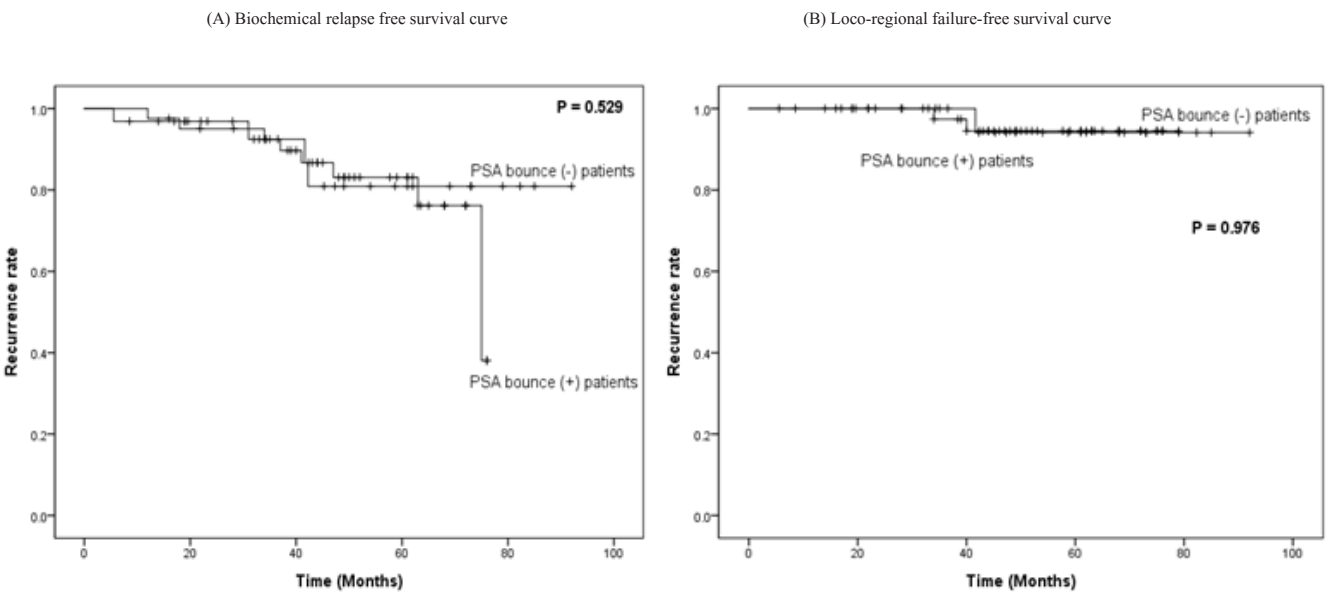

Figure 2. Biochemical relapse free survival and loco-regional failure-free survival according to the presence of prostate specific antigen (PSA) bounce. **(a)** Biochemical failure-free survival curve; **(b)** lo-co-regional failure-free survival curve

frequently. There could be also a biological variation. If PSA tests were performed every 3 months, the incidence of PSA bounce might have been 25.7% (**Table 3**). However, many studies dealing with PSA bounce usually do not report or focus on this issue (**Table 4**) and there is no specific guideline.

Another significant predictive factor for PSA bounce in our study was 'young age,' consistent with findings in other studies[9-12]. In recently published meta-analysis[14] indicated that younger age is associated with greater PSA bounce occurrence and amplitude. This is consistent with the findings of the systematic literature review, in which 29 of the 50 papers analyzed identify younger age as a predictor of bounce[14]. The exact reason is unknown why younger patients showed higher PSA bounce. However, our study results showed if we test PSA frequently often in younger patients, the incidence of PSA bounce might be high, and we can get a clue that PSA bounce could be a technical phenomenon rather than a clinical one in some patients. In a study evaluate the correlation of PSA level and ejaculation found that combination of being sexually active or masturbating ≥ 4 times/week was associated with a higher PSA level of 27% in healthy patients[23].

In another study which evaluate PSA bounce with erectile dysfunction found that International Index of Erectile Function-15 score correlates with the PSA bounce in prostate cancer patients undergoing brachytherapy, and an occurrence of PSA bounce seems to be more likely in those who are more sexually active[24]. Our study results supported these results. It seems the level of androgen level and frequency of sexual activities could affect the PSA level and the incidence of PSA bounce, rather than the disease or treatment characteristics.

Our study is the first study which suggest the PSA test frequency could affect the incidence of PSA bounce. Although the treatment techniques were similar, the incidence of PSA bounce was largely different. Our analysis concluded this difference was due to the difference of PSA test frequency (median 4 times vs. 10 times per year).

Although some limitations exist because of the retrospective nature of this study with relatively short term follow up. In addition, our findings include large odds ratio estimates and wide confidence intervals, suggesting possible sparse-data bias as noted by Greenland et al.[25] These results should be interpreted with caution, particularly in settings with small sample sizes or low event rates. However, out study results clearly showed frequent PSA test and young age are important factors which affects the incidence of PSA bounce. When we interpret the PSA test results we should carefully focus on the intervals between PSA tests, and whether sexual activities were performed before PSA tests.

CONCLUSIONS

Frequent PSA test and young age are important factors which affects the incidence of PSA bounce in patients treated by SBRT. These observations suggest potential factors for consideration in future studies.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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