Original Article

Prostate cancer detection rate in patients with fluctuating prostate–specific antigen levels on the repeat prostate biopsy

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Purpose: To evaluate whether the risk of prostate cancer was different according to the pattern of fluctuation in prostate-specific antigen (PSA) levels in patients undergoing repeat transrectal ultrasound-guided prostate biopsy (TRUS-Bx).

Methods: From March 2003 to December 2012, 492 patients underwent repeat TRUS-Bx. The patients were stratified into 3 groups based on the PSA fluctuation pattern: group 1 (continuous elevation of PSA, n = 169), group 2 (PSA fluctuation with PSA velocity [PSAV] ≥ 1.0 ng/mL/yr, n = 123), and group 3 (PSA fluctuation with PSAV < 1.0 ng/mL/yr, n = 200).

Results: Prostate cancer was detected in 112 of 492 patients (22.8%) in the repeat biopsy set. According to the PSA fluctuation pattern, prostate cancer detection rates at repeat TRUS-Bx were 29.6% (50/169) for patients with continuously increasing PSA, 30.1% (37/123) for PSA fluctuation with PSAV ≥ 1.0 ng/mL/yr, and 12.5% (25/200) for PSA fluctuation with PSAV < 1.0 ng/mL/yr. Multivariate analysis showed that PSA fluctuation pattern and high grade prostatic intraepithelial neoplasia at initial TRUS-Bx were the predictive parameters for positive repeat biopsies. Among the 96 patients (85.7%) who underwent radical prostatectomy, no significant differences in pathologic outcomes were found according to the PSA fluctuation pattern.

Conclusions: The current study shows that the risk of prostate cancer at repeat TRUS-Bx was higher in men with a fluctuating PSA level and PSAV ≥ 1.0 ng/mL/yr than in those with a fluctuating PSA level and PSAV < 1.0 ng/mL/yr.

Keywords: Prostate-specific antigen, Prostatic neoplasms, Biopsy, Needles

INTRODUCTION

Transrectal ultrasound-guided prostate biopsy (TRUS-Bx) is the most effective method for diagnosis of prostate cancer; however, TRUS-Bx may underestimate the presence of cancer. Therefore, repeat biopsy must be considered in patients with persistent diagnostic doubts after an initial negative biopsy. In the Medicare population, the risk of repeat biopsy in men with a negative first biopsy was 11.6% at 1 year and 38.0% at 5 years [1]. Although TRUS-Bx is generally considered safe,

many urologists have experienced a conflict between the risk of prostate cancer and biopsy-related morbidity that includes rectal bleeding and infectious complications [2-5]. Because of the aforementioned concerns, the use of alternative biomarkers or predicting factors has become mandatory in predicting the presence of prostate cancer in cases where clinically suspected cancer is not supported by initial histologic findings.

Prostate-specific antigen (PSA) is the universally accepted tumor marker for diagnosis of prostate cancer. Many urologists frequently encounter patients with fluctuating PSA levels

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after initial TRUS-Bx. Traditionally, these patients were considered as having a lower risk of prostate cancer than patients with steadily increasing PSA levels; however, there is paucity of firm evidence for this hypothesis [6,7].

The aim of the current study was to evaluate whether the risk of prostate cancer was different according to the PSA fluctuation pattern in patients undergoing repeat TRUS-Bx for suspected prostate cancer.

MATERIALS AND METHODS

From March 2003 to December 2012, 5,828 consecutive men with a mean age of 64.8 ($\pm$9.3) years underwent TRUS-Bx with a mean of 12.6 ($\pm$1.3) biopsy cores. The indication for initial TRUS-Bx was either an elevated PSA level (≥ 3 ng/mL) or abnormal digital rectal examination (DRE). Prostate cancer was detected in 2,047 men (35.1%) at initial TRUS-Bx. Of the 3,781 patients whose biopsy result was negative, 492 underwent repeat TRUS-Bx because of the high risk of prostate cancer with prior high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation of prostate, persistently elevated PSA, or increase in PSA level during follow-up. In all patients, the prostate was routinely biopsied bilaterally near the base, midgland, and apex with at least six biopsies per side. All biopsy cores were reviewed by a single board-certified uropathologist (K.Y.C.) using contemporary diagnostic criteria. In the presence of prostate cancer, either radical prostatectomy or radiation therapy was recommended.

After approval by the Institutional Review Board at Seoul National University Bundang Hospital (B-1310-222-109), clinical and pathologic data, including patient age, PSA, PSA density, PSA velocity (PSAV), and PSA fluctuation pattern were analyzed using our computerized database. PSAV was calculated as PSA level at the time of second biopsy minus PSA level at the time of first biopsy divided by the time elapsed in years between two measurements. PSA fluctuation was defined as a PSA series with at least one PSA value lower than the one immediately preceding it. The patients were stratified into three groups based on the PSA fluctuation pattern: group 1 (continuous elevation of PSA, n=169), group 2 (PSA fluctuation with PSAV≥ 1.0 ng/mL/yr, n=123), and group 3 (PSA fluctuation with PSAV< 1.0 ng/mL/yr, n=200).

All statistical analysis was performed using IBM SPSS ver. 19.0 (IBM Co., Armonk, NY, USA). Demographics and clinical parameters were analyzed with the chi-square test for categorical variables and the one-way analysis of variance test or the Kruskal-Wallis test, as appropriate for continuous variables. Two-sided null hypotheses of no difference were

Table 1. Baseline patient characteristics

Characteristic	Value
Age (yr)	65.2±7.8
Body mass index (kg/m^2)	23.7±4.8
PSA at initial biopsy (ng/mL)	8.2±0.3
PSA at repeated biopsy (ng/mL)	9.9±0.4
Prostate volume (mL)	48.8±21.1
Transition zone volume (mL)	25.7±17.6
PSA density (ng/mL/mL)	0.16±0.09
PSA velocity (ng/mL/yr)	1.05±1.90
Abnormal DRE	48 (9.8)
Abnormal TRUS	73 (14.8)
Months interbiopsy interval	16.0±12.1

Values are presented as mean±standard deviation or number (%).
PSA, prostate-specific antigen; DRE, digital rectal examination; TRUS, transrectal ultrasound.

rejected if P-values were less than 0.05.

RESULTS

The baseline characteristics of the cohort are presented in Table 1. The mean age of the patients was 65.2 years; their mean PSA levels before the initial and repeat biopsy sets were 8.2 and 9.9 ng/mL, respectively ($P=0.016$). Only 11 of the 492 patients (2.2%) experienced adverse events after repeat TRUS-Bx, with acute prostatitis in 7 patients, rectal bleeding in 3 patients, and acute urinary retention in 1 patient.

Prostate cancer was detected in 112 of 492 patients (22.8%) in the repeat biopsy set; 6 of 40 patients (15.0%) in the third biopsy set; and 1 of 4 patients (25.0%) in the fourth biopsy set. According to the PSA fluctuation pattern, prostate cancer detection rates at repeat TRUS-Bx were 29.6% (50/169) for patients with continuously increasing PSA, 30.1% (37/123) for PSA fluctuation with PSAV≥ 1.0 ng/mL/yr, and 12.5% (25/200) for PSA fluctuation with PSAV< 1.0 ng/mL/yr.

There was no statistical significance between patients with and without prostate cancer at repeat TRUS-Bx for age (66.8 years vs. 64.7 years, $P=0.089$), body mass index (23.6 kg/m^2 vs. 23.7 kg/m^2, $P=0.867$), and prostate volume (46.3 mL vs. 49.4 mL, $P=0.249$). Patients with prostate cancer had higher PSA levels at repeat TRUS-Bx (10.2 ng/mL vs. 9.1 ng/mL, $P=0.012$), higher PSA density (0.21 ng/mL/mL vs. 0.14 ng/mL/mL, $P=0.041$), and higher PSAV (1.23 ng/mL/yr vs. 0.91 ng/mL/yr, $P<0.001$). Multivariate analysis showed that PSA fluctuation pattern and HGPIN at initial TRUS-Bx were the predictive parameters for positive biopsies (Table 2).

Ninety-six patients (85.7%) underwent radical prostatectomy. Table 3 presents the pathologic results of the surgical specimen. Pathologic stage was organ confined in 90.6% of

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Table 2. Univariate and multivariate logistic regression analysis predicting the presence of prostate cancer at repeated TRUS-Bx

Factor	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.045	1.001–1.076	0.042	1.026	0.934–1.055	0.125
PSA	1.159	1.035–1.287	0.035	1.089	0.893–1.238	0.094
Prostate volume	0.945	0.607–1.455	0.381	-	-	-
Transition zone volume	0.927	0.709–1.224	0.401	-	-	-
PSA fluctuating pattern						
Group 1	3.012	1.704–5.322	<0.001	3.151	1.771–5.608	<0.001
Group 2	2.941	1.725–5.015	<0.001	2.996	1.747–5.139	<0.001
Group 3	Reference			Reference		
Abnormal DRE findings	1.605	0.783–3.049	0.426	-	-	-
HGPIN at initial TRUS-Bx	2.163	1.508–4.896	0.002	2.019	1.439–4.323	0.004
ASAP at initial TRUS-Bx	1.209	0.793–2.128	0.411	-	-	-

TRUS-Bx, transrectal ultrasound guided prostate biopsy; OR, odds ratio; CI, confidence interval; PSA, prostate-specific antigen; DRE, digital rectal examination; HGPIN, high grade prostatic intraepithelial neoplasia; ASAP, atypical small acinar proliferation of prostate.

Table 3. Pathologic characteristics of the 96 patients who underwent radical prostatectomy after diagnosis of prostate cancer at repeated TRUS-Bx

	Overall (n=96)	Group 1 (n=44)	Group 2 (n=31)	Group 3 (n=21)	*P*-value
T stage					0.859
pT2a	17 (17.7)	7 (15.9)	6 (19.4)	4 (19.0)	
pT2b	1 (1.0)	0 (0)	1 (3.2)	0 (0)	
pT2c	69 (71.9)	32 (72.7)	21 (67.7)	16 (76.2)	
pT3a	8 (8.3)	4 (9.1)	3 (9.7)	1 (4.8)	
pT3b	1 (1.0)	1 (2.3)	0 (0)	0 (0)	
N stage					0.463
N0	38 (39.6)	19 (43.2)	13 (41.9)	6 (28.6)	
N1	1 (1.0)	0 (0)	1 (3.2)	0 (0)	
Nx	57 (59.4)	25 (56.8)	17 (54.8)	15 (71.4)	
Gleason score					0.784
≤6	56 (58.3)	25 (56.8)	17 (54.8)	14 (66.7)	
7	36 (37.5)	17 (38.6)	12 (38.7)	7 (33.3)	
≥8	4 (4.2)	2 (4.5)	2 (6.5)	0 (0)	
Tumor volume, mean (range)	8.9 (1–25)	9.2 (1–25)	9.5 (1–20)	7.7 (1–20)	0.177
Positive surgical margin	14 (14.6)	7 (15.9)	5 (16.1)	2 (9.5)	0.758

Values are presented as number (%) unless otherwise indicated.
TRUS-Bx, transrectal ultrasound guided prostate biopsy.

the patients and was locally advanced in only 9.4%. No significant differences in pathologic outcomes were found among patients according to the PSA fluctuation pattern.

DISCUSSION

When a patient presents with an initial negative prostate biopsy, a repeat biopsy should be performed because of persistent clinical suspicions of prostate cancer, such as abnormal DRE findings, increasing PSA level, and pathologic findings at initial biopsy. The number of positive prostate biopsies decreases with repeat biopsy (34% for the first prostate biopsy, 25% for the second, 24% for the third, and 21% for the fourth and fol-

lowing biopsies) [1]. According to the different techniques used for prostate biopsy, cancer detection rates in repeat saturation prostate biopsy range from 13.7% to 45.0% [8-11]. Use of an extended prostate biopsy protocol with at least 12 cores resulted in an overall diagnostic yield for prostate cancer of 10.8%–26.2% [12,13], which is in line with the 22.8% yield in our study. Currently, despite several efforts to improve the detection rate of prostate cancer, there exists a challenging cohort of patients with substantial risk for prostate cancer who had a first negative biopsy.

Fluctuating serum PSA levels is a common clinical situation encountered in daily practice. Earlier studies have evaluated the clinical significance of PSA fluctuation after initial

negative prostate biopsy [6,14]. Celhay et al. [6] analyzed the cancer detection rate of repeat prostate biopsy according to fluctuating PSA levels. The percentage of prostate cancer was lower in the fluctuating PSA group than in the group with steady or steadily increasing PSA, but the difference was not significant (21.5% vs. 32.1%, $P = 0.14$). Similarly, Taverna et al. [14] reported that there were no significant differences between patients with fluctuating PSA and steadily increasing PSA in terms of prostate cancer detection, or clinical or pathological stage. These findings are not consistent with those of our study. In our study, PSA fluctuation pattern was a significant predictive parameter for positive repeat biopsy. However, the number of patients in these prior studies was limited, and the results may be statistically underrepresented. Furthermore, fluctuating PSA level in their study was defined as a PSA series with at least one PSA value lower than the one immediately preceding it. Under such a definition only, the effect of biological variations in PSA may be underestimated. Therefore, it is important to understand the biological and analytical variations that constitute a significant change in serum PSA.

PSA variation, even when PSA is measured in the same laboratory, is now well established. Roehrborn et al. [15] identified patients who underwent two serum PSA measurements within less than 90 days, with the first PSA being less than 10 ng/mL. They reported that only 6% of their patients had the same PSA value on both occasions; 55% had decreased PSA levels and 40% had increased PSA levels at the second sampling. Nixon et al. [16] reported that the median critical change ensuring a statistically significant difference between two PSA measurements was 20.5% and that an increase of 45.8% in PSA concentration would need to be observed to be certain that an increase in PSA was statistically significant for 95% of men. Boddy et al. [17] analyzed the intraindividual variability of PSA by obtaining four PSA values over 4 weeks in 64 men with benign prostate biopsies. The median coefficient of PSA variation was 9.5%, and there was a clear linear relationship between the mean PSA level and the standard deviation. The results indicated that patients who cause the most clinical concern because of their higher PSA are also those who have the most variation in PSA. Thus, analyzing the risk of prostate cancer using PSA fluctuation alone might be a clear indication of a methodological problem.

In the current study, we classified the patients with PSA fluctuation according to the PSAV: PSA fluctuation with PSAV ≥ 1.0 ng/mL/yr and PSA fluctuation with PSAV < 1.0 ng/mL/yr. Several authors have reported that PSAV is an independent predictor of prostate cancer. Carter et al. [18] suggest a

cutoff value of 0.75 ng/mL/yr for PSAV for identification of men with prostate cancer or benign prostatic disease with a PSA level greater than 4 ng/mL. The recent study by Ulmert et al. [19] analyzed data from the Malmö Preventive Medicine study to justify the significance of using PSAV alone compared with PSA and PSAV in detecting prostate cancer in clinical practice. They found that PSAV had a strong association with a subsequent diagnosis of prostate cancer on univariate and multivariate analysis (area under the curve [AUC], 0.771). Using the PSAV risk count proposed by Carter et al. [20], Loeb et al. [21] demonstrated that after adjusting for PSA level and age, men with two serial PSAV measurements of > 0.4 ng/mL/yr (risk count 2) had an 8.2-fold increase in the risk of prostate cancer compared with those with a risk count of ≤ 1. In our study, we found that patients with PSA fluctuation and PSAV ≥ 1.0 ng/mL/yr had a 2.996-fold increase in the risk of prostate cancer by adopting the concept of PSAV for analyzing the clinical significance of PSA fluctuation pattern.

The current study has several limitations. First, although we tried to control factors that might have influenced the results by using multivariate analysis, ours is a retrospective study in a single institution. Although there is less chance of missing a cancer after at least two sets of biopsies are performed [22], we do not know how many cancers were missed in our TRUS-Bx protocol. Finally, we did not analyze the PSA fluctuation pattern in patients who did not undergo repeat TRUS-Bx as a control. Physicians tended to perform repeat biopsy less frequently for patients with PSA fluctuation; however, we cannot be certain that patients who did not undergo repeat biopsy did not have prostate cancer.

In conclusion, the current study shows that the risk of prostate cancer at repeat TRUS-Bx was higher in men with a fluctuating PSA level and PSAV ≥ 1.0 ng/mL/yr than in those with a fluctuating PSA level and PSAV < 1.0 ng/mL/yr. Further studies are required to determine the detailed clinical relevance of these findings in order to reduce the number of unnecessary biopsies.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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