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Delaying a Biopsy With Serial Prostate-Specific Antigen Checkup Helps to Identify a Significant Prostate Cancer: A Strategy to Evade Unnecessary Procedures

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Purpose: To differentiate a non-cancer-related temporary increase in prostate-specific antigen (PSA) triggering unnecessary biopsy, we intentionally delayed biopsy with a serial follow-up, then investigated the efficacy of this strategy in identifying a significant prostate cancer (PCa).

Materials and Methods: Retrospective data of patients who initially presented with a suspicious level of serum PSA (3–20 ng/mL), managed using the delayed strategy, and then eventually underwent biopsy were obtained from 4 tertiary centers between 2018–2020.

Results: The collected 271 subjects had a median (interquartile range) PSA, age, and prostate volume of 5.03 ng/mL (4.46–7.79 ng/mL), 67 years (61–73 years), and 38 g (28–50 g), respectively. During the delay period of 8 weeks (4–19 weeks), most were managed with alpha-blockers (85.6%, n=232). Ninety-four (34.7%) experienced a PSA decrease of 20.53% (8.82–38.16). Eventual biopsy revealed 115 PCa cases (42.5%) including 82 significant ones and 46 high-risk diseases. Men with a PSA decrease had a lower probability of PCa (31.9% vs. 48%, p=0.014), a significant disease (21.3% vs. 35.0%, p=0.026), and high-risk PCa (7.4% vs. 22.0%, p=0.002) than the PSA-elevated counterparts. However, the degree of PSA decrease was not associated with the presence or the severity of PCa. In patients with PSA normalization (≤3 ng/mL), though 4 patients of them (66%) had PCa including a single significant disease, none had high-risk disease.

Conclusions: About one-third of individuals initially indicated for transrectal biopsy experienced a decrease in PSA, and their chance for significant PCa was diminished. This retrospective study suggests PSA normalization could be an acceptable notion, though requires further investigation.

Key Words: Prostate cancer, Prostate biopsy, Significant prostate cancer

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INTRODUCTION

Widespread screening for prostate-specific antigen (PSA) and increased life expectancy have led to an increased incidence of prostate cancer (PCa) in many Asian countries.[1,2] However, the benefits of PSA-based mass screening policies have remained controversial since 2012,[3,4] when the US preventive study task force recommended against PSA mass screening mainly due to the lack

of evidence that PSA screening positively affects survival and the risk of overdiagnosis and treatment of so-called insignificant disease.[5]

Nevertheless, serum PSA testing continues to play a pivotal role in the detection of PCa, given that the majority of early phase PCa cases do not manifest specific symptoms besides ambiguous male lower urinary tract symptoms (LUTS), which originate more frequently from concomitant benign prostate hyperplasia (BPH). Several additional serum tumor markers were introduced to reduce the detection of insignificant cancer while maintaining high specificity for significant PCa to compensate for this major drawback of PSA screening, these markers include 4K score, prostate health index, and several PSA-derived variables. However, the use of these markers increases medical costs and their socioeconomic benefits have not been proven.[6,7]

Regarding the specificity of PSA testing, it is well-known that serum PSA levels are influenced by several clinicopathological conditions unassociated with the development of malignant disease; most commonly BPH, LUTS, and prostatitis. However, there is a long list of other nonpathologic daily phenomena that may cause a temporary increase in PSA levels, such as prostate massage, cystoscopy, hemodialysis,[8] ejaculation, bicycle riding,[9] and even diurnal changes.[10] To distinguish between the presence of significant PCa and these non-cancer-related conditions that eventually trigger unnecessary biopsy, we intentionally delayed transrectal biopsy (TrBx) and administered empirical medications, and serially followed PSA levels in patients that at initial presentation had a suspicious PSA level (3–20 ng/mL). We postulated that changes in PSA from baseline during a delay period would be associated with the severity of PCa. The purpose of this study was to investigate the oncologic safety and efficacy of this strategy.

MATERIALS AND METHODS

1. Patient Selection and Acquisition of Data

Retrospective data for patients with PSA levels between 3 and 20 ng/dL at initial presentation and managed by delaying the immediate biopsy strategy and who received empirical medications for at least 2 weeks for male LUTS and/or prostatitis were obtained from 4 tertiary urologic centers in a single Korean province (Daegu metropolitan city) between January 2018 and December 2020. The study inclusion criteria were (1) an initial visit to a tertiary hospital with a chief complaint of an elevated PSA level or male LUTS/BPH symptoms in aged over 50 years, and (2) serial PSA testing with minimal 2 weeks interval of PSA follow-up, and (3) the implantation of TrBx regardless of the PSA change following empirical medication.

The exclusion criteria applied were; (1) receipt of 5 alpha-reductase inhibitors including finasteride and dutasteride, or (2) a previous prostate biopsy history, or (3) a transperineal biopsy procedure, or (4) <12 biopsy cores, or (5) receipt of fusion biopsy using magnetic resonance imaging. Data collected included PSA levels from initial to last tests just before TrBx. Empirical medications were categorized as; (1) alpha-blockers, which were divided into 12 subcategories by type and daily dose (tamsulosin 2 mg, tamsulosin 4 mg, alfuzosin 10 mg, naftopidil 50 mg, naftopidil 75 mg, doxazosin 4 mg, terazosin 2 mg, terazosin 4 mg, terazosin 5 mg, terazosin 10 mg, silodosin 4 mg, and silodosin 8 mg), (2) oral antibiotics (cephalosporins, quinolones, nitrofurantoin), (3) antimuscarinics (fesoterodine, solifenacin, propiverine, imidafenacin), (4) beta-3 agonist (mirabegron), and (5) desmopressin. For patients in whom PCa was detected by TrBx, clinical stages and biopsy Gleason scores were collected to determine the PCa severity. As is required by

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the privacy guidelines of the Health Insurance Portability and Accountability Act, all personal identification numbers were encrypted before data processing. The Institutional Review Boards of the 4 tertiary urologic centers approved all procedural and ethical aspects of the study beforehand (approval number: YUMC 202103070).

2. Study Design and Outcome Measurements

Based on the information collected, the change in PSA levels from baseline was categorized as decreases or increases, regardless of the amount of the difference. The ratio of change at its peak level was also calculated based on its baseline level. When serial PSA levels fluctuated during the follow-ups, the lowest value from baseline was selected, because we focused on the clinical value of PSA decrease during the short period of follow-up. The return of PSA to the reference level below 3 ng/mL was defined as PSA normalization in this study.

The primary study endpoint was to determine

Table 1. The characteristics of the patients enrolled

Variable	The change of PSA during follow-up period			
	Total patients	PSA increased group (n=177)	PSA decreased group (n=94)	p-value
Age (yr)	66.9±8.3	67.5±7.7	65.8±9.3	0.101
≤67 (median)	145 (53.5)	92 (63.4)	53 (36.6)	0.524
>67	126 (46.5)	85 (67.5)	41 (32.5)	
Prostate volume (g)	42.4±22.4	42.2±24.0	42.8±18.7	0.851
≤38 (median)	110 (40.6)	75 (68.2)	35 (31.8)	0.438
>38	161 (59.4)	102 (63.4)	59 (36.6)	
Initial PSA (ng/mL)	6.5±3.0	5.8±2.6	7.7±3.3	<0.001
≤5.8 (median)	136 (50.2)	103 (75.7)	33 (24.3)	<0.001
>5.8	135 (49.8)	74 (54.8)	61 (45.2)	
Last PSA (ng/mL)	12.9±82.3	16.5±101.7	6.0±2.5	0.318
>3	261 (96.3)	173 (66.3)	88 (33.7)	0.1
≤3	10 (3.7)	4 (40.0)	6 (60.0)	
Duration of emprical medication (wk)	25.8±57.3	28.7±62.0	20.7±47.6	0.354
>8	165 (60.9)	113 (68.5)	52 (31.5)	0.192
≤8	106 (39.1)	64 (60.4)	42 (39.6)	
Biopsy outcome				0.014
Negative	156 (57.6)	92 (59.0)	64 (41.0)	
Prostate cancer detected	115 (42.4)	85 (73.9)	30 (26.1)	
Prostate cancer significance				0.172
Insignificant cancer	37 (32.2)	24 (64.9)	13 (35.1)	
Significant cancer	78 (67.8)	61 (78.2)	17 (21.8)	
Positive core number (among 12 cores)				0.12
0	4 (2.7)	1 (25.0)	3 (75.0)	
1	27 (18.5)	18 (66.7)	9 (33.3)	
2	15 (10.3)	13 (86.7)	2 (13.3)	
3	6 (4.1)	5 (83.3)	1 (16.7)	
4	8 (5.5)	7 (87.5)	1 (12.5)	
5	8 (5.5)	4 (50.0)	4 (50.0)	
6	16 (11.0)	11 (68.8)	5 (31.3)	
7	8 (5.5)	5 (62.5)	3 (37.5)	
8	4 (2.7)	4 (100)	0 (0)	
9	7 (4.8)	5 (71.4)	2 (28.6)	
10	4 (2.7)	3 (75.0)	1 (25.0)	
11	7 (4.8)	7 (100)	0 (0)	
12	32 (21.9)	17 (53.1)	15 (46.9)	

Values are presented as mean±standard deviation or number (%).

PSA: prostate-specific antigen.

whether PSA changes especially the decrease could predict the presence of significant PCa. In this study, the definition of significant disease was (1) Gleason group (GG) 1 and ≥6 positive core among 12 standard TrBx specimens, or (2) GG ≥2 and ≥ positive cores, or (3) GG of ≥3 regardless of the positive core count.

3. Statistical Analysis

The Student's t-test was used to compare continuous variables, and the chi-square test was used to compare binary and categorical variables. If a decrease in PSA or the presence of significant PCa was found to be significantly associated with a variable by the chi-square test, then the variables concerned, such as kind and duration of empirical medication, age, initial PSA level, prostate volume, and empirical medication duration, were subjected to multivariate analysis using the logistic regression model. The analysis was performed using IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA). For all comparisons, statistical significance was accepted for p-values of <0.05.

RESULTS

1. The Characteristics of the Patients Selected and the Types of Empirical Medication Used

Of 455 patients that underwent delayed biopsy, 271 patients met the study inclusion criteria. Median (interquartile range) initial PSA, age, and prostate volume were 5.03 ng/mL (4.46–7.79 ng/mL), 67 years (61–73 years), and 38 g (28–50 g), respectively (Table 1). During the median delay of 8 weeks (4–19 weeks) until the eventual biopsy, the empirical medications prescribed were in the order of alpha-blockers (85.6%, n=232, with 12 different components), beta 3 antagonists (mirabegron 50 mg, 12.5%, n=34), antibiotics (10.3%, n=28), desmopressin (4.1%, n=11), and anticholinergics (1.5%, n=4). Table 2 summarizes empirical medication proportions and durations of use.

Table 2. The list of empirical medications for lower urinary symptoms includes the incidence and duration of drug administration

Category	No. (%)	Mean±SD	p-value*
Alpha-blockers	232 (85.6)	25.88±57.31	0.942
Tamsulsin 2 mg	73 (26.9)	16.55±41.48	
Tamslosin 4 mg	20 (7.4)	36.89±38.13	
Alfuzosin 10 mg	38 (14)	32.08±91.08	
Naftopidil 75 mg	23 (8.5)	26.95±63.35	
Doxazosin 4 mg	12 (4.4)	41.33±47.28	
Terazosin 2 mg	7 (2.6)	10.75±5.19	
Terazosin 4 mg	2 (0.7)	18.50±3.54	
Terazosin 5 mg	9 (3.3)	16.50±21.53	
Terazosin 10 mg	3 (1.1)	7.00±2.00	
Silodosin 4 mg	2 (0.7)	21.50±9.19	
Silodosin 8 mg	11 (4.1)	32.36±58.26	
Unknown	32 (11.8)	19.38±37.74	
Antibiotics	28 (10.3)	9.04±7.78	
Mirabegron (50 mg)	34 (12.5)	20.18±26.20	
Desmopressin	11 (4.1)	20.23±34.23	
Anticholinergics	4 (1.5)	10.50±2.52	

SD: standard deviation.
*Difference of medication duration between each components.

2. Summary of PSA Change and Final Biopsy Outcome

Among the 271 study subjects, 34.7% (n=94) experienced a PSA decrease with a median change of 1.32 ng/mL (0.57–2.63 ng/mL) from baseline (a decrease of 20.53% [8.82–38.16]). In 35% among them (n=33), PSA was decreased below 4 ng/mL, and 6 subjects (6.4%) had PSA normalization (≤3 ng/mL) during the follow-up period. For the subjects who experienced a PSA increase, the median change was 1.51 ng/mL (0.76–3.54 ng/mL) (an increase of 30.31% [14.25–61.26]). From the eventual biopsy, 115 cases (42.5%) with PCa were identified and 71.3% of these (n=82) had a significant disease from our definition. High-risk cancers (GG ≥4) were found in 40% of them (n=46).

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3. Factors Associated With the PSA Decrease From the Baseline

Table 3 summarized the outcome of multivariate analysis which impacts the PSA decrease from the baseline. The PSA decrease was negatively associated with the presence of PCa (hazard ratio [HR], 0.43; p=0.004), which occurred more frequently in patients with higher PSA levels (≥5.8 ng/mL, the median value). However, the duration and type of empirical medication had no impact on the PSA decrease.

4. Factors Associated With the Presence of Significant Prostate Cancer

Men with a PSA decrease had a lower probability of PCa than those who experienced PSA elevation (31.9% vs. 48%, p=0.014). They also had a lower chance of a significant disease (21.3% vs. 35.0%, p=0.026), and high-risk PCa (7.4% vs. 22.0%, p=0.002) than the PSA-elevated counterparts. From the multivariate analysis, a PSA decrease was negatively associated with the presence of PCa (HR, 0.43; p=0.005), the significant disease (HR, 0.421;

Table 3. The summary of logistic regression on the variables associated with the decrease of PSA following empirical medication and serial checkups

Variable (reference)	p-value	Exp(B)	95% CI for Exp(B)
The presence of prostate cancer on biopsy (absence)	0.004	0.434	0.244–0.771
Initial PSA ≥5.8 ng/dL (<5.8 ng/dL)	<0.001	2.942	1.711–5.059
Age ≥67 yr (<67 yr)	0.733	0.91	0.530–1.563
Prostate volume >38 g (≤38 g)	0.7	1.116	0.638–1.953
Empirical medication duration <8 wk (≥8 wk)	0.246	0.729	0.428–1.243
Alpha-blockers use (nonuse)	0.872	1.057	0.540–2.069
Anticholinergics use (nonuse)	0.505	2.022	0.256–15.996
Beta3 antagonist use (nonuse)	0.14	1.851	0.817–4.196
Antibiotics use (nonuse)	0.399	1.432	0.622–3.297
Desmopressin use (nonuse)	0.129	0.282	0.055–1.444

PSA: prostate-specific antigen, CI: confidence interval.

Table 4. The summary of logistic regression on the variables associated with the presence of prostate cancer, significant disease, and high-risk tumor

Variable (reference)	p-value	Exp(B)	95% CI for Exp(B)
Prostate cancer			
The decrease of PSA (the increase of PSA)	0.005	0.438	0.247–0.776
Initial PSA ≥5.8 ng/dL (<5.8 ng/dL)	0.009	2.03	1.191–3.460
Age ≥67 yr (<67 yr)	0.005	2.116	1.247–3.589
Prostate volume >38 g (≤38 g)	<0.001	0.36	0.211–0.614
Empirical medication duration <8 wk (≥8 wk)	0.962	0.987	0.581–1.676
Significant prostate cancer			
The decrease of PSA (the increase of PSA)	0.007	0.421	0.223–0.793
Initial PSA ≥5.8 ng/dL (<5.8 ng/dL)	0.005	2.262	1.272–4.022
Age ≥67 yr (<67 yr)	0.009	2.142	1.207–3.801
Prostate volume >38 g (≤38 g)	<0.001	0.307	0.173–0.545
Empirical medication duration <8 wk (≥8 wk)	0.564	1.183	0.668–2.093
High-risk prostate cancer			
The decrease of PSA (the increase of PSA)	0.003	0.257	0.106–0.626
Initial PSA ≥5.8 ng/dL (<5.8 ng/dL)	0.073	1.886	0.943–3.773
Age ≥67 yr (<67 yr)	0.002	3.022	1.483–6.161
Prostate volume >38 g (≤38 g)	0.003	0.35	0.174–0.703
Empirical medication duration <8 wk (≥8 wk)	0.646	0.847	0.417–1.720

PSA: prostate-specific antigen, CI: confidence interval.

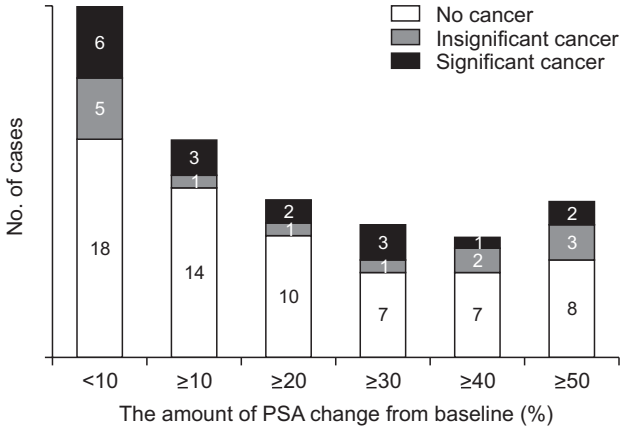

Fig. 1. Prostate-specific antigen (PSA) decreases categorized by final histology outcomes.

p=0.007), and high-risk cancer (HR, 0.25; p=0.003) as well. Reversely, the probability of PCa was significantly higher in subjects with higher initial PSA (≥5.8 ng/dL), elderly (≥67 years), and small prostate volume (≤38 g) (Table 4).

However, the degree of PSA decrease from the baseline during the follow-up period was not associated with the presence of tumor (p=0.513), or the severity of PCa (p=0.356) (Fig. 1). Among those with PSA decrease ≤4 ng/mL before the biopsy, 30.3% (n=10) had PCa including 5 significant diseases and 2 high-risk tumors. In patients with PSA normalization (≤3 ng/mL), though 4 patients of them (66%) had PCa including a single significant one, none had high-risk disease.

DISCUSSION

Nowadays, the majority of PCa cases are detected in the nonmetastatic stage, mainly due to enhanced public awareness of the prostatic disease and increased detection by PSA screening. As a result, the incidence of PCa in Korea has increased more than 12 times in over 2 decades according to updated national-wide cancer registry data (1,258 in 2000 vs. 14,857 in 2018). As such, PCa has become the 3rd most prevalent cancer among Korean men, and the 2nd most common male cancer in men aged over 65.[11] The more the population is exposed to PSA screening, the more patients require a biopsy to confirm the presence of the disease. However, because the majority of those with a suspicious PSA level are elderly, the risks posed by biopsy-induced adverse events are not insignificant. Indeed, the mean age of patients in this study was 67 years. Also, a lot of events cause a non-cancer-related temporary increase of PSA which could be distinguished by the decrease of PSA in serial follow-up. Therefore, we proposed delaying biopsy to minimize the number of unnecessary biopsies and increase the predictability of significant PCa in subjects with initial PSA under high-risk PCa criteria (<20 ng/mL).

This is an exploratory study investigating the oncologic efficacy of this notion utilizing retrospective data. Some noteworthy findings were obtained during the present study. Among those with a suspicious PSA level at baseline, about one-third showed a PSA decrease during the median serial follow-up of 8 weeks before the prostate biopsy. In contrast to other subjects with PSA elevation, the probability of PCa among those with a PSA reduction was decreased by over 15% (48% vs. 31.9%). This gap has been maintained for the patients with significant disease (35.0% vs. 21.3%), as well as for the high-risk PCa generating about a three-fold difference (22.0% vs. 7.4%). When other confounding factors were considered, the multivariate analysis also demonstrated similar findings.

There are several series that traced the clinical implication of PSA decrease following BPH/LUTS medication, including alpha-blockers and antibiotics. Tubaro et al.[12] reported outcomes from their prospective study administrating tamsulosin 0.4 mg for 8 weeks to 80 subjects with PSA level of ≥4 ng/dL and a maximum flow rate of <15 mL/sec

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who subsequently underwent 12-core TrBx. They found a significant increment in the PSA level in the patient with PCa, and a significant decrease in the PSA level in the patients with negative biopsy. They suggested the definition of a 'significant' PSA decrease as ≤4.0 ng/mL or a decrease ≥20% from the baseline. Based on these criteria, only a single case was finally confirmed to have PCa among 38 patients, and they reported a sensitivity of 96.6%, specificity of 72.5%, and diagnostic accuracy of 81%. Their findings were supported by the other small prospective series administrated tamsulosin 0.2 mg for 48 males with BPH/LUTS,[13] but not reproduced in this series, even though 85% of the recruited subjects had alpha-blockers for a median of 8 weeks. Indeed, the chance of PCa was also decreased in the present study, but a serious number of patients still had a significant disease or high-risk PCa just by dividing the subjects whether by the increase or decrease of PSA from the baseline. Though the relationship between the degrees of PSA decrease and the presence/severity of PCa has been investigated as shown in Fig. 1, no significant one was identified from our data.

A decrease in PSA in suspicious levels was also reported in studies that administered antibiotics[14,15] because subclinical inflammation of the prostate could elevate serum PSA in an asymptomatic way. In a recent meta-analysis of 31 different series including 8 randomized clinical trials, more than 2 weeks of antibiotic therapy was reported to be beneficial for detecting PCa when PSA was <20 ng/mL.[16] However, the impact of antibiotics on PSA changes in this present study was limited, as only 10.3% of selected patients had utilized antibiotics over a median duration of 9 weeks. It is also noteworthy that the type and duration of medication from our series have no impact on the change of PSA in a multicapitate analysis.

Rather, our data show that PSA normalization is a valuable indicator of the presence of significant and high-risk PCa. To determine the safety of this strategy, we categorized the patients and found that 98.7% of significant PCa cases had the lowest PSA level above 3.0 ng/mL even after receiving empirical medication. In subjects who experienced PSA normalization, none have high-risk PCa criteria including GG over 4. However, this suggestive cutoff is arbitrary and hypothesis-generating, requiring further investigation.

The authors are well aware of several limitations of this series. First, although about half of the subjects (40.4%, 184 of 455) originally considered were excluded, this study was not free from the inherited nature of the retrospective design. Only 35% of the 271 selected subjects experienced a PSA decrease, which was substantially lower than 47.5% reported to show a PSA decrease over 8 weeks after alpha-blocker administration,[12] even compared with the range of 17%–80% in PSA decrease of antibiotic studies with shorter-term duration.[15] Because the majority of the subject who agreed to delay their biopsy by initial presentation was willing to go to refuse the planned biopsy after the normalization of PSA level from the baseline, their cancer status was not investigated in this study. Second, the direct effect of alpha-blockers on the production of PSA needs to be considered, which has been reported consistently in several *in vitro* studies,[17-19] as it was the most common empirical medication in this series. Third, while we adopted a PSA cutoff of 3 ng/mL as a definition for PSA normalization in accord with the threshold mentioned in contemporary guidelines on prostate biopsy,[20] the lowest PSA level for our criteria of significant PCa determined in this study was 2.56 ng/mL. However, it deserved to address that this is the sole case who have significant disease among the subjects obtained with PSA normalization during the follow-up period. An additional prospective study is needed to specify the criteria in detail that triggers the imminent need for

prostate biopsy, balancing between the detection of the significant disease and the prevention of over-treatment.

CONCLUSIONS

About one-third of individuals initially indicated for TrBx experienced a decrease in PSA, and their chance for significant PCa was diminished significantly. This retrospective study suggests PSA normalization could be an acceptable notion especially in identifying high-risk diseases. These outcomes spur a prospective study that may delineate a detailed protocol that permits a prolonged delay of prostate biopsy.

NOTES

• Conflicts of Interest: No potential conflict of interest relevant to this article was reported.

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