Original Article

Indications for a second prostate biopsy in patients suspected with prostate cancer after an initial negative prostate biopsy

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A B S T R A C T

Background: The present study aimed to evaluate the indications for a second prostate biopsy in patients suspected with prostate cancer after an initial negative prostate biopsy.
Methods: The present study included 421 patients who underwent repeat prostate biopsy between January 2007 and December 2015 at three hospitals. Clinicopathological data, including patient age, body mass index, history of prostate biopsy, prostate volume, prostate-specific antigen (PSA) level, PSA density, PSA velocity, and PSA fluctuation patterns, were analyzed. The patients were stratified into two groups based on the first PSA pattern (increase/decrease) within 1 year after the initial negative prostate biopsy.
Results: Prostate cancer was detected in 100 (23.8%) of the 421 patients at the second prostate biopsy. In patients with a PSA decrease at the first follow-up, prostate volume and number of increases in the PSA level from the initial prostate biopsy were predictors for prostate cancer diagnosis at the second prostate biopsy. In patients with a steady PSA increase after the initial prostate biopsy, prostate volume and number of biopsy cores were predictors for prostate cancer diagnosis at the second prostate biopsy.
Conclusion: The indications for a second prostate biopsy are a low prostate volume and a high number of increases in the PSA level among patients with a PSA decrease at the first follow-up and a low prostate volume and a high number of biopsy cores among patients with a PSA increase at the first follow-up.

1. Introduction

The only diagnostic method for confirming prostate cancer (PCa) is prostate biopsy. Prostate-specific antigen (PSA) is the most novel serum marker used for the early detection and management of PCa.[1,2] However, PSA testing involves some issues owing to the relative lack of cancer specificity.[3] Moreover, in a previous study, approximately 20–30% of patients with potential PCa were not identified at the first prostate biopsy.[4] Appropriate interpretation of PSA findings is necessary after an initial negative biopsy, and the interpretation can be complex in patients suspected with PCa, such

as those with abnormal digital rectal examination (DRE) findings, a high PSA level, and pathological findings at the initial biopsy. The use of various imaging-guided biopsy approaches, including Doppler-targeted biopsy protocols, contrast-enhanced ultrasound, sonoelastography, and multiparametric prostate magnetic resonance imaging (mpMRI) has increased the cancer detection rate. With regard to concerns about overdiagnosis and overtreatment of PCa related to cost effectiveness, most urologists select methods involving a high number of biopsy cores and additional targeted biopsy.[5]

The National Comprehensive Cancer Network (NCCN) guidelines recommend that patients with an initial negative biopsy result should undergo PSA assessment and DRE at 1-year intervals initially and then undergo a repeat biopsy based on risk stratification and/or the results of biomarkers that have high specificity, such as prostate health index, Prostate CAncer gene 3 (PCA3) and

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free/total prostate-specific antigen ratio (%fPSA).[6] No definite indications for the second prostate biopsy have been identified, and the time to use additional approaches, such as biomarker assessment, mpMRI-targeted biopsy, and saturation biopsy, is unclear.

The aim of the present study was to evaluate the indication for a second prostate biopsy in patients suspected with PCa after an initial negative prostate biopsy.

2. Materials and methods

A total of 9,908 patients underwent prostate biopsy at three hospitals [Sinchon Severance Hospital ($n = 5,567$), Gangnam Severance Hospital ($n = 2,063$), and National Health Insurance Service Ilsan Hospital ($n = 2278$)] between January 2007 and December 2015. The reason for the initial prostate biopsy was a high PSA level of ≥ 3 ng/mL. Of the 6,737 patients whose initial biopsy result was negative, 527 consecutive patients initially underwent 12-core to 14-core prostate biopsy, with negative results, and then underwent a second prostate biopsy because of a high risk of PCa. The risk factors included prior high-grade prostatic intraepithelial neoplasia or atypical small acinar proliferation of the prostate, evaluation of biochemical failure after definitive treatment, such as prostatectomy and radiotherapy, an increase in the PSA level during follow-up, and abnormal DRE findings. Patients with a previous diagnosis of PCa, a history of receiving 5-alpha reductase inhibitors, a history of transurethral resection of the prostate, a pathological diagnosis of prostatic intraepithelial neoplasia or atypical small acinar proliferation, or a history of undergoing various imaging-guided biopsies before repeat prostate biopsy were excluded from the study cohort. Finally, 421 patients were included in the analysis. PSA follow-up after the initial negative biopsy was performed every 3−6 months.

Clinicopathological data, including patient age, body mass index, history of prostate biopsy, prostate volume, PSA level, PSA density, PSA velocity (PSAV), and PSA fluctuation patterns, were analyzed using our computerized database. PSAV was calculated as the PSA level at one time point minus the PSA level at another time point divided by the time elapsed in years between these two measurements. The patients were stratified into two groups based on the first PSA pattern (increase/decrease) within 1 year after the initial negative prostate biopsy.

This retrospective study was performed in accordance with the Institutional Review Board practice guidelines. Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as number of occurrences and frequency. Student's *t* test was used for statistical comparisons of the continuous and categorical variables. Additionally, simple and multiple logistic regression analyses were performed. All statistical analyses were performed using SPSS version 21 (IBM Corporation, Armonk, NY, USA). A *P* value of < 0.05 was considered statistically significant.

3. Results

The baseline characteristics of the cohort are presented in Table 1. The mean age of the patients was 66.1 years, and the mean PSA levels before the initial and second biopsies were 8.90 ng/mL and 10.01 ng/mL, respectively. The mean time from the initial biopsy to the second biopsy was 25.6 months, and the mean follow-up duration for PSA screening before PCa detection was 48.5 months. Among the 421 patients, 100 (23.8%) were diagnosed with PCa at the second prostate biopsy. There were no statistically significant differences in the PSA levels at the initial and second biopsies between patients with PCA and those without PCa at the second prostate biopsy ($P = 0.533$ and $P = 0.426$, respectively). However, the prostate volume, PSA densities at the initial and second biopsies, and number of prostate biopsy cores were higher in patients with PCa than in those without PCa at the second prostate biopsy (prostate volume: 38.16 cc vs. 50.66 cc, $P < 0.001$; PSA densities: 0.24 ng/mL/cc vs. 0.19 ng/mL/cc, $P < 0.024$ and 0.29 ng/mL/cc vs. 0.22 ng/mL/cc, $P < 0.016$; number of prostate biopsy cores: 14.24 vs. 13.06, $P = 0.039$, respectively).

Multivariate analysis showed that age [hazard ratio (HR) = 1.06, 95% confidence interval (CI) = 1.021−1.101, $P = 0.003$), prostate volume (HR = 0.97, 95% CI = 0.950−0.985, $P < 0.001$), number of prostate biopsy cores (≥ 13 vs. 12; HR = 2.56, 95% CI = 1.332−4.926, $P = 0.005$), number of increases in the PSA level at the time from before the time for the duration between the initial and repeat biopsy (≥ 1 vs. 0; HR = 3.56, 95% CI = 1.385−9.167, $P = 0.008$) were the predictive factors for a positive biopsy (Table 2).

On comparing the groups based on the first PSA pattern (increase/decrease) within 1 year after the initial negative prostate biopsy, we noted that the PSA level at the initial prostate biopsy was lower, the PSA density at the initial prostate biopsy was lower, the mean PSA level before the initial prostate biopsy was lower, the mean PSA level for the duration between the initial and second

Table 1
Baseline patient characteristics.

	Total	Prostate cancer (+)	Prostate cancer (−)	*P*
No. of patients	421	100 (23.8)	321 (76.2)	
Age at initial PBx (yr)	66.1 ± 8.1	67.9 ± 7.3	65.5 ± 8.29	0.009
PSA at initial PBx (ng/mL)	8.90 ± 7.13	8.46 ± 6.51	9.04 ± 7.32	0.533
PSA at repeat PBx (ng/mL)	10.01 ± 8.77	10.67 ± 10.13	9.80 ± 8.31	0.426
Prostate volume (cc)	47.62 ± 22.94	38.16 ± 16.32	50.66 ± 23.94	< 0.001
PSA density at initial PBx (ng/mL/cc)	0.20 ± 0.14	0.24 ± 0.18	0.19 ± 0.12	0.024
PSA density at repeat PBx (ng/mL/cc)	0.23 ± 0.23	0.29 ± 0.24	0.22 ± 0.17	0.016
No. of PBx core (*n*)	13.34 ± 4.42	14.24 ± 5.18	13.06 ± 0.41	0.039
No. of PSA down at the first follow up after initial PBx	106 (25.2)	29 (29.0)	77 (24.0)	0.849
Levels of PSA down at the first follow up after initial PBx (ng/mL)	0.15 ± 0.91	−1.58 ± 9.05	0.68 ± 9.07	0.073
PSAV before the initial PBx (ng/mL/yr)	0.56 ± 27.15	2.88 ± 15.31	−0.06 ± 29.55	0.619
PSAV before the repeat PBx (ng/mL/yr)	0.31 ± 25.68	−3.17 ± 48.52	1.41 ± 11.28	0.461
PSAV between the initial and repeat PBx (ng/mL/yr)	4.51 ± 34.94	8.93 ± 44.78	3.11 ± 31.21	0.258
Average of PSA levels before the initial PBx (ng/mL)	8.76 ± 7.38	8.65 ± 7.94	8.80 ± 7.21	0.875
Standard deviation of PSA levels before the initial PBx (ng/mL)	3.20 ± 6.53	1.85 ± 3.23	3.66 ± 7.25	0.008
Average of PSA levels for the follow-up duration (ng/mL)	9.26 ± 6.75	9.37 ± 7.41	9.22 ± 6.54	0.866
Standard deviation of PSA levels for the follow-up duration (ng/mL)	2.73 ± 4.31	2.52 ± 4.47	2.79 ± 4.26	0.656
Average of PSA levels after the repeat PBx (ng/mL)	7.29 ± 6.55		7.29 ± 6.55	0.812
Standard deviation of PSA levels after the repeat PBx (ng/mL)	2.93 ± 6.32		2.93 ± 6.32	0.842

Data are presented as *n* (%) or mean ± SD.
PBx, prostate biopsy; PSA, prostate cancer-specific antigen; PSAV, PSA velocity.

Table 2
Univariate and multivariate logistic regression analyses for predictors of the presence of prostate cancer at the second prostate biopsy.

	Univariate				Multivariate			
	HR	95% CI		P	HR	95% CI		P
Age at initial PBx*	1.04	1.009	1.070	0.010	1.06	1.021	1.101	0.003
PSA at initial PBx*	0.99	0.952	1.031	0.650				
PSA at repeat PBx*	1.01	0.984	1.037	0.450				
Prostate volume*	0.97	0.950	0.980	< 0.001	0.97	0.950	0.985	< 0.001
No. of PBx core (≥13 vs. 12)	1.83	1.096	3.044	0.021	2.56	1.332	4.926	0.005
No. of PSA decrease at the first follow-up after initial PBx*	1.51	0.817	2.778	0.189				
Levels of PSA decrease at the first follow-up after initial PBx*	1.01	0.958	1.063	0.741				
PSAV before the initial PBx*	0.99	0.952	1.031	0.650				
PSAV before the repeat PBx*	1.00	0.996	1.012	0.296				
PSAV between the initial and repeat prostate biopsy*	1.00	0.995	1.003	0.648				
Average of PSA levels before the initial PBx*	1.00	0.982	1.019	0.978				
Standard deviation of PSA levels before the initial PBx*	0.94	0.868	1.018	0.130				
Average of PSA levels for the follow-up duration*	0.94	0.853	1.038	0.225				
Standard deviation of PSA levels for the follow-up duration*	1.02	0.975	1.056	0.469				
No. of PSA increase from the initial PBx before the repeat biopsy (≥ 4 vs. 0–3)	1.87	1.008	3.460	0.047	1.33	0.665	2.654	0.421
No. of PSA increase at the time from before the time for the follow-up duration (≥ 1 vs. 0)	3.41	1.287	9.015	0.014	3.56	1.385	9.167	0.008

*, Continous variable.
CI, confidence interval; HR, hazard ration; PBx, prostate biopsy; PSA, prostate cancer-specific antigen; PSAV, PSA velocity.

prostate biopsies was higher, and the standard deviation of the PSA level for the duration between the initial and second prostate biopsies was lower in the group that showed a PSA decrease than in the group that showed a PSA increase ($P < 0.001$, $P < 0.001$, $P = 0.026$, $P < 0.001$, and $P < 0.001$, respectively; Table 3).

In multivariate analysis of patients with a PSA decrease at the first follow-up after the initial prostate biopsy, prostate volume (HR = 0.96, $P = 0.006$) and number of increases in the PSA level from the initial prostate biopsy before the repeat biopsy (≥ 2 vs. 0–1) (HR = 3.21, $P = 0.031$) were significant predictors of the diagnosis of PCa at the second prostate biopsy (Table 4). Additionally, in multivariate analysis of patients with a steady PSA increase at the first follow-up after the initial prostate biopsy, prostate volume (HR = 0.95, $P = 0.12$) and number of prostate biopsy cores (≥ 13 vs. 12; HR = 4.34, $P = 0.008$) were significant predictors of the diagnosis of PCa at the second prostate biopsy (Table 4).

4. Discussion

For patients with an initial negative prostate biopsy, the second prostate biopsy should be considered when there are persistent clinical indications of PCa, such as a steady increase in the PSA level and abnormal DRE findings. We found that old age, low prostate volume, high number of prostate biopsy cores, and one more time of increase PSA at the time compared to before the time are useful for predicting PCa. For patients with a decrease in the PSA level after the initial prostate biopsy, the second prostate biopsy was recommended at the second instance (or further instances) of a PSA level higher than that at the initial prostate biopsy, and a high number of biopsy cores had no benefit for the detection of PCa. For patients with a steady increase in the PSA level after the initial prostate biopsy, a high number of biopsy cores could predict PCa.

Prostate biopsy is the only diagnostic method to confirm PCa. However, 20–30% of the cases of PCa might be missed at the initial

Table 3
Characteristics of the patients stratified into two groups based on the first prostate-specific antigen pattern (increase/decrease) within 1 year after an initial negative prostate biopsy.

	PSA decrease at the first follow-up after initial prostate biopsy ($n = 106$)	PSA increase at the first follow-up after initial prostate biopsy ($n = 125$)	P
No. of patients	29 (27.4)	25 (20.0)	0.849
Age at initial PBx (yr)	65.50 ± 8.72	66.39 ± 7.55	0.854
PSA at initial PBx (ng/mL)	7.10 ± 4.74	10.67 ± 8.35	< 0.001
PSA at repeat PBx (ng/mL)	10.12 ± 7.47	10.06 ± 9.67	< 0.001
Prostate volume (cc)	44.67 ± 18.37	53.11 ± 25.23	0.892
PSA density at initial PBx (ng/mL/cc)	0.18 ± 0.13	0.22 ± 0.15	< 0.001
PSA density at repeat PBx (ng/mL/cc)	0.25 ± 0.19	0.21 ± 0.18	< 0.001
No. of PBx core (n)	13.16 ± 3.57	12.92 ± 3.19	0.898
Levels of PSA decrease at the first follow-up after initial PBx (ng/mL)	2.56 ± 3.57	−3.77 ± 6.68	< 0.001
PSAV before the initial PBx (ng/mL/yr)	−12.16 ± 61.13	−5.69 ± 63.03	0.003
PSAV before the repeat PBx (ng/mL/yr)	−0.72 ± 20.94	21.77 ± 199.58	0.234
PSAV between the initial and repeat PBx (ng/mL/yr)	5.92 ± 12.28	0.25 ± 13.17	< 0.001
Average of PSA levels before the initial PBx (ng/mL)	7.84 ± 5.41	9.95 ± 9.09	0.026
Standard deviation of PSA levels before the initial PBx (ng/mL)	2.82 ± 4.20	4.93 ± 9.28	0.176
Average of PSA levels for the follow-up duration (ng/mL)	9.39 ± 6.46	8.47 ± 5.83	< 0.001
Standard deviation of PSA levels for the follow-up duration (ng/mL)	2.52 ± 2.78	2.63 ± 5.10	< 0.001
Average of PSA levels after the repeat PBx (ng/mL)	5.35 ± 2.55	7.68 ± 4.44	0.112
Standard deviation of PSA levels after the repeat PBx (ng/mL)	1.29 ± 1.69	4.08 ± 6.34	0.146

Data are presented as n (%) or mean ± SD.
PBx, prostate biopsy; PSA, prostate cancer-specific antigen; PSAV, PSA velocity.

Table 4
Univariate and multivariate logistic regression analyses for predictors of prostate cancer based on the first prostate-specific antigen pattern (increase/decrease) within 1 year after an initial negative prostate biopsy.

	PSA decrease at the first follow-up after initial PBx						PSA increase at the first follow-up after initial PBx					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age at initial PBx*	1.00	0.944 1.057	0.968				1.04	0.992 1.098	0.102			
PSA at initial PBx*	0.93	0.857 1.012	0.093				1.08	0.987 1.174	0.095			
PSA at repeat PBx*	0.98	0.929 1.038	0.522				1.04	0.982 1.090	0.202			
Prostate volume*	0.96	0.935 0.987	0.004	0.96	0.938 0.989	0.006	0.96	0.926 0.992	0.016	0.95	0.917 0.989	0.012
No. of PBx core ($\geq$ 13 vs. 12)	3.77	1.145 12.385	0.029	2.82	0.711 11.215	0.140	3.46	1.280 9.327	0.014	4.34	1.465 12.859	0.008
PSAV before the initial PBx*	1.00	0.989 1.020	0.585				1.01	0.995 1.017	0.328			
PSAV before the repeat PBx*	1.00	0.993 1.005	0.671				1.00	0.977 1.015	0.660			
PSAV between the initial and repeat PBx*	1.00	0.974 1.035	0.789				1.01	0.983 1.047	0.380			
No. of PSA increase from the initial PBx before the repeat biopsy ($\geq$ 4 vs. 0−3)	3.00	0.799 11.263	0.104				1.99	0.776 5.125	0.152			
No. of PSA increase from the initial PBx before the repeat biopsy ($\geq$ 2 vs. 0−1)	3.31	1.254 8.736	0.016	3.21	1.114 9.227	0.031	1.28	0.528 3.112	0.583			

*, Continous variable.

CI, confidence interval; HR, hazard ration; PBx, prostate biopsy; PSA, prostate cancer-specific antigen; PSAV, PSA velocity.

prostate biopsy.[4] The detection rates have been reported to decrease with repeat biopsies (34% for the first biopsy, 25% for the second, and 24% for the third).[7] For patients who underwent a second prostate biopsy, the PCa detection rate was similar between the present study (23.8%) and this previous study.

The concept of PSAV suggested by Carter et al[8] has been widely used.[8] Several studies have reported regarding the benefits of using PSAV.[9] A previous study reported that PSAV (cutoff value: 0.75 ng/mL/y) helped to identify men with PCa.[10] Ulmert et al[11] showed that PSAV alone could significantly detect PCa on multivariate analysis.[11] However, these results are not consistent with those of our study among patients who underwent a second prostate biopsy. We found that the PSAV between the initial and second prostate biopsies was not a predictor of PCa ($P = 0.648$).

Several clinicians experienced difficulty in reproducing results with 1- and 2-year intervals between PSA assessments because PSA assessments were performed with intervals of several years and patients showed fluctuating PSA values (increases and decreases).[12] The definition of PSA fluctuation was not consistent in previous studies, and the effect of PSA fluctuation on the detection of PCa remains controversial. Previous studies have reported that there was no statistically significant difference in the positive rate of repeat biopsy between patients with fluctuating PSA levels and those with steadily increasing PSA levels.[12,13] However, Park et al[14] analyzed 492 patients who underwent repeat prostate biopsy and reported that the PSA fluctuation pattern was a significant predictor of a positive repeat biopsy.[14] When PSA fluctuation was considered according to the number of increases in the PSA level at the time from before the time for the duration between the initial and second prostate biopsy, the detection rate of PCa was significantly higher in the group with fluctuating PSA levels than in the group with steadily increasing PSA levels (25.5% vs. 10.3%, $P = 0.010$).

Previous studies have evaluated the relation between PSA variation and PCa. In a previous study that evaluated 64 men, the coefficient of variation, calculated by dividing the standard deviation of each set of serum PSA levels by the mean of the levels and multiplying by 100, was used as a parameter that reflected the intra-individual variability of PSA.[15] The coefficient of variation has been reported to be lower in patients with cancer than in those without cancer (5.7% vs. 9.7%). In our study, the mean and standard deviation of the PSA levels for the duration between the initial and repeat prostate biopsies had no influence on the diagnosis of PCa. The coefficient of variation determined by obtaining two or more PSA values over a period of 4 weeks is similar to that in the prior study in part of only higher in without PCa than with PCa (27.1% vs. 25.4%, $P = 0.619$). However, the number of patients was low, and the mean PSA might have been higher in patients with PCa than in those without PCa in the prior studies, indicating that the results might have been statistically underrepresented.

The number of increases in the PSA level appears to be a useful indicator for prostate biopsy. Marberger et al[16] found that biopsy based on a single increase in the PSA level was important for PCa detection according to data from the Reduction by Dutasteride in Prostate Cancer Events study.[16] However, a recent review article showed that biopsy based on an increase in the PSA level for a patient using dutasteride may result in the exclusion of a substantial proportion of Gleason 7−10 cases (42.9%).[17] The NCCN guidelines recommend that patients with an initial negative biopsy should undergo PSA assessments and DRE at 1-year intervals initially. Therefore, we stratified the patients into two groups based on the first PSA pattern (increase/decrease) within 1 year after the initial negative prostate biopsy, and we established a clinically useful strategy according to the PSA pattern.

To increase the detection rate for patients to plan a repeat biopsy, several strategies including extended biopsies, targeted biopsy of mpMRI-suspicious areas, and transperineal saturation biopsies, were suggested.[18,19] mpMRI is recommended in men who are candidates for repeat biopsy, the detection rate for PCa is between 39% and 59%, and the incidence of cancer located only in the anterior zone is 20%.[20−22] Although various biopsies protocol before repeat prostate biopsy showed higher detection rate than standard transrectal ultrasound (TRUS)-biopsy, mpMRI is not reimbursed for patients suspected with PCa in Korea. Transperineal saturation biopsies permit the operator easily to reach the anterior zone of prostate the gland and lowering the risk of sepsis.[23] Transperineal saturation biopsies are not generally considered instead of TRUS-biopsy at our institutions. Biomarkers were recommended in patients who underwent at least one negative biopsy for a repeat biopsy. The cost of the test remains a significant barrier to its utilization in most markets. Therefore, this study focused on determining better indication and easier selection in patients using further evaluation in the population of men with prior negative biopsies and persistent suspicion of PCa.

The present study has several limitations. Multiple factors influenced the clinical decision making regarding the implementation of a repeat biopsy, such as PSA and DRE. However, several characteristics could account for the heterogeneity in the results, including the multiple physicians and a patient preference.

The indication to repeat biopsy lacked standardization, and a selection bias may have existed. Nevertheless, we believe that this effect is inherent in any retrospective study and may reflect real-world clinical practice in which the decision for repeat biopsy is not standardized. Additionally, we were unaware of the number of cases that were missed because of not recommending repeat biopsy. Finally, this was a retrospective study, and the small number of patients might have influenced the results. Further studies with a larger number of patients are required to determine the detailed clinical relevance of our findings in order to help reduce the number of unnecessary biopsies.

5. Conclusion

The indications for a second prostate biopsy are a low prostate volume and high number of increases in the PSA level among patients with a PSA decrease at the first follow-up and a low prostate volume and a high number of biopsy cores among patients with a PSA increase at the first follow-up.

Conflicts of interest

None.

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