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

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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...
free-total prostate-specific antigen ratio (fPSA).\(^5\) 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 = 2,278)] 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 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 for the duration between the initial and second

Table 1

| 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 ± 4.1 | 0.039 |
| No. of PSA down at the first follow up after initial PBx | 106 (25.2) | 29 (29.8) | 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) | 2.60 ± 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.
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 (\( \geq 2 \) 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 (\( \geq 13 \) 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

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**Table 2**

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

|                      | Univariate |                      |                      |
|----------------------|------------|----------------------|----------------------|
|                      | HR         | 95% CI               | \( P \)               |
|                      |            |                      |                      |
| Age at initial PBx   | 1.04       | 1.009                | 1.070                |
|                      | 0.010      |                      |                      |
| 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     |                      |                      |
| No. of PBx core (\( \geq 13 \) vs. \( 12 \)) | 1.16       | 1.096                | 1.044                |
|                      | 0.021      |                      |                      |
| No. of PSA decrease at the first follow-up after initial PBx* | 1.38       | 0.817                | 2.277                |
|                      | 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 (\( \geq 4 \) vs. \( 0-3 \)) | 1.00       | 1.008                | 3.460                |
|                      | 0.047      |                      |                      |
| No. of PSA increase at the time from before the time for the follow-up duration (\( \geq 1 \) vs. \( 0 \)) | 3.41       | 1.287                | 9.015                |
|                      | 0.014      |                      |                      |

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

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**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 ± 8.33                                                                    | <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)  | 11.16 ± 3.57                                                                     | 12.92 ± 3.19                                                                    | 0.058                |
| 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.
prostate biopsy. 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). 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 has been widely used. Several studies have reported regarding the benefits of using PSAV. A previous study reported that PSAV (cutoff value: 0.75 ng/mL/y) helped to identify men with PCA. Ulmert et al showed that PSAV alone could significantly detect PCa on multivariate analysis. However, these results are not consistent with those of our study and previous 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 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. 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%). 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. 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%. 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.

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.

### Table 4

| Prostate Cancer Events study | Univariate | Multivariate | Univariate | Multivariate |
|----------------------------|------------|-------------|------------|-------------|
| PSA decrease at the first follow-up after initial PBx | HR (95% CI) | P | HR (95% CI) | P |
| Age at initial PBx | 1.00 (0.94–1.057) | 0.968 | 1.04 (0.992–1.098) | 0.102 |
| PSA at initial PBx* | 0.95 (0.857–1.012) | 0.093 | 0.97 (0.917–1.04) | 0.276 |
| PSA at repeat PBx* | 0.98 (0.929–1.038) | 0.522 | 0.98 (1.090–2.02) | 0.102 |
| Prostate volume* | 0.96 (0.935–0.987) | 0.004 | 0.96 (0.926–0.992) | 0.016 |
| No. of PBx core (≥ 13 vs. 12) | 1.34 (1.145–12.385) | 0.029 | 1.34 (1.145–12.385) | 0.029 |
| PSAV before the initial PBx* | 1.00 (0.993–1.015) | 0.671 | 1.00 (1.005–1.015) | 0.66 |
| PSAV before the repeat PBx* | 1.00 (0.974–1.035) | 0.789 | 1.00 (1.005–1.015) | 0.66 |
| PSAV between the initial and repeat PBx* | 1.08 (1.035–1.015) | 0.06 | 1.08 (1.035–1.015) | 0.06 |
| No. of PSA increase from the initial PBx before the repeat biopsy (≥ 4 vs. 0–3) | 0.99 (0.776–1.047) | 0.152 | 0.99 (0.776–1.047) | 0.152 |
| No. of PSA increase from the initial PBx before the repeat biopsy (≥ 2 vs. 0–1) | 0.99 (0.776–1.047) | 0.152 | 0.99 (0.776–1.047) | 0.152 |

*Continuous variable.

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