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Prostate-Specific Antigen Doubling Time in Prediction of Prostate Cancer on Negative-Needle Biopsy

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Abstract

Objective: To identify the role of prostatic specific antigen doubling time (PSADT) in predicting for cancer detection in patients with persistently elevated PSA after a previous negative biopsy.

Methods: From 2009 to 2011, 110 patients with the initial negative transrectal ultrasound guided prostate biopsy were followed with sequential PSA and repeated biopsy if indicated (persistently elevated PSA more than 4 ng/ml). The patient evaluation included age, prostate characteristics by digital rectal examination (DRE), total PSA (tPSA), percent free PSA (%fPSA), PSADT (month), PSA velocity (PSAV) (ng/ml/y), interval between first and second biopsy (month), prostate volume by ultrasound, number of core biopsy, and pathologic result of the second biopsy.

Result: Fourteen patients (12.7%) were diagnosed adenocarcinoma of prostate after the second biopsy. The mean age (66.1,66.1), tPSA (15.6,9.7), %freePSA (21.1,23.8) and prostate volume (47.1,56.9) in the group of positive biopsy were comparable with the negative biopsy group. The mean PSAV of the positive biopsy group was 1.8 ng/ml/yr versus 0.38 ng/ml/yr for the negative group ($p<0.001$) while the mean PSADT of the positive biopsy group was 6.4 months versus 27.8 months for the negative group ($p<0.001$). The prevalence of prostate cancer among PSADT groups (<5, 5-10, >10 month) was 4.5%, 8.2% and 0%, respectively. There was no positive biopsy in patients with PSADT more than 10 months.

Conclusion: The mean value of PSADT in the patients who needed to repeat biopsy differed significantly between men with and without prostate cancer, and this information can aid in the decision making for patients to avoid unnecessary repeat prostate biopsies.

Keywords: prostate cancer, PSA doubling time, TRUS biopsy, predictive factor

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Introduction

The incidence of prostate cancer in Thailand elderly is increasing more than 0.75 percent per year [1]. Early detection of prostate cancer is performed by prostate biopsy and indication of the procedure depends on age, prostate finding on digital rectal examination, and serum level of prostate-specific antigen (tPSA). Transrectal ultrasound guide prostate biopsy (TRUS) prostate biopsy has increased due to the spread of prostate cancer screening. Abnormal digital rectal examination and PSA >4 ng/dl are the indications for TRUS[2]. Regular TRUS prostate biopsy in men with age >50 years reveals ~5-35% of positive rate for prostate cancer. Although an initial biopsy has high negative rates for prostate cancer, aged men with PSA persistently >4 ng/dl have high risk or suspicion of occult cancer[3,4] and need to receive a repeat prostate biopsy to rule out occult prostate cancer.

The disadvantage of TRUS biopsy is increased morbidity to patients with indication for repeat biopsy[5]. Lowering the number of unnecessary repeat biopsies can reduce morbidity and mortality. So we used predictive factors such as PSADT, to identify some cases in aged men with PSA persistently >4 ng/ml where repeat biopsy were not necessary, and the choice is to follow PSA without aggressive procedures[6,7].

Patients and Methods

The Ethical Committee of Maharaj Nakhon Chiangmai Hospital approved this presentation. December 2009 to September 2011, 660 men underwent initial TRUS prostate biopsy at Maharaj Nakorn Chiangmai Hospital. Prostate cancer was detected in 174 cases (26.4%) and 486 cases had negative initial TRUS prostate biopsy (73.6%). 110 cases with negative initial TRUS prostate biopsy repeated TRUS prostate biopsy because of persistently elevated PSA of more than 4 ng/ml after 3 to 24 months. The remaining patients with negative findings showed gentle fluctuation of tPSA and were selected for observation. Patients with high-grade prostate intraepithelial neoplasia or atypical small acinar proliferation were excluded from the study, because these pathologic findings are an issue of precancerous lesions[8].

Prostate biopsy was performed transrectally with an 18 G needle under ultrasound guidance (TRUS). At the initial biopsy 2 apex cores, 2 middle cores, and 1-2 base cores were taken bilaterally (total 10-12 cores). At a repeat biopsy, cores were taken from the same areas with two or more from each of the anterior-lateral areas (total 12-14 cores). Whole prostate volume was measured by ultrasound (LogicQ 5 pro). PSA velocity and PSADT were calculated from tPSA level.

Measurement of PSA and PSA Kinetics

AxSYM PSA immonoassays (Abbot, America) kits were used for assaying tPSA and %fPSA. PSA velocity (difference per year) was calculated by the formula (PSA2 - PSA1) ÷ (time elapsed between measurements); and PSA doubling time was calculated using PSADT (month) = log2[9logPSA2-logPSA1)/time]. At least three component PSA measurements are used in the calculations.

Statistical Analysis

X^2 test, Mann-Whitney's U-test, and student's t-test were used and $p<0.001$ was considered to be significant.

Results

Of 110 cases who received a repeat TRUS prostate biopsy at Maharaj Nakhon Chiangmai Hospital, prostate cancer was found in 14 cases (12.7%). All cancer was adenocarcinoma histologi-

cally. With cancer issues, we found one of 2 positive cores, four of 4 positive cores, four of 6 positive cores, one of 10 positive cores, four of 12 positive cores. Of 14 cancer cases Gleason scores of cancer tissues were found to be ≤6, 7, 8 and 9 in 6, 1, 6 and 1 cases, respectively. In 14 cases of adenocarcinoma PSA persistently increased during the interval between initial and repeat biopsy.

Age, initial PSA, interval between initial and following PSA, prostate volume, core of biopsy, %freePSA, and characteristic by DRE showed no difference between cancer and no cancer cases. PSA velocity and PSADT were significantly different between cancer and no cancer cases ($p<0.001$). Sensitivity of PSADT <10 months was 28.57% and PSADT >10 months was 21.43%.

Shorter PSADT was associated with higher PSA and higher prostate cancer risk but was unrelated to age, and DRE. Cancer cases had no PSADT >10 months. The prevalence of prostate cancer among PSADT groups (<5, 5-10, >10 months) was 4.5% (5/110), 8.2% (9/110) and 0%, respectively. Factors between cancer and no cancer are shown in Table 1 and sensitivity and specificity of PSA double time are show in Table 2. Distribution of PSADT between cancer and no cancer cases is shown in Figure 1. Distribution of %free PSA between cancer and no cancer cases is show in Figure 2.

Discussion

Complications of TRUS biopsy include increased morbidity to patient to repeat biopsy, hematuria, sepsis, rectal bleeding, feeling faint, pelvic discomfort, hematospermia and increased rate of admission. Modern TRUS guided prostate needle biopsy is associated with frequent minor (range 60% to 79%) and rare major (range 0.4% to 4.3%) complications and the need for hospitalization ranges from 0.4% to 3.4%[9,10].

Sequential biopsy following negative initial TRUS biopsy gradually reduced positive rates to ~5-30%[11,12]. The appropriate interval between the initial and repeat biopsies remains controversial. In the Maharaj Nakhon Chiangmai Hospital every 3-12 months for following PSA is used in practice. European randomized study for prostate cancer recommended a 4-year interval, showing reduction of rate of death by 20%[13]. However, men with persistently elevated PSA after a negative biopsy pose a diagnostic challenge and risk for occult prostate cancer, thus selection of cases is necessary for repeat biopsy.

Many predictive factors have been discussed concerning indication for repeat TRUS biopsy after negative initial biopsy. Age is an important factor since appearance of cancer increases along with age. Many reports indicated that PSA transitional zone density, %freePSA/tPSA and PSA velocity are common predictive factors. However PSA density and %free PSA/tPSA cannot distinguish cancer at repeat biopsy in cases with tPSA level more than 4 [14]. Others reported PSA velocity seems to be one of the predictive factors for detection of cancer but is controversial after the initial negative biopsy[15].

PSADT is a reliable predictive factor, useful for helping distinguish cancer at repeat biopsy and selecting cases in which a repeat biopsy might not been performed soon after a negative initial biopsy, but the appropriate value varies[6,16].

The calculation of PSA velocity and PSA doubling time uses the mean of 2 values and at least three components PSA measurements. No single factor has been reported which distinguishes cancer in all cases with an initial biopsy[17]. This report shows PSAV <0.5 ng/ml/month did not indicate prostate cancer.

To avoid missing cancers and minimized unnecessary TRUS biopsies, PSADT is used for selecting cases for repeat biopsy but the valued of

Table 1 *Prostate-Specific Antigen Doubling Time in Prediction of Prostate Cancer on Negative-Needle Biopsy Demographic Data*

variable	Cancer N=14	BPH N=96	p-value
Age (years)			
mean (SD)	66.1 (8.7)	66.1 (4.2)	0.976
PSA initial (ng/ml)			
mean (SD)	15.6 (23.4)	9.7 (5.9)	0.037
PSA follow (ng/ml)			
mean (SD)	19.4 (32.1)	12.5 (7.2)	<0.001
PSADT(ng/ml)			<0.001
<5	5 (35.7)	0	
5-10	9 (64.3)	1 (1.1)	
>10	0	95 (98.9)	
mean (SD)	6.4 (2.9)	27.8 (16.8)	
Interval (ml)			
mean (SD)	6 (2.1)	7.8 (3.8)	0.085
Prostate volume (ml)			
mean (SD)	47.1 (18.3)	56.9 (23.8)	0.142
core of biopsy			
mean (SD)	11.8 (1.9)	11.2 (1.1)	0.099
PSA free (ng/ml)			
mean (SD)	21.1 (4.1)	23.8 (5.8)	0.092
PSA velocity			
mean(SD)	1.8 (2.4)	0.38 (0.2)	<0.001
DRE			0.161
Normal	6 (42.8)	60 (62.5)	
hard nodule	8 (57.2)	36 (37.5)	

Table 2 *Sensitivity and specificity of PSA doubling time*

PSA double time (months)	Sensitivity (%)	Specificity (%)
<10	28.57%	N/A
>10	21.43%	N/A

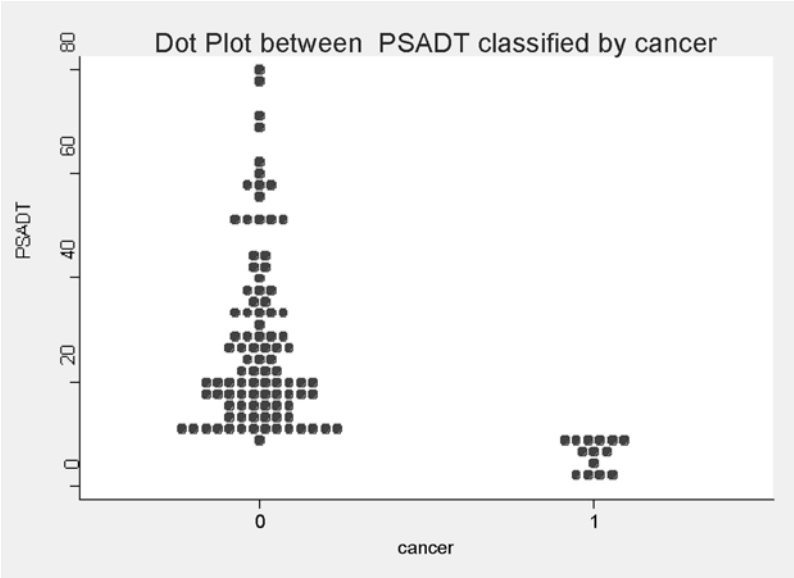

Fig. 1 *Prostate-specific antigen (PSA) doubling time of cases between cancer and no cancer dotplot PSADT, over (cancer) center title ("Dot Plot between PSADT classified by cancer")*

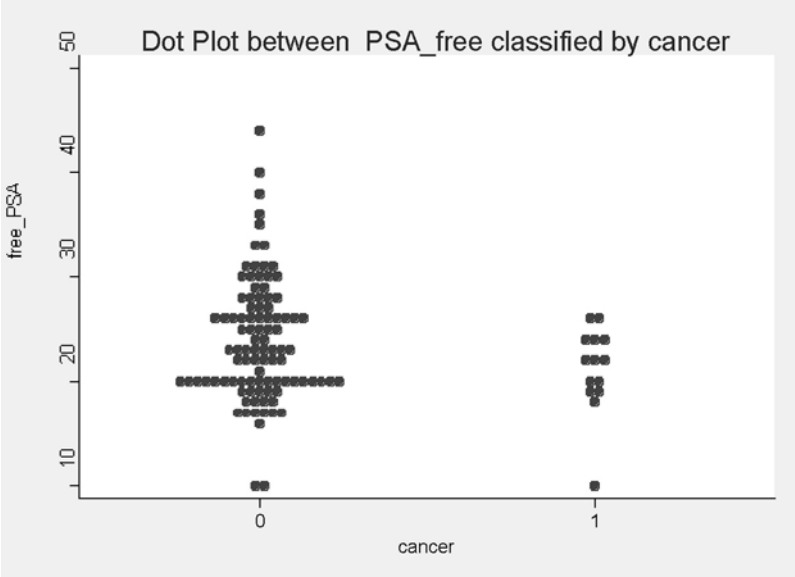

Fig. 2 *Free PSA of cases between cancer and non cancer*

appropriated PSADT was unknown especially in Thailand. Therefore, result of the present study may contribute to lowering unnecessary repeat TRUS biopsies. Cases with stable or long PSA doubling times (>10 months) are considered for follow up, while cases with PSA doubling time <10 months are selected for repeat biopsy. This factor will be taken for indication to repeat biopsy in case of negative initial TRUS biopsy.

Our study found that the sensitivity of PSADT less or more than 10 were not significantly different (28.57, 21.43) and less than pervious studies, ~36% at 30 months which can be explained from the small sample size[6]. However, the predictive factor for the detection of prostate cancer using PSADT still faces limitations in daily practice because it is difficult to calculate, and further study is needed with more patients to determine the most appropriate cut off value.

Conclusions

Among men undergoing repeated biopsy for PSA >4.0 ng/mL, PSADT provides further PC risk separation. If validated in future studies, these data support that PSADT can be use for making the decision to repeat TRUS biopsy in men with negative initial biopsy. The cut off value of PSADT was 10 months. Thus, the value of PSADT is that it can avoid the complication of unnecessary TRUS biopsies.

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Conflict of interest statement

None of declared.

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