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The Prostate Cancer Detection Rate on the Second Prostate Biopsy according to Prostate-Specific Antigen Trend

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Purpose: To identify the prostate cancer detection rate on the patients who had second prostate biopsy out of the patients who were reported negative in their first biopsy.
Materials and Methods: From July 2006 to February 2012, prostate biopsy was performed on 843 patients with over 4 ng/ml and on 618 biopsy negative patients PSA was performed from between 6 months and 9 months after biopsy. On 164 patients, second biopsy was performed, and 42 patients were selected. If there was less than 10% change between PSA before the prostate biopsy and PSA measured during 6 to 9 months after the first biopsy it was considered as no change. If above 10% increase, it was considered increase and if above 10% decrease it was considered as decrease.
Results: The cancer detection rate in PSA increase group was 20%, the detection rate in no change in PSA level but still over the normal range group 8.3%, and that in the PSA decrease group was 0%. When comparing prostate cancer group and non-cancer group, it is more probable to have prostate cancer when they are older, prostate volume is smaller and PSA density is higher.
Conclusions: The second biopsy is strongly recommended when PSA level shows no change or increase, age is older, prostate volume is smaller or PSA density is higher.

Key Words: *Biopsy; Prostate; Prostate-specific antigen; Prostatic neoplasms*

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INTRODUCTION

Prostate cancer is diagnosed through prostate needle biopsy when there is an abnormal finding in screening tests such as prostate-specific antigen (PSA), digital rectal examination (DRE), or transrectal ultrasonography (TRUS). If the patient shows a consistently abnormal finding in the above screening tests during follow-up observation, even when prostate cancer is not diagnosed at the first needle biopsy, prostate biopsy should be performed again to check for the presence of prostate cancer [1]. However, it is not easy to perform a second biopsy, because of low awareness of the patients, pain associated with the biopsy, and complications such as proctorrhagia, hematochezia, hematuria, acute urinary retention, septicemia, and vasovagal reflex [2]. Accordingly, PSA velocity (PSAV) and free-to-total PSA ratio have been used as useful predictive factors to reduce the unnecessary prostate biopsy retrials up to now, but there is as yet no clear and definite predictive factor. In the present study, therefore, we aimed to identify the relationship between PSA change and the prostate cancer diagnosis rate in patients who had a PSA value higher than 4 ng/ml and underwent a second prostate biopsy at this hospital. For the analysis, the patients were classified according to PSA change as PSA increase, no change, and PSA decrease (but still above the normal range).

MATERIALS AND METHODS

From July 2006 to February 2012, prostate biopsy was performed on 843 patients whose blood PSA was elevated over 4 ng/ml. Regardless of PSA level, patients who underwent biopsy in whom nodularity or asymmetry was shown in the DRE or in whom hypoechoic lesions were detected on TRUS were excluded. Among the patients who underwent prostate biopsy, 225 patients (26.7%) were diagnosed as having

TABLE 1. Characteristics of all patients stratified by second biopsy results

Characteristic	Total	Cancer	No cancer	p-value
Total no. of patients	42	5 (11.9)	37 (88.1)	
Age (yr)	65.2±8.7	73.1±3.4	64.2±9.4	0.01
Prostate volume (cc)	72.5±22.4	40.6±20.1	77.0±10.5	0.03
PSA1 (ng/ml/cc)	7.6±2.9	5.4±1.1	7.7±3.2	0.208
PSA2 (ng/ml/cc)	7.2±3.7	7.6±2.4	8.4±4.1	0.709
PSAD	0.117±0.05	0.206±0.06	0.107±0.05	0.04

Values are presented as number (%) or mean±SD.
PSA, prostate-specific antigen; PSA1, PSA levels before the first prostate biopsy; PSA2, PSA levels before the second biopsy measured between 6 to 9 months after the first biopsy; PSAD, prostate-specific antigen density.

prostate cancer. Out of 618 patients whose prostate biopsy result was reported to be negative, 469 patients had a PSA test between 6 and 9 months after the first biopsy, and 289 patients had a blood PSA value less than 4 ng/ml. In 186 patients, the blood PSA level was still elevated to over 4 ng/ml, and among these patients, 164 underwent a second prostate biopsy. Excluding the patients who took 5-alpha-reductase inhibitor agents after the first biopsy (101 patients) or in whom prostatitis was diagnosed from the biopsy (21 patients), 42 patients were selected as the subjects of this study. They were classified as having PSA increase, no change in PSA, or PSA decrease but still over the normal range. The patients' records were analyzed retrospectively.

PSA change was calculated by comparing the PSA value before the first biopsy with that before the second biopsy measured between 6 and 9 months after the first biopsy. A change of less than 10% was ignored and was defined as no change, an increase of over 10% was regarded as PSA increase, and a decrease of more than 10% was regarded as PSA decrease.

To measure blood PSA, the CLIA (chemiluminescence immunoassay, Abbott Laboratories, Abbott Park, IL, USA) method was used. Prostate biopsy was executed by using an 18-gauge needle under transrectal ultrasound guidance, and for both biopsy trials a 12-core biopsy was performed. For the statistical analysis, independent t-test and analysis of variance were performed. Results were judged statistically significant if the p-value was less than 0.05. For the statistics, SPSS ver. 12 (SPSS Inc., Chicago, IL, USA) was used.

RESULTS

The mean age of the patients who underwent a second prostate biopsy was 65.2 years, and their mean prostate volume was 72.5 g. The prostate cancer detection rate in the second biopsy was 11.9%. There was a meaningful difference in mean age, prostate volume, and PSA density (PSAD) between the prostate cancer group and the noncancer group (Table 1).

The prostate cancer detection rate in the PSA increase group was 20%, that in the no change group was 8.3%, and that in the PSA decrease group was 0% (Table 2). There were no significant differences between groups in average age, prostate volume, mean PSA before the first biopsy (PSA1), mean PSA before the second biopsy (PSA2), or mean PSAD (Table 3).

TABLE 2. Prostate cancer diagnosis rate in the second biopsy by PSA change

	Increase	Plateau	Decrease	Total (no.)
No. of PSA > 10 (ng/ml)	2	3	4	9
No. of Pca	0	0	0	0
No. of 4 < PSA < 10 (ng/ml)	18	9	6	33
No. of Pca	4	1	0	5
No. of total Pca (%)	4 (20.0)	1 (8.3)	0 (0)	5 (11.9)

PSA, prostate-specific antigen; Pca, prostate cancer.

DISCUSSION

Up to now, PSA level, DRE, and TRUS have been used as screening tests for prostate cancer. When the PSA level is over 4 ng/ml, the DRE shows prostate nodules or asymmetry, or TRUS detects hypoechoic lesions in the peripheral zone, prostate cancer can be clinically present and TRUS-guided needle biopsy should be performed to diagnose prostate cancer.

It is known that a second prostate biopsy must be done if the blood PSA level shows a constant increase, if there are continuously abnormal findings in the DRE or TRUS, if there is high-grade prostatic intraepithelial neoplasia or atypical cells in the first prostate biopsy, or if the patient has a prostate cancer family history, even if the result of the first prostate biopsy is negative [1]. In these cases, a prostate cancer detection rate of 10 to 31% has been reported, and although some differences were noted by reporters, the necessity of the second prostate biopsy was strongly supported [3].

According to Durkan and Greene [4], 15 of 48 patients (31%) who showed a consistently abnormal PSA level after a negative finding on the first biopsy were diagnosed as

TABLE 3. Characteristics of the groups and analysis of variance results

Characteristic	Increase	Plateau	Decrease	p-value
Total no. of patients	20	12	10	
Age (yr)	66.7±7.7	62.4±6.0	65.6±7.8	0.285
Prostate volume (cc)	68.8±39.1	67.3±30.3	86.8±36.2	0.373
PSA1 (ng/ml/cc)	6.9±2.55	6.6±2.5	9.5±4.2	0.141
PSA2 (ng/ml/cc)	9.9±3.3	6.5±2.2	7.2±3.1	0.55
PSAD	0.131±0.08	0.094±0.06	0.125±0.06	0.395

Values are presented as mean±SD.
PSA, prostate-specific antigen; PSA1, PSA levels before the first prostate biopsy; PSA2, PSA levels before the second biopsy measured between 6 to 9 months after the first biopsy; PSAD, prostate-specific antigen density.

having prostate cancer in the second prostate biopsy. According to Okada et al. [5], 36% of patients who were not diagnosed as having prostate cancer at the first prostate biopsy were diagnosed as having prostate cancer when the second biopsy was performed at a 2-year interval. In Korea, according to Park et al. [6], 25 of 243 prostate cancer patients (10.3%) were diagnosed as having prostate cancer in the second or third biopsy after a negative result on the first biopsy. The detection rate in the patients whose PSA was in the gray zone before the second biopsy was 13.1%, which is consistent with the results of this study (15.15%). Although PSA is an important serum tumor marker for diagnosing prostate cancer with DRE, it has limitations in clinical usefulness, showing 79% sensitivity and 59% specificity [7].

To compensate for the limitations of PSA, PSAD and PSAV were introduced. PSAD is the corrective value of the prostate volume, and its clinical usefulness is being studied in differentiating benign prostatic hyperplasia (BPH) and prostate cancer. Bazinet et al. [8] diagnosed prostate cancer in 23 patients out of 42 who did not have prostate cancer-suspicious results on the DRE or TRUS but in whom the PSA level was 4 to 10 ng/ml. The overall prostate cancer diagnosis rate was 16%. They reported that it would be ideal to perform prostate biopsy when the PSAD is over 0.15 ng/ml/cc. On the other hand, Littrup et al. [9] proposed that prostate biopsy be performed when the PSAD is over 0.12 ng/ml/cc. In this study, the mean PSAD of the prostate cancer group was 0.206, whereas the mean PSAD of the normal group was 0.107, which is consistent with the aforementioned study results with a statistically significant difference. Contrarily, Hayek et al. [10] addressed that the volume of the prostate measured by TRUS could vary by the inspector and that PSAD would not have statistical meaning as a prostate cancer predictive factor in the second biopsy group. PSAV is the annual speed of increase of the serum PSA level, and Stamey et al. [11] reported that PSAV could be used for the differential diagnosis of the two because BPH showed a PSAV of 0.3 ng/ml/yr, whereas prostate cancer showed a PSAV of 3.5 ng/ml/yr. According to Carter et al. [12], serum PSA increased significantly according to time from 5 years before prostate cancer diagnosis when compared with healthy people. They reported that the specificity of a cutoff value of 0.75 ng/ml/yr was over 90% when the PSA was in the gray zone and less than 4. The sensitivity of a cutoff value of 0.75 ng/ml/yr was reported to be 79% when PSA was in the gray zone and 11% when PSA was less than 4. Ito et al. [13] addressed that PSAV would be a very useful index in prostate cancer early diagnosis because it could the improve prostate cancer detection rate if PSAV were considered additionally at the time of biopsy in patients with a PSA of less than 4 ng/ml who showed abnormal findings in DRE, and positive predictive value could be improved even in cases with PSA of 4 to 6 ng/ml. We could not confirm their proposal in the present study because we did not measure PSAV and classified the patients according to the increase or decrease in PSA over a period of 6 to 9 months, which was relatively shorter than 1 year.

There are reports regarding the relationship between serum PSA change and prostate cancer diagnosis as analyzed by the difference between PSA in the first biopsy and that in the second biopsy. Durkan and Greene [4] reported that prostate cancer patients showed significantly higher serum PSA in the second biopsy (24.7 ng/ml) than in the first biopsy (18.9 ng/ml). In this study, we found that the prostate cancer detection rate was 20.0% in the PSA increase group and was higher than in the plateau group (8.3%) and PSA decrease group (0%), which is consistent with other studies.

Transrectal prostate biopsy, a diagnosis method of prostate cancer, may cause pain in 65 to 90% of patients, and thus patients may be hesitant to undergo a repeat biopsy by this method [14]. The pain in prostate biopsy occurs when the biopsy needle is injected to the prostatic capsule or when the ultrasound probe is inserted [15]. At present, to reduce the pain associated with biopsy, 1% lidocaine or endorectal topical anesthetic jell injection are administered before prostate biopsy periprostatic nerve block. Other methods are also used, such as nonsteroidal anti-inflammatory drug injection, intravenous anesthesia using propofol, and general anesthesia using inhalation anesthetics such as N_2O [16]. In the hospital of this study, acetaminophen 650 mg is given in the form of oral administration and endorectal anesthetic is injected to adjust for pain after the intravenous injection of tramadol, which

gives satisfactory results.

The other important point in repetitive trials of prostate biopsy is a PSA cutoff value. Generally, 4.0 ng/ml has been accepted as the PSA cutoff value [17]. In this study, prostate biopsy was performed with the normal value of PSA, which is 4. However, according to Schmid et al. [18] in 2004, the prostate cancer detection rate according to PSA range was 10 to 20% for PSA of 2.5 to 4.0 ng/ml, 25% for PSA of 4 to 10 ng/ml, and 50 to 60 % for PSA over 10.0 ng/ml. Therefore, some have suggested reducing the PSA cutoff value to 2.5 ng/ml for the early detection of prostate cancer that can be completely cured, because 20% of prostate cancer patients have a PSA value in the range of 2.6 to 4.0 ng/ml [19]. On the other hand, others assert that reducing the PSA cutoff value will cause unnecessary prostate biopsies and increase the number of clinically meaningless prostate cancer cases [20]. In Korea, Cho et al. [21] reported in 2008 that the number of patients undergoing prostate biopsy would increase 1.75 times and 2.49 times, respectively, if the PSA cutoff value were reduced from 4.0 ng/ml to 3.0 ng/ml and 2.5 ng/ml. Some propose that the decision should be made carefully because of the additional financial expenses. Additionally, it is not clear whether PSA screening test and PSA cutoff value adjustment would decrease the mortality rate of prostate cancer [22].

PSA age-specific reference values are one method for increasing the specificity of prostate cancer screening test diagnosis. According to Oesterling et al. [23], there was significant correlation between age and PSA in 3 years' PSA follow-up observation of 537 patients aged 40 to 79 years whose PSA increased 3.2% (0.04 ng/ml per year) every year. They proposed reference values of 0.0 to 2.5 ng/ml for ages 40 to 49, 0.0 to 3.5 ng/ml for ages 50 to 59, 0.0 to 4.5 ng/ml for ages 60 to 69, and 0.0 to 6.5 ng/ml for ages 70 to 79. They proposed that the rate of diagnosis of curable prostate cancer could be improved among the younger population by improving the sensitivity and that unnecessary prostate biopsy could be removed in the older population by improving the specificity. However, because there are reports showing that age-specific reference values differ by race [24], and that the clinical usefulness of age-specific references has been reported with different efficiency, there is as yet no accepted standard. In Korea, Jeon et al. [25] reported the PSA reference by age based on the PSA value in 120,439 domestic males in their 30s to 70s. According to Jeon et al. [25], the PSA reference value for Korean males is 1.88 ng/ml for men in their 30s, 1.92 ng/ml for men in their 40s, 2.37 ng/ml for men in their 50s, 3.56 ng/ml for men in their 60s, and 5.19 ng/ml for men in their 70s. In the hospital of the study, prostate biopsy was performed if the PSA level was over 3.0 ng/ml in the population younger than 60 years of age considering the age-specific reference value.

CONCLUSIONS

In this study, the prostate cancer detection rate in the PSA increase group was 20%, that in the no change group was 8.3%, and that in the PSA decrease group (PSA decreased but was still higher than the normal rage) was 0%. There were no significant differences in average age, prostate volume, mean PSA before the first biopsy, mean PSA before the second biopsy, or mean PSAD among the groups. However, in the comparison between the cancer group and the noncancer group, it was found that those who were older, had smaller prostate volume, and had higher PSAD were more likely to have prostate cancer. Therefore, if PSA does not show a change or increases, if the patient's age is comparatively higher, or if the patient's prostate volume is comparatively lower or the PSAD is higher, repeat biopsy is strongly recommended. However, this study included a very small population of subject; accordingly, large-scale follow-up study should be performed in the future.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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