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Role of Prostate-Specific Antigen Change Ratio at Initial Biopsy as a Novel Decision-Making Marker for Repeat Prostate Biopsy

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Purpose: Prostate biopsy is used to confirm the prostate cancer. Although first biopsy result was benign, repeat biopsy is recommended for the patient who has higher risk of prostate cancer. In this study, we investigated the PSA change ratio (post-biopsy PSA to baseline PSA) whether it could be predictive factor of prostate cancer and helpful when decided to perform repeat biopsy.

Materials and Methods: 151 patients, first diagnosed as benign, but underwent repeat biopsy due to clinical suspicion of prostate cancer were included. Post-biopsy PSA was checked 60 minutes later after biopsy. PSA change ratio was defined as post-biopsy PSA to baseline PSA. According to results of repeat biopsy, patients were divided into benign group (group A) and cancer groups (group B). Between two group baseline PSA, PSA density, post-biopsy PSA and PSA change ratio were compared, and most effective cut-off value was analyzed using receiver operating characteristic (ROC).

Results: 129 men were benign, 22 men were prostate cancer according to results of repeat biopsy. Between two groups, post-biopsy PSA and PSA change ratio were statically significant differences. ($p < 0.001$, < 0.001) The effective cut-off value was 3.0, 3.5 and 4.0 according to ROC. At ROC curve, PSA change ratio was statistically significant for diagnosis of prostate cancer. (AUC 0.800, $p < 0.001$).

Conclusions: PSA change ratio is thought be a predictive factor for prostate cancer. If the PSA change ratio was less than 3.0-4.0, repeat biopsy should be considered to confirm the diagnosis.

Key Words: Prostate-specific antigen; Prostatic hyperplasia; Prostatic neoplasms

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INTRODUCTION

Prostate-specific antigen (PSA) and digital rectal examination (DRE) are well known as the most valuable screening tests for diagnosis of prostate cancer. Commonly, when serum PSA is increased or the DRE shows an unusual aspect, transrectal ultrasound-guided prostate biopsy (TRUS biopsy) is used to confirm the prostate cancer. In clinical practice, however, a significant number of negative biopsies are found according to these criteria. Generally, a negative biopsy rate of 76% can be expected [1]. Therefore, it is necessary to consider repeat prostate biopsy when patients have any clinical suspicion of prostate cancer, even if the initial prostate biopsy has a benign result. The eco-nomic burden and physical discomfort to the patient make it hard to decide whether to perform repeat biopsy. PSA, PSA density, and PSA velocity are commonly assessed to determine the necessity of repeat biopsy, but each of these tools has limitations to some extent. To overcome these limitations, many urologists are making an effort to find more reliable diagnostic tools that can be used to more accurately select patients who need repeat biopsy. Eventually, these efforts will lead to a reduction of unnecessary biopsies.

According to Lin et al. [2], the serum PSA ratio (baseline total serum PSA and post-TRUS biopsy total serum PSA) of patients with benign prostatic hypertrophy (BPH) is higher than that of prostate cancer patients. Choi et al. [3] reported similar results in a study from Korea.

In this study, we investigated whether the PSA change ratio (ratio of post-biopsy PSA to baseline PSA) at the initial biopsy could be a predictive factor of prostate cancer and helpful when deciding whether to perform a repeat prostate biopsy.

MATERIALS AND METHODS

From January 2007 to December 2010, 1,636 patients overall underwent TRUS biopsy in our clinic Kyung-pook National University Hospital for diagnosis of prostate cancer because of serum PSA elevation of more than 3 ng/ml or abnormal DRE findings. Of the 1,636 patients, 151 patients who underwent repeat prostate biopsy due to clinical suspicion of prostate cancer (sustained or elevated PSA, abnormal DRE, or hypoechoic lesion on follow-up TRUS) despite initial benign results were included in this retrospective study.

At the first prostate biopsy, all patients took oral quinolone antibiotics for 4 days from 1 day before the procedure to 3 days after. Biopsy was done by use of an 18G biopsy needle under the guidance of transrectal ultrasound (ACUSON Sequoia512, Siemens AG, Medical Solutions, Forchheim, Germany) with the patient in the left-lateral decubitus position. We performed routine 10-core biopsy but took more cores in the case of hypoechoic lesions on TRUS or abnormal nodules on the DRE.

The baseline serum PSA was measured right before prostate biopsy, PSA density was calculated as baseline serum PSA divided by total prostate volume, and post-biopsy serum PSA blood sampling was done 60 minutes after the last biopsy core was attained. The PSA change ratio was defined as the ratio of post-biopsy total serum PSA to baseline total serum PSA at the initial biopsy.

We divided the patients into two groups according to the results of the repeat biopsy: benign prostate patients (group A) and prostate cancer patients (group B). We compared age, biopsy interval, baseline PSA, PSA density, post-biopsy PSA, and the PSA change ratio between the two groups. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated at each PSA change ratio cut-off (1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0). The most effective cut-off was analyzed by use of receiver operating characteristic (ROC) curves.

The data were compared and analyzed with the Student's t-test and paired t-test. All analyses were performed with SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). Values of $p < 0.05$ were considered statistically significant for all procedures.

RESULTS

Of the 151 patients, 129 (85.4%) patients were diagnosed with benign prostate (group A) and 22 (14.6%) patients were diagnosed with prostate cancer (group B) according to the repeat biopsy results. Mean age and biopsy interval were 64.82 years and 9.48 months in group A and 66.40

TABLE 1. Comparison of patient characteristics between the two groups

Characteristic	Group A (benign)	Group B (cancer)	p-value
No. of patients	129	22	
Age (yr)	64.82±6.59	66.27±5.47	0.331
Biopsy interval (mo)	9.48±5.05	8.91±4.42	0.619
Baseline PSA level (ng/ml)	7.45±4.89	8.84±2.92	0.196
PSA density (ng/ml/cc)	0.177±0.083	0.198±0.052	0.227
Post-biopsy PSA level (ng/ml)	64.87±99.26	24.29±12.86	<0.001
PSA change ratio	11.03±17.09	2.98±1.88	<0.001

Values are presented as the mean±standard deviation.
PSA, prostate-specific antigen.

years and 8.91 months in group B, respectively.

Mean serum baseline PSA, PSA density, post-biopsy PSA, and PSA change ratio were 7.45 ng/ml, 0.177 ng/ml/cc, 64.87 ng/ml, and 11.03 in group A and 8.84 ng/ml, 0.198 ng/ml/cc, 24.29 ng/ml, and 2.98 in group B, respectively. There were significant differences in post-biopsy PSA and the PSA change ratio between the two groups ($p < 0.001$ and $p < 0.001$, respectively) (Table 1).

Sensitivity, specificity, PPV, and NPV at each cut-off of the PSA change ratio are shown in Table 2. The effective cutoffs were 3.0, 3.5, and 4.0 according to the ROC curve analysis. Taking 3.0, 3.5, and 4.0 as the cut-off values, sensitivity, specificity, PPV, and NPV were 68.2%, 74.4%, 31.3%, and 93.2%; 72.7%, 69.0%, 28.6%, and 93.7%; and 77.3%, 65.1%, 27.4%, and 94.4%, respectively. In the ROC curve analysis, the PSA change ratio showed statistical significance for diagnosis of prostate cancer (area under the curve, 0.800; 95% confidence interval, 0.706 to 0.893; p < 0.01) (Fig. 1).

DISCUSSION

Prostate cancer is the most common malignant tumor in American males and is dramatically increasing in Korea because of changes in diet, the increasing population of elderly people, and the development of diagnostic techniques. According to Song et al. [4], the estimated prostate cancer detection rate in Korean men aged 55 years or older is 3.36%. Moreover, according to the Ministry of Health and Welfare's annual report of cancer statistics in 2008 in Korea, prostate cancer took 4th place in Korean males with a 5-year prevalence of 8.2% of all cancers and took 5th place in 5-year incidence as 7% of all cancers.

For the diagnosis of this increasing prostate cancer, serum PSA and DRE are very widely used as screening tests, and if prostate cancer is clinically suspected, prostate biopsy is recommended to confirm the prostate cancer [5-7].

Serum PSA is the most common screening test for diagnosis of prostate cancer and is a very specific marker for the

TABLE 2. Sensitivity, specificity, positive predictive value, and negative predictive value at each cutoff value of the PSA change ratio
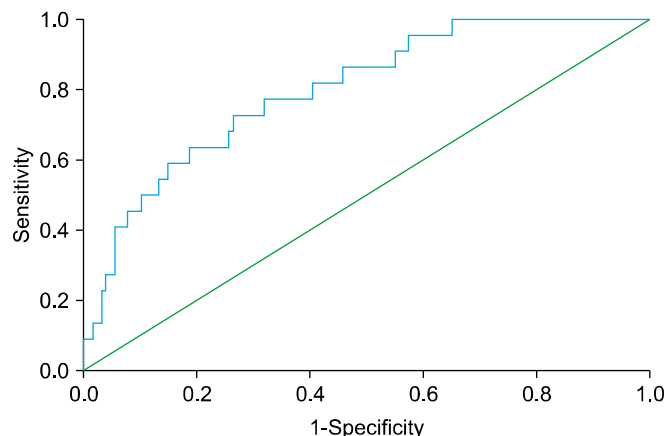
	Group A (benign)	Group B (cancer)	Sensitivity/ specificity (%)	PPV/NPV (%)
Cutoff value 1.5				
PSA ratio < 1.5	3	3	13.6/97.6	50.0/86.9
PSA ratio ≥ 1.5	126	19		
Cutoff value 2.0				
PSA ratio < 2.0	7	7	31.8/96.8	50.0/89.1
PSA ratio ≥ 2.0	122	15		
Cutoff value 2.5				
PSA ratio < 2.5	23	13	59.1/82.2	36.1/92.2
PSA ratio ≥ 2.5	106	9		
Cutoff value 3.0				
PSA ratio < 3.0	33	15	68.2/74.4	31.3/93.2
PSA ratio ≥ 3.0	96	7		
Cutoff value 3.5				
PSA ratio < 3.5	40	16	72.7/69.0	28.6/93.7
PSA ratio ≥ 3.5	89	6		
Cutoff value 4.0				
PSA ratio < 4.0	45	17	77.3/65.1	27.4/94.4
PSA ratio ≥ 4.0	84	5		
Cutoff value 4.5				
PSA ratio < 4.5	52	17	77.3/59.7	24.6/93.9
PSA ratio ≥ 4.5	77	5		
Cutoff value 5.0				
PSA ratio < 5.0	58	18	81.8/55.0	23.7/94.7
PSA ratio ≥ 5.0	71	4		

PSA, prostate-specific antigen; PPV, positive predictive value; NPV, negative predictive value.

FIG. 1. Receiver operating characteristics (ROC) curve using multiple cutoff values of the prostate-specific antigen (PSA) ratio (AUC 0.800, $p < 0.01$).

prostate. Normally, the serum PSA density is low in disease-free adult males, and it is a traditionally well-known indication for prostate biopsy when it is higher than 4 ng/ml [8]. In recent studies, however, the diagnosis of prostate cancer was shown to be more effective if prostate biopsy is recommended when serum PSA is higher than 2.5 ng/ml [9]. Various PSA cut-off values for prostate biopsy indication are used by different clinics [10]. The biopsy indication at our clinic is when the PSA is elevated to more than 3 ng/ml.

Although serum PSA is the most commonly used indicator for prostate cancer screening and shows high specificity, it also increases in variable situations such as DRE, cystoscopy, TRUS, bacterial prostatitis, and acute urinary retention. Thus, there are limitations to prostate cancer screening by use of PSA only. Many other markers are used to reduce this limitation. For example, age-adjusted PSA, PSA velocity, percent free PSA, and PSA density are used to increase sensitivity and specificity [11-15].

Despite much effort to increase the sensitivity and specificity of prostate cancer screening, the negative detection rate of prostate biopsy is reported to be up to 75% [1]. Also, according to Rabbani et al. [16], the false-negative rate of prostate biopsy is reported as 23%. Considering these high

false-negative rates, patients need repeat biopsy if they have clinical suspicion of prostate cancer even though the first biopsy shows benign results. Several studies have shown that the cancer detection rate is as high as 24.3 to 36.2% from a systematic 10- or 12-core biopsy procedure in patients who previously had a negative sextant biopsy result [17,18]. Many predictors of prostate cancer at the repeat biopsy have been reported. For example, according to Djavan et al. [19], it is necessary to consider repeat prostate biopsy when percent free PSA is less than 30% or transition zone PSA density is more than 0.26 ng/ml/cc to reduce unnecessary biopsies and increase specificity. This research shows that the sensitivity and specificity of repeat prostate biopsy were 90% and 50% when the percent free PSA cutoff value was set at 30%, and 78% and 52% when the transition zone PSA density cutoff value was set as 0.26 ng/ml/cc. Some research suggests that it is necessary to consider repeat prostate biopsy when the first biopsy result shows high-grade prostatic intraepithelial neoplasm or atypical small acinar cell proliferation [20]. Furthermore, according to Horinaga et al. [21], α1-antichymotrypsin-PSA complex adjusted for transition zone volume has significance for determining whether to perform repeat prostate biopsy.

Charrie et al. [22] first stated the phenomenon of a significant increase of the serum prostate acid phosphatase and PSA after a prostate aspiration biopsy, and the PSA increase was significantly greater in patients with BPH than in those with prostate cancer. Furthermore, Yuan et al. [23] and Ornstein et al. [24] reported that prostate biopsy causes a transient increase in free and total PSA.

To explain these phenomena, Lin et al. [2] hypothesized that the PSA clearance and conjugation mechanism of prostate cancer patients is on alert because the cancerous tissue has been continuously leaking PSA. By contrast, PSA clearance in BPH patients is slower than that of prostate cancer patients, and benign prostate tissue leaks more PSA than does prostate cancer tissue per unit when the prostate biopsy is performed. They analyzed the relation-

ship between the PSA change ratio and cancer detection rate on prostate biopsy and reported that sensitivity, specificity, PPV, and NPV were 78.1%, 94.1%, 92.5%, and 82.1%, respectively, when the PSA change ratio cut-off value was 2.0, and the analysis was statistically significant.

Choi et al. [3] performed similar research regarding the role of the PSA change ratio in Korea, but their results were solely limited to the first prostate biopsy and were not confirmed by re-biopsy. If the patients who showed a benign result initially were clinically suspicious in the follow-up, they should have been given second or third biopsies. Our study complements the limitations of this previous research with further follow-up and repeat prostate biopsies.

The result of the present study show that the PSA change ratio at the initial biopsy has statistical significance for predicting prostate cancer in the repeat prostate biopsy (p < 0.01; cut-off value, 3.0 to 4.0). The PSA change ratio is thought to have a great role when doctors are faced with making the decision of whether to perform a repeat prostate biopsy. However, our results show a higher cut-off value than that previously reported in the studies of Lin et al. [2] or Choi et al. [3]. It may be hard to distinguish whether the prostate cancer detected at the repeat biopsy was newly developed after the first biopsy or whether undetected cancer from the first biopsy was discovered at the second biopsy. Also, our results have a limitation due to the small scale of the patient group. Accordingly, we need to identify a strict cut-off value of the PSA change ratio in a larger patient group. Another limitation of our study is that the PSA ratio was compared only at the first prostate biopsy. We did not compare the PSA change ratio at the repeat biopsy.

Further investigations with third or later biopsy results are necessary to confirm our initial findings in this relatively small patient series.

CONCLUSIONS

The PSA change ratio could be a novel decision-making marker for performing repeat prostate biopsies. According to the results of our study, it is recommended that doctors consider repeat prostate biopsy when the PSA change ratio is less than 3.0 to 4.0. The PSA change ratio could reduce unnecessary prostate biopsies; however, we cannot completely exclude prostate cancer even if the PSA change ratio is more than 3.0 to 4.0. Active follow-up is still necessary for patients who are clinically suspicious for prostate cancer. Further investigations with large-scale, multicenter studies are necessary to identify strict cut-off values of the PSA change ratio.

CONFLICTS OF INTEREST
The authors have nothing to disclose.

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