Urological Oncology

Predictive Factors for Prostate Cancer in Biopsy of Patients with Prostate-Specific Antigen Levels Equal to or Less Than 4 ng/ml

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Purpose: This study was conducted to identify the predictive factors for prostate cancer in patients with prostate-specific antigen (PSA) levels equal to or less than 4 ng/ml.
Materials and Methods: A retrospective study of medical records was conducted on 292 patients with initial serum PSA ≤4 ng/ml among 2,305 patients who underwent prostate biopsy from January 2003 to December 2008. Prostate biopsy was performed on patients with PSA ≤4 ng/ml in the case of abnormal findings in the digital rectal examination (DRE) or transrectal ultrasonography (TRUS) or in those with a PSA level higher than the age-adjusted PSA levels. The patients were divided into the group diagnosed with prostate cancer and the non-prostate-cancer group. Subsequently, the variables of the two groups were compared.
Results: The patients' mean age was significantly higher in the prostate cancer group (n=28) than in the non-prostate-cancer group (n=264; p=0.033). In addition, for the patients with a PSA range of 2.0-2.9 ng/ml, their age (p=0.049) and PSA density (PSAD; p=0.042) were significantly higher and the prostate volume (p=0.028) was significantly smaller in the prostate cancer group than in the non-prostate-cancer group.
Conclusions: Of the patients with PSA ≤4 ng/ml, the age of the patients who showed abnormal findings in the DRE or TRUS or who had a PSA level higher than the age-adjusted PSA level was a significant predictive factor for prostate cancer. In particular, for the PSA range of 2.0-2.9 ng/ml, a thorough screening test for prostate cancer was required if the patients had conditions such as higher age, smaller prostate, and higher PSAD.

Key Words: Prostate-specific antigen; Prostatic neoplasms

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INTRODUCTION

Prostate cancer is one of the most common malignancies among men and was in first place in United States for male cancer morbidity and in second place for cancer mortality, next to lung cancer, in 2009 [1]. Increasing mortality rates due to prostate cancer have been observed worldwide. In Korea, prostate cancer incidence increased up to 28.2% between 1996-1998 and 1999-2001, and mortality increased 12.7-fold over a 20-year period [2].

Because prostate cancer generally progresses imperceptively, patients are unlikely to seek medical help during the early stages. For these reasons, screening programs aimed at early detection have been developed [3,4]. The serum prostate-specific antigen (PSA) level is among the best of the screening tools available in medicine today and is recognized as the best marker for early detection. The most challenging problem in the use of PSA as the screening test, however, is that PSA lacks specificity. Because the PSA level is organ-specific rather than tumor-specific, it also increases in cases of benign prostatic hyperplasia and prostatic inflammation. Since the introduction of the prostate cancer screening test with PSA, much research has been published on the determination of the PSA cutoff value for prostate biopsy in patients with increased PSA. At present, a PSA level of 4 ng/ml is widely used as the cutoff value for the performance of a

prostate biopsy. In this case, however, the sensitivity is 67.5% to 80%, but the specificity is only 20% to 30% [5,6]. The incidence of prostate cancer in patients with PSA < 4 ng/ml has been known to be approximately 15%. It was reported that biopsy-detected prostate cancer, including high-grade cancers, is not rare among men with PSA levels of 4 ng/ml or less [7,8]. Until now, however, the criteria for performing a prostate biopsy on patients with PSA < 4 ng/ml have not been established clinically.

Many studies have been conducted on the intermediate-PSA group with PSA in the range of 4-10 ng/ml. On the other hand, only a few studies on the predictive factors for prostate cancer in prostate biopsy have been conducted in patients with PSA < 4 ng/ml. Furthermore, no comprehensive analysis of various variables stratified with the PSA level has been reported so far in Korea.

Accordingly, this study was conducted to investigate the predictive factors for prostate cancer in patients with PSA equal to or less than 4 ng/ml, by analyzing the correlation of the variables with the results of the biopsy.

MATERIALS AND METHODS

A retrospective study of medical records was conducted on 292 patients with initial serum PSA ≤ 4 ng/ml among 2,305 patients who underwent a transrectal ultrasound-guided prostate needle biopsy at Korea University hospital from January 2003 to December 2008. A prostate needle biopsy was performed on patients with PSA ≤ 4 ng/ml in cases of abnormal findings in the digital rectal examination (DRE) or transrectal ultrasonography (TRUS) or on patients with a PSA level higher than the age-adjusted PSA level. Abnormal DRE findings were defined as palpable induration, nodularity, irregularity, or asymmetry. Abnormal TRUS findings were defined as capsular irregularity, deformation, or existence of a hypoechoic region. PSA was measured by using enzyme immunoassay, and it was measured before the DRE or TRUS to minimize interference.

For the reference value of the age-adjusted PSA, 1.88 ng/ml for people in their 30s, 1.92 ng/ml for people in their 40s, 2.37 ng/ml for people in their 50s, 3.56 ng/ml for people in their 60s, and 5.19 ng/ml for people in their 70s were used, according to the study of Jeon et al [9]. The prostate volume was calculated by measuring the height, width, and length by using TRUS and by subsequently putting such figures into the ellipsoid formula of 3.14/6x(height)x(width)x(length). The 12-core biopsy scheme used in our institution includes a standard sextant, which was originally described by Hodge et al [10], as well as a lateral sextant scheme (lateral apex, lateral mid-gland, lateral base) [11]. The biopsy policy of our institution consists of an additional two core biopsies in cases of palpable nodules in the DRE or suspicious lesions in TRUS. Biopsies were performed under ultrasound guidance by use of an 18-gauge, 2 cm, Trucut core needle biopsy.

The patients were divided into a group diagnosed with prostate cancer and the non-prostate-cancer group accord-ing to prostate needle biopsy. Subsequently, the age, prostate volume, PSA, PSA density (PSAD: the ratio of total PSA to prostate volume), percentage of free PSA (%fPSA: free PSA/total PSA ratio), International Prostate Symptom Score (IPSS), maximal flow rate, and abnormal findings in the DRE and TRUS of the two groups were compared. In addition, the PSA level was divided into ranges of 0.0-1.9 ng/ml, 2.0-2.9 ng/ml, and 3.0-4.0 ng/ml, followed by analysis.

In the prostate cancer group and the non-prostate-cancer group, the age, prostate volume, PSA, PSAD, %fPSA, IPSS, and maximal flow rate were compared by using the Student's t-test. The abnormal findings in the DRE and TRUS were compared by using the Pearson's chi-square test. In addition, to identify the predictive factors for prostate cancer in a prostate needle biopsy, a multiple logistic regression analysis was conducted. As a result of this analysis, potential predictive factors for prostate cancer were identified. Their diagnostic validity was evaluated by receiver operating characteristic (ROC) curve analysis. SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA) software was used for the statistical analysis. MedCalc ver. 11.4.3 (MedCalc Software, Mariakerke, Belgium) software was used to compare the area under the curve (AUC) of each predictive factor with the ROC curve. In all cases of hypothesis testing, two-sided testing was used, and probability values (p-values) of less than 0.05 were considered statistically significant.

RESULTS

Of the 2,305 patients who underwent a prostate needle biopsy, 292 had a PSA ≤ 4 ng/ml. The mean age of the patients was 63.1 years old; their prostate volume, 37.3 cc; their PSA, 2.9 ng/ml; their PSAD, 0.08 ng/ml/cc; their %fPSA, 0.23; their IPSS, 15.6; their maximal flow rate, 15.16 ml/s; and the frequencies of abnormal findings in the DRE and TRUS, 36.9% and 31.5%, respectively.

For the patients with PSA ≤ 4 ng/ml, when the prostate cancer group (n=28) was compared with the non-prostate-cancer group (n=264), no significant differences in prostate volume (33.8 vs. 37.7 cc), PSA (3.0 vs. 2.9 ng/ml), PSAD (0.10 vs. 0.08 ng/ml/cc), %fPSA (0.18 vs. 0.23), IPSS (17.8 vs. 15.4), maximal flow rate (12.8 vs. 15.4 ml/s), frequency of palpable lesions in the DRE (14.2% vs. 11.3%), or frequency of hypoechoic lesions in the TRUS (42.8% vs. 30.3%) were found between the two groups in the univariate and multivariate analyses, respectively. On the other hand, mean age was significantly higher in the prostate cancer group than in the normal group (66.9 vs. 62.7 years old, p=0.033 in univariate analysis, p=0.034 in multivariate analysis, odds ratio=1.052) (Table 1). The diagnostic validity based on age was low, however, and the AUC in the ROC curve was only 0.607 (95% confidence interval [CI]: 0.507-0.707).

Of the 28 prostate cancer patients, 25 patients (89%) had a Gleason score of 6 or less, 1 patient (4%) had a score of 7, and 2 patients (7%) had a score of 8 or above.

TABLE 1. Predictive factors in the cancer and the non-cancer group with PSA value of less than 4 ng/ml

	Total	Cancer	Non-cancer	p-value	
				Univariate	Multivariate
No. of patients	292	28	264		
Age (yr)	63.1±9.9	66.9±7.4	62.7±10.1	0.033[a]	0.034[a]
Prostate volume (cc)	37.3±15.7	33.8±16.3	37.7±15.7	0.212	0.178
PSA (ng/ml)	2.9±0.8	3.0±0.8	2.9±0.8	0.559	0.558
PSAD (ng/ml/cc)	0.08±0.04	0.10±0.05	0.08±0.04	0.057	0.061
%fPSA	0.23±0.54	0.18±0.06	0.23±0.57	0.623	0.624
IPSS	15.6±7.6	17.8±6.7	15.4±7.6	0.110	0.112
Qmax (ml/sec)	15.16±31.5	12.8±5.1	15.4±33.0	0.689	0.688
DRE (+)	36.9% (34/292)	14.2% (4/28)	11.3% (30/264)	0.882	0.648
TRUS (+)	31.5% (92/292)	42.8% (12/28)	30.3% (80/264)	0.252	0.178

PSA: prostate-specific antigen, PSAD: PSA density, %fPSA: percent free PSA, IPSS: International Prostate Symptom Score, Qmax: maximal flow rate, DRE: digital rectal examination, TRUS: transrectal ultrasonography, [a]: statistically significant ($p < 0.05$)

A Pearson's chi-square test was performed to see if the PSA level was higher than the age-adjusted PSA levels in the patients with a PSA ≤ 4 ng/ml. The test results were 57.1% (16/28) in the prostate cancer group and 64.7% (171/264) in the non-prostate-cancer group, which showed no significant difference (p=0.852).

The detection rate of prostate cancer was 9.6% in the patients with PSA ≤ 4 ng/ml. When the PSA level was divided into ranges of 0-0.9 ng/ml, 1.0-1.9 ng/ml, 2.0-2.9 ng/ml, and 3.0-4.0 ng/ml, the detection rates were 10%, 5.7%, 8.2%, and 11.1%, respectively, which showed no statistically significant difference. In addition, when the patients' ages were divided into groups of 59 years or less, 60-69 years, and 70 years or more, the detection rates were 4.6%, 12%, and 10.9%, respectively. No statistically significant difference was found among the detection rates. However, as shown in Table 2, the detection rate was higher in the patients aged 60 years or more than in the other age brackets. In addition, the detection rate for patients whose PSA was higher than age-adjusted PSA was 8.5% (Table 2).

When the PSA level was divided into ranges of 0.0-1.9 ng/ml, 2.0-2.9 ng/ml, and 3.0-4.0 ng/ml, followed by the conduct of a univariate analysis between the prostate cancer group and the non-prostate-cancer group, mean age was significantly higher in the prostate cancer group with a PSA range of 2.0-2.9 ng/ml (64.7 vs. 71.5 years old, p=0.049), whereas prostate volume was smaller (39.0 cc vs. 26.9 cc, p=0.028) and the PSAD was higher (0.07 vs. 0.09, p=0.042) than in the non-prostate-cancer group. No significant difference in the variables was found in the PSA ranges of 0.0-1.9 ng/ml and 3.0-4.0 ng/ml, respectively, however (Table 3). The results of the multivariate analysis of the PSA range of 2.0-2.9 ng/ml showed that the statistically significant predictive factors of prostate cancer in a prostate needle biopsy were the patient's age and prostate volume (p=0.028 and 0.014, respectively; odds ratio=1.200 and 0.845, respectively).

The variables that were statistically significant in the univariate or multivariate analysis in the PSA range of

TABLE 2. Cancer detection rates according to PSA level, age, and age-adjusted PSA level with PSA value of less than 4 ng/ml

PSA (ng/ml)	No. of patients	No. cancer patients	Detection rate (%)
0-0.9	10	1	10
1.0-1.9	35	2	5.7
2.0-2.9	85	7	8.2
3.0-4.0	162	18	11.1
Age (yr)			
<59	86	4	4.6
60-69	133	16	12
70<	73	8	10.9
Total	292	28	9.6
$\geq$Age-adjusted PSA	187	16	8.5

PSA: prostate-specific antigen

2.0-2.9 ng/ml, such as the patient's age, prostate volume, and PSAD, were analyzed by ROC curve. The AUCs of each factor were 0.691 (95% CI: 0.582-0.787), 0.813 (95% CI: 0.714-0.890), and 0.749 (95% CI: 0.643-0.837), respectively (Fig. 1). No AUC showed a significant difference. At the cutoff value of 36 cc for prostate volume, sensitivity and specificity were 92.4% and 50.0%, respectively, and at the cutoff value of 35 cc, sensitivity and specificity were 85.7% and 51.3%, respectively. At the cutoff value of 0.066 for PSAD, sensitivity and specificity were 90.1% and 54.1%, respectively, and at the cutoff value of 0.070, sensitivity and specificity were 85.7% and 57.7%, respectively. The criteria for prostate volume and PSAD, which set the sensitivity of the diagnosis of prostate cancer as 90% or higher by the ROC curve analysis, were a prostate volume ≤ 36 cc and a PSAD ≥ 0.06 ng/ml/cc.

DISCUSSION

Screening tests such as PSA measurement, DRE, and

TABLE 3. Characteristics of patients in different total PSA ranges

Variable	Serum PSA range								
	0.0-1.9 ng/ml			2.0-2.9 ng/ml			3.0-4.0 ng/ml		
	BPH	PCa	p-value	BPH	PCa	p-value	BPH	PCa	p-value
No. of patients	42	3		78	7		144	18	
Age (yr)	63.0	67.0	0.542	64.7	71.5	0.049[a]	61.5	65.1	0.157
Prostate vol (cc)	32.3	25.6	0.327	39.0	26.9	0.028[a]	38.5	37.8	0.865
PSA (ng/ml)	1.36	1.20	0.552	2.5	2.4	0.522	3.56	3.52	0.592
PSAD (ng/ml/cc)	0.04	0.05	0.531	0.07	0.09	0.042[a]	0.10	0.11	0.607
%fPSA	0.23	0.21	0.834	0.31	0.15	0.665	0.19	0.19	0.934
IPSS	14.8	18.3	0.410	15.7	17.7	0.485	15.4	17.8	0.235
Qmax (ml/sec)	12.6	9.1	0.402	11.8	15.5	0.090	18.1	12.4	0.592
DRE (+)	9	1	1.000	11	1	1.000	10	2	0.874
TRUS (+)	19	2	0.905	27	4	0.438	34	6	0.541

PSA: prostate-specific antigen, BPH: benign prostatic hyperplasia, PCa: prostate cancer, PSAD: PSA density, %fPSA: percent free PSA, IPSS: International Prostate Symptom Score, Qmax: maximal flow rate, DRE: digital rectal examination, TRUS: transrectal ultrasonography, [a]: statistically significant ($p < 0.05$)
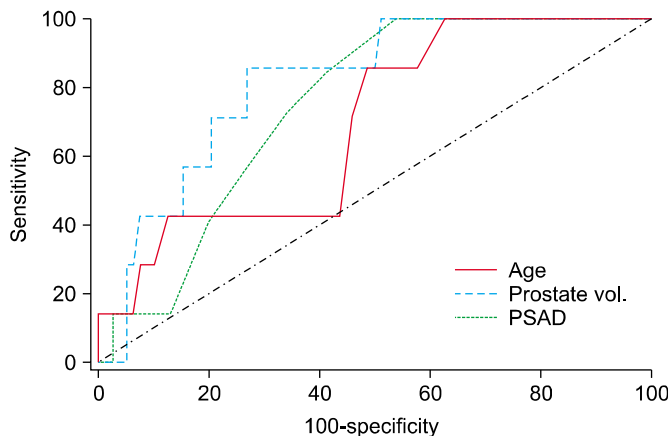

FIG. 1. Receiver operating characteristic curve analysis of age, prostate volume, and PSAD with PSA value of 2.0-2.9 ng/ml. PSAD: prostate-specific antigen density, PSA: prostate-specific antigen.

TRUS are commonly used to diagnose prostate cancer. The results of such tests show that if the serum PSA level increases, or if abnormal findings are observed in the prostate in the DRE or TRUS, an ultrasound-guided prostate needle biopsy is performed to confirm the prostate cancer. PSA, a tumor marker of prostate cancer, was initially introduced for postoperative follow-up and was gradually used as a screening test, which brought about tremendous change in the morbidity and mortality of prostate cancer. In particular, because prostate cancer is diagnosed during early stages as the result of PSA testing, the number of advanced-stage prostate cancer patients has rapidly decreased from the late 1980s to the early 1990s [12]. The cutoff value of PSA for prostate cancer diagnosis is still controversial, however, and decision-making on the performance of a prostate biopsy on the basis of only the PSA cutoff value has limitations with respect to sensitivity, specificity, and positive predictive value. Many studies have been

conducted to determine the PSA cutoff value. Catalona et al reported that a PSA level of 4 ng/ml or higher was appropriate as the PSA cutoff value for the screening of prostate cancer. Since then, this value has been most commonly used clinically; whereas its sensitivity is 67.5-80%, its specificity is only 20-30% [13].

In general, the detection rates of prostate cancer based on the PSA level are 10-20% at 2.5-4.0 ng/ml; 25% at 4.1-10.0 ng/ml; and 50-60% at 10 ng/ml or higher [14]. Kobayashi et al reported that the detection rate of prostate cancer was 23.6% both in the group with PSA of 2.0-4.0 ng/ml and in the group with PSA of 4.1-10.0 ng/ml, and no difference in pathological features was found [15]. Park et al also reported that no difference in the detection rate of prostate cancer and its pathological features was found between the group with PSA of 3.0-4.0 ng/ml and the group with PSA of 4.1-10.0 ng/ml [16]. According to the study of Thompson et al, 15.2% of the cases of prostate cancer diagnosed in prostate biopsy showed normal findings in the DRE, and their PSA level was less than 4 ng/ml. In addition, 14.9% of the prostate cancer turned out to be prostate cancer with high-grade Gleason score of 7 or higher [8]. According to the study of Kwon et al, normal DRE findings were shown in 55% of patients with a PSA < 4 ng/ml who underwent a radical prostatectomy, of whom 64% were diagnosed with prostate cancer at a level higher than a Gleason score of 7 [17]. Therefore, a significant number of patients with PSA < 4 ng/ml show clinically significant prostate cancer. Many studies reported that good outcomes were obtained from prostate cancer patients with low PSA levels when they underwent a radical prostatectomy [18-20]. Therefore, some studies have proposed that active screening tests for prostate cancer be conducted on patients with PSA < 4 ng/ml [21-23]. Catalona et al proposed that the PSA cutoff value be decreased to 2.5 ng/ml to detect prostate cancer early in patients who can be completely cured, because 20% of prostate cancer patients have PSA

in the range of 2.6-4.0 ng/ml [24]. When the PSA cutoff value is decreased, early diagnosis of prostate cancer is theoretically possible, and good outcomes may be obtained. This may increase the detection rate of clinically unimportant cancers with a low disease stage and low histologic grade, however, which nonsignificantly affect patients' prognoses even if the cancers are unidentified. This may cause unnecessary treatment of prostate cancer and complications. Furthermore, it is controversial whether lowering the PSA cutoff value will reduce the mortality of total prostate cancer.

According to the study by Gretzer and Partin in Americans, the detection rate of prostate cancer was 25% in patients with PSA in the range of 4-10 ng/ml, whereas according to the study by Lee et al in Koreans, the detection rate of prostate cancer was 15.9% [25,26]. In this study, the detection rate of prostate cancer was 14.9% (177/1,187) in the patients with PSA of 4-10 ng/ml, which is lower than the 25% rate in the United States but similar to the 15.8% rate in Korea. The detection rate of prostate cancer in patients with PSA < 4 ng/ml was 9.6%, which is lower than the 12.4% reported in the study by Lee et al in Koreans [26]. The lower detection rate of prostate cancer in Koreans is likely attributable to the low morbidity of prostate cancer.

Bozeman et al reported that a high PSA level is associated with prostate cancer diagnosis, although the PSA level in their study was less than 4 ng/ml in patients who showed abnormal findings in their DRE. Their study further reported that the patient's age is also a predictive factor of prostate cancer [27]. Al-Azab et al reported that a smaller prostate size is associated with prostate cancer in patients with PSA of 2.0-9.0 ng/ml [28]. In addition, Stephan et al reported that for a PSA < 4 ng/ml, the PSAD showed a better performance than tPSA or %fPSA for prostate cancer detection, and that the AUC was 0.739 for PSA of 2-4 ng/ml. They suggested that the cutoff value be 0.06 ng/ml/cc when the diagnostic sensitivity of prostate cancer is 90% or higher and 0.05 ng/ml/cc when the diagnostic sensitivity of prostate cancer is 95% or higher [29].

The results of this study showed that although PSA, as a predictive factor for prostate cancer, was less associated with prostate cancer in patients with PSA ≤ 4 ng/ml, the patient's age was important and there was an increased possibility of getting a positive result in the prostate needle biopsy as the patient's age increased. When the patient's age was divided into 59 years or less, 60-69 years, and 70 years or more, the detection rates were 4.6%, 12%, and 10.9%, respectively. In addition, the results of this study showed that higher age and smaller prostate volume are associated with prostate cancer in patients with PSA of 2.0-2.9 ng/ml, wherein the PSAD is considered a useful predictor, consistent with the aforementioned study results. In this study, for the PSA range of 2.0-2.9 ng/ml, the AUCs of prostate volume and PSAD were 0.813 and 0.749, respectively. It was possible to set the sensitivity of the diagnosis of prostate cancer as 90% or higher when the prostate volume was ≤ 36 cc and the PSAD was ≥ 0.06 ng/ml/cc,

which is consistent with the results of the study of Stephan et al [29]. The patient's age will be useful in determining the need to perform a prostate needle biopsy in patients with PSA ≤ 4 ng/ml. A prostate needle biopsy will be required for early diagnosis of prostate cancer in patients with higher age, prostate volume ≤ 36 cc, and PSAD ≥ 0.06 ng/ml/cc among patients with PSA of 2.0-2.9 ng/ml. Only the PSA 2.0-2.9 ng/ml group showed significance for age, prostate volume, and PSAD. First, at the PSA level of 0.0-1.9 ng/ml, the number of patients was too small. In the analysis performed at the PSA level of 2.0-4.0 ng/ml, the patients' age was a significant predictor (62.6 vs. 66.9 years old, p=0.040). In this study, we believe that age is clearly a predictor of prostate cancer. Table 3 shows that in the BPH group, prostate volumes are nearly the same even if the PSA level increases, whereas in the prostate cancer group, prostate volume increased as the PSA level increased. It is believed that although the prostate volume of the prostate cancer group was lower than that of the BPH group at the PSA level of 3.0-4.0 ng/ml, the prostate volume of the prostate cancer group increased as much as that of the BPH group in accordance with the increase in PSA level. Thus, no significant difference was observed in the prostate volume between the two groups. As such, at the PSA level of 3.0-4.0 ng/ml, prostate volume and PSAD were not significantly correlated with prostate cancer.

This study had some limitations. First, the subject size was relatively small and the subject diversity was low due to the sourcing of the data from a single hospital. Thus, a multi-center study that includes patients with various characteristics will be required in the future. Second, patients who showed abnormal findings in their TRUS or DRE, or who had a higher PSA level than the age-adjusted PSA level, were chosen, but they do not represent the whole patient group with PSA ≤ 4 ng/ml. Third, referring to the study of Ellis et al, which showed that among patients who were not diagnosed with prostate cancer in the initial prostate biopsy, 20% were diagnosed with prostate cancer when subjected to a repeat prostate biopsy, there is a possibility that prostate cancer would be diagnosed in patients who were negative in the prostate needle biopsy that was conducted in this study if the prostate needle biopsy were repeated [30]. Despite the aforementioned limitations, this study is valuable in that it proposed criteria for active screening to improve the detection rate of prostate cancer in patients with PSA ≤ 4 ng/ml.

CONCLUSIONS

Among patients with PSA ≤ 4 ng/ml, the age of the patients who showed abnormal findings in their DRE or TRUS or with a PSA level higher than the age-adjusted PSA level was a significant predictive factor for prostate cancer. In the aforementioned patients, the possibility of detecting prostate cancer increased as age increased. In particular, for the PSA range of 2.0-2.9 ng/ml, more thorough screening tests for prostate cancer should be performed in pa-

tients with a higher age, prostate volume ≤ 36 cc, and PSAD ≥ 0.06 ng/ml/cc.

Conflicts of Interest

The authors have nothing to disclose.

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-49.
2. Park SK, Sakoda LC, Kang D, Chokkalingam AP, Lee E, Shin HR, et al. Rising prostate cancer rates in South Korea. Prostate 2006;66:1285-91.
3. Brawer MK. Screening for prostate cancer. Semin Surg Oncol 2000;18:29-36.
4. Pelzer AE, Tewari A, Bektic J, Berger AP, Frauscher F, Bartsch G, et al. Detection rates and biologic significance of prostate cancer with PSA less than 4.0 ng/mL: observation and clinical implications from Tyrol screening project. Urology 2005;66:1029-33.
5. Bunting PS. Screening for prostate cancer with prostate-specific antigen: beware the biases. Clin Chim Acta 2002;315:71-97.
6. Schilsky RL, Taube SE. Tumor markers as clinical cancer tests--are we there yet? Semin Oncol 2002;29:211-2.
7. Fowler JE Jr, Bigler SA, Farabaugh PB, Wilson SS. Prostate cancer detection in Black and White men with abnormal digital rectal examination and prostate specific antigen less than 4 ng/mL. J Urol 2000;164:1961-3.
8. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level ≤ 4.0 ng per milliliter. N Engl J Med 2004;350:2239-46.
9. Jeon HJ, Kim YS, Kang DR, Nam CM, Kim CI, Seong DH, et al. Age-specific reference ranges for serum prostate-specific antigen in Korean men. Korean J Urol 2006;47:586-90.
10. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol 1989;142:71-4.
11. Presti JC Jr, O'Dowd GJ, Miller MC, Mattu R, Veltri RW. Extended peripheral zone biopsy schemes increase cancer detection rates and minimize variance in prostate specific antigen and age related cancer rates: results of a community multi-practice study. J Urol 2003;169:125-9.
12. Hankey BF, Feuer EJ, Clegg LX, Hayes RB, Legler JM, Prorok PC, et al. Cancer surveillance series: interpreting trends in prostate cancer--part I: evidence of the effects of screening in recent prostate cancer incidence, mortality and survival rates. J Natl Cancer Inst 1999;91:1017-24.
13. Catalona WJ, Smith DS, Ratliff TL, Basler JW. Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. JAMA 1993;270:948-54.
14. Schmid HP, Riesen W, Prikler L. Update on screening for prostate cancer with prostate-specific antigen. Crit Rev Oncol Hematol 2004;50:71-8.
15. Kobayashi T, Nishizawa K, Ogura K, Mitsumori K, Ide Y. Detection of prostate cancer in men with prostate-specific antigen levels of 2.0 to 4.0 ng/mL equivalent to that in men with 4.1 to 10.0 ng/mL in a Japanese population. Urology 2004;63:727-31.
16. Park HK, Hong SK, Byun SS, Lee SE. Comparison of the rate of detecting prostate cancer and the pathologic characteristics of the patients with a serum PSA level in the range of 3.0 to 4.0 ng/mL and the patients with a serum PSA level in the range 4.1 to 10.0 ng/mL. Korean J Urol 2006;47:358-61.
17. Kwon T, Jeong IG, Hong JH, Ahn H, Kim CS. Analysis of the clinicopathologic characteristics of men with prostate cancer undergoing radical prostatectomy in the prostate-specific antigen range of less than 4 ng/ml. Korean J Urol 2009;50:320-6.
18. Shekarriz B, Upadhyay J, Bianco FJ Jr, Tefilli MV, Tiguert R, Gheiler EL, et al. Impact of preoperative serum PSA level from 0 to 10 ng/mL on pathological findings and disease-free survival after radical prostatectomy. Prostate 2001;48:136-43.
19. Berger AP, Volgger H, Rogatsch H, Strohmeyer D, Steiner H, Klocker H, et al. Screening with low PSA cutoff values results in low rates of positive surgical margins in radical prostatectomy specimens. Prostate 2002;53:241-5.
20. Freedland SJ, Aronson WJ, Kane CJ, Terris MK, Presti JC Jr, Trock B, et al. Biochemical outcome after radical prostatectomy among men with normal preoperative serum prostate-specific antigen levels. Cancer 2004;101:748-53.
21. Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements. JAMA 1997;277:1452-5.
22. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. JAMA 1995;273:289-94.
23. Lee HW, Kwak KW, Choi YH, Choi HY, Lee HM. New thresholds for prostate-specific antigen velocity for prostate cancer screening in Korean patients younger than 60 years old. Korean J Urol 2008;49:113-7.
24. Catalona WJ, Ramos CG, Carvalhal GF, Yan Y. Lowering PSA cutoffs to enhance detection of curable prostate cancer. Urology 2000;55:791-5.
25. Gretzer MB, Partin AW. PSA levels and the probability of prostate cancer on biopsy. Eur Urol 2002;(Suppl 1):21-7.
26. Lee DH, Yang WJ, Chung BH, Kim SI, Kim SJ, Kim YS, et al. A multicenter study of the detection rate for prostate cancer according to the serum prostate-specific antigen level in Korean men. Korean J Urol 2005;46:433-7.
27. Bozeman CB, Carver BS, Caldito G, Venable DD, Eastham JA. Prostate cancer in patients with an abnormal digital rectal examination and serum prostate-specific antigen less than 4.0 ng/mL. Urology 2005;66:803-7.
28. Al-Azab R, Toi A, Lockwood G, Kulkarni GS, Fleshner N. Prostate volume is strongest predictor of cancer diagnosis at transrectal ultrasound-guided prostate biopsy with prostate-specific antigen values between 2.0 and 9.0 ng/mL. Urology 2007;69:103-7.
29. Stephan C, Stroebel G, Heinau M, Lenz A, Roemer A, Lein M, et al. The ratio of prostate-specific antigen (PSA) to prostate volume (PSA density) as a parameter to improve the detection of prostate carcinoma in PSA values in the range of < 4 ng/mL. Cancer 2005;104:993-1003.
30. Ellis WJ, Brawer MK. Repeat prostate needle biopsy: who needs it? J Urol 1995;153:1496-8.