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Original Article

The implications of prostate-specific antigen density to predict clinically significant prostate cancer in men ≤ 50 years

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Abstract: To investigate the appropriate cut-off level of PSA or other clinical parameters at aged ≤ 50 years. The rate of detection of PCa in young men will continue to rise associated with the advancement of the current and evolving practices of screening and detection. In this study, we determined whether to investigate the appropriate cut-off level of PSA or other clinical parameters at aged ≤ 50 years. The study population included 106 patients aged ≤ 50 years who had prostate biopsy at our institute. The differences of clinical variables including various PSA related parameters between the patients with significant PCa and insignificant PCa were analyzed. Receiver operating characteristics (ROC) curves and the corresponding areas under the ROC curves (AUC) were calculated. There were no significant differences between no-PCa and PCa patients regarding PSA value, prostate volume (P vol), PSA density (PSAD), transition zone volume (TZ vol), PSATZ density (PSATZD). When the patients meeting the following criteria, Gleason score was ≤ 6 with less than 2 positive biopsy cores, were classified as having insignificant prostate cancer, PSAD could become a useful predictor of significant PCa in men. The AUC was significantly greater in PSAD (0.801) than for the other parameters. The sensitivity and specificity of a PSAD threshold of 0.32 were 85.7% and 77.8%, respectively. In conclusion, PSAD can be a useful and very effective predictor in a man aged ≤ 50 and we can counsel patients with discretion regarding the likelihood of significant PCa.

Keywords: Prostate cancer, prostate biopsy, PSA density, insignificant prostate cancer

Introduction

Prostate cancer (PCa) represents the most frequent cancer diagnosed in men in Western country [1]. Prostate specific antigen (PSA) is widely used to screen for prostate cancer in the asymptomatic male population, although many controversy exists regarding its appropriate implementation [2, 3].

In many cases nowadays prostate cancers is estimated to have a protracted natural history and pose little threat to patients during their lifetime. Patient age is a crucial issue in the treatment decision-making process. Recent studies showed that the use of lower PSA cutoffs may contribute to detect prostate cancer that is more frequently in its curable stage [4-6]. In clinical practice, the number of patients ≤ 50 years old with elevated PSA values has been increasing because of the wide spread of serum PSA testing for early detection or the use of a standard battery of laboratory tests. However, the incidence and appropriate cutoff level of PSA at aged 50 years or less has not been fully characterized yet. PSA testing at lower ages is a debatable issue [7-11].

In this study, we aimed to analyze the useful and effective predictor of PCa in men aged ≤ 50, focusing especially on the prediction of clinically 'significant' prostate cancer.

Patients and methods

The study population for the current analysis included 106 patients aged ≤ 50 years who had prostate biopsy between Jan 2004 and Dec 2011 at Keio University and Saitama city hospital. Institutional review board approvals were

Table 1. Clinical characteristics of 106 patients ≤ 50 years of age subjected to prostate biopsy

Characteristics	Total	non-PCa	PCa	*p* value
No. of patients	106	91	15	
Age	47.1 ± 4.1	46.9 ± 3.9	47.9 ± 5.1	0.087
PSA (ng/ml)	6.8 ± 4.2	6.5 ± 3.5	8.4 ± 7.7	0.939
Prostate volume (cm^3)	30.1 ± 14.2	30.2 ± 14.2	29.0 ± 14.1	0.535
Transition zone volume (cm^3)	13.0 ± 8.7	12.9 ± 8.4	13.2 ± 10.3	0.596
PSAD ($ng/ml/cm^3$)	0.26 ± 0.17	0.24 ± 0.15	0.32 ± 0.24	0.237
PSATZD ($ng/ml/cm^3$)	0.67 ± 0.51	0.64 ± 0.43	0.91 ± 0.81	0.344

Table 2A. Clinical parameters of the patients among NEM, Group non-S and Group S

Characteristics	Group: NEM	Group: non-S	Group: S	*p* value
No. of patients	91	8	7	
Age	46.9 ± 4.2	46.8 ± 6.8	49.2 ± 1.8	0.226
PSA (ng/ml)	6.5 ± 3.3	5.9 ± 1.1	11.3 ± 10.9	0.834
Prostate volume (cm^3)	30.2 ± 14.2	34.6 ± 15.2	22.6 ± 10.2	0.139
Transition zone volume (cm^3)	12.9 ± 8.4	17.0 ± 12.3	8.8 ± 5.6	0.093
PSAD ($ng/ml/cm^3$)	0.24 ± 0.15	0.20 ± 0.09	0.47 ± 0.27	0.023
PSATZD ($ng/ml/cm^3$)	0.64 ± 0.43	0.53± 0.43	1.35 ± 0.95	0.027

NEM: no evidence of malignancy, non-S: insignificant cancer, S: Significant cancer.

Table 2B. Clinical parameters of the patients with Group S and Group non-S

	NEM & insignificant PCa	significant PCa	
Characteristics	Group: non-S	Group: S	*p* value
No. of patients	99	7	
Age	46.9 ± 4.2	49.2 ± 1.8	0.126
PSA (ng/ml)	6.5 ± 3.2	11.3 ± 10.9	0.689
Prostate volume (cm^3)	30.6 ± 14.3	22.6 ± 10.2	0.067
Transition zone volume (cm^3)	13.2 ± 8.8	8.8 ± 5.6	0.052
PSAD ($ng/ml/cm^3$)	0.24 ± 0.15	0.47 ± 0.27	0.008
PSATZD ($ng/ml/cm^3$)	0.63 ± 0.43	1.35 ± 0.95	0.012

obtained. Trans-rectal ultrasound-guided biopsy (TRUS-Bx) was recommended for patients with an elevated PSA value or suspicious findings by digital rectal examination (DRE). The initial prostate biopsy was performed in the vast majority of our patients following the extended biopsy scheme (10-12 cores). Before obtaining the biopsy cores, prostate volume and transition zone volume were routinely measured using TRUS.

The clinical variables assessed included age, family history of PCa, PSA value, DRE findings, prostate volume (P vol), transition zone volume (TZ vol), number of positive core, PSA density (PSA divided by prostate volume), PSA density of the transition zone: PSATZD (PSA divided by transition zone volume), and Gleason score.

Receiver operating characteristics (ROC) curves and the corresponding areas under the ROC curves (AUC) were calculated and used to analyze the sensitivity and specificity of PSA, P vol, TZ vol, PSAD, and PSATZD for prostate cancer or clinically significant prostate cancer. The positive predictive value (PPV) was calculated by dividing the number of clinically significant tumors detected by the number of all men meeting the criteria being evaluated. We compared the number of clinically significant tumors detected between new cut-off values. Logistic regression was used to predict significant PCa. When comparing patients with a high GS (≥ 7), we assessed the differences in their clinicopathological profile using chi-squared test and MannWhitney test. Multivariate analysis was performed according to logistic regression models to identify independent predictors of positive PCa or high GS. Institutional review board approval was obtained.

Table 3. ROC curve analysis and AUC in predicting siginificant prostate cancer

ROC	AUC	SE	95% CI	*p*-value
PSA	0.545	0.127	0.296-0.795	0.689
PV	0.246	0.122	0.052-0.532	0.067
TZV	0.254	0.123	0.037-0.521	0.052
PSAD	0.801	0.106	0.593-1.000	0.008
PSATZD	0.786	0.108	0.575-0.998	0.012

The SPSS software package version 21.0 was used for statistical analysis. Statistical significance was defined as $p < 0.05$.

Results

The clinical characteristics of the 106 patients evaluated in this study are shown in **Table 1**. Of the 15 patients with PCa (12.3%), Gleason score was 6 or lower in nine patients. Six patients had Gleason score 7. There were no significant differences between no-PCa and PCa patients regarding PSA value, P vol, PSAD, TZ vol or PSATZD (**Table 1**). ROC curves were constructed for PSA (AUC: 0.494), Prostate volume (AUC: 0.450), Transition zone volume (AUC: 0.457), PSAD (AUC: 0.596), and PSATZD (AUC: 0.618). There was no statistically significance of the AUC.

Thus, we made a new classification of the 15 PCa patients according to clinically significant or insignificant PCa in order to find a useful predictor of significant PCa in men aged ≤ 50 or less. Patients meeting the inclusion criteria were classified as having insignificant prostate cancer if their Gleason score was ≤ 6 and had less than 2 positive biopsy cores. Of the 15 PCa patients, eight were newly classified as insignificant and seven patients as significant PCa (**Table 2A**). The average PSA, P vol, PSAD, TZ vol and PSATZD among those subgroups of PCa patients are shown in **Table 2**. There was no significant difference of PSA and prostate volume among those subgroups. Whereas, there was a significant difference of PSAD ($p = 0.023$) and PSATZD ($p = 0.027$) among them.

Thereafter, we considered the eight insignificant PCa patients and the 91 NEM patients as one group. Then we reassessed data and compared the clinical parameters of the seven patients with significant PCa (Group S) with the other (**Table 2B**).

There was no significant difference of PSA, P vol, TZ vol between the two Groups. Nevertheless, the difference of PSAD ($p = 0.008$) and PSATZD ($p = 0.012$) between them was statistically significant.

ROC curves were constructed for PSA, Prostate volume, Transition zone volume, PSAD, and PSATZD. The AUC was significantly greater in PSAD (0.801, $p = 0.008$) than for the other parameters (**Table 3**). These results indicated that PSAD could become a useful parameter to predict significant PCa in men aged ≤ 50. The ROC analysis revealed an inflection point of plots of PSAD was 0.32. Then we re-evaluated the cut-off value 0.32 of PSAD using sensitivity, specificity, positive predictive value. The sensitivity and specificity for the PSAD threshold of 0.32 was 85.7% and 77.8%, respectively. Positive predictive value (PPV) was 21.4%.

Discussion

The rate of detection of PCa in young men will continue to rise associated with the advancement of the current and evolving practices of screening and detection [1, 4-11]. Although death due to prostate cancer may occur as early as in their 40 s according to data from the Surveillance, Epidemiology, and End Results program, it is a relatively infrequent event and worldwide men in their 40 s are not commonly subjected to PSA screening. It is impossible to prevent these untimely deaths without actively screening for PCa before age 50. The rationale of PSA screening for younger men is the following. The incidence of BPH is lower in young men. PSA screening in younger men enables the detection of curable localized cancer. Younger patients are less likely to have significant medical comorbidity and are more likely to have access to definitive treatments.

Age represents a crucial issue concerning treatment decision for patients with PCa. A Recent study demonstrated that young men with high-grade tumors have significantly worse disease specific survival (DSS) outcomes, although younger men as a group were more likely to have better overall survival and cancer specific survival at 10 years compared with older men [6]. Useful clinical parameters have been expected for PCa screening in younger men [7-11]. Because radical prostatectomy improves survival in young men with early PCa, timely detection is essential.

Recent reports showed that the benefits of screening have been shown to differ based on the initial PSA level at various ages, suggesting the predictive value of a single baseline PSA measurement at an early time [12-15]. It has been reported that the median PSA level is 0.7 ng/ml for men aged 40 to 49 years and 0.9 ng/ml for men aged 50 to 59 [12]. A baseline PSA level between the medium and 2.5 ng/ml is associated with 14.6 fold and 7.6 fold increased risk of PCa in men aged 40 to 49 and 50 to 59 years, respectively. Moreover, baseline PSA measurement at a young age is a significant predictor of disease-specific survival. These results suggested that baseline PSA testing may be used for risk stratification and to guide screening protocols. These data can be used to help determine when to recommend biopsy. NCCN and EAU guidelines recommend a risk-based screening strategy for prostate cancer, whereby informed men undergo baseline PSA testing beginning in their 40 s as a means of stratifying them into PCa risk. However, there is no useful parameter, other than PSA, to recommend young men with an elevated PSA value to undergo prostate biopsy. Therefore, a useful clinical parameter for PCa screening in young men has long been necessary.

Our present results indicated that PSAD could become a useful predictor of significant PCa in men aged ≤ 50. The sensitivity and specificity of a PSAD threshold of 0.32 were 85.7% and 77.8%, respectively. Active surveillance (AS) has emerged as an alternative treatment options for men with low-risk disease and continues to be intensely investigated [16]. The objective of AS is to avoid unnecessary treatment and its related morbidity in patients with low-risk PCa. Although AS is increasingly offered among the standard management options for low-risk localized PCa and may help reduce overtreatment, most criteria and programs target men with limited life expectancy. The proposed value of PSAD as a parameter to evaluate during. AS is 0.15 according to the Johns Hopkins Study Group [17, 18] and 0.2 in the PRIAS study [19-21]. The cut-off level proposed in this study is 0.32. These results indicated that if in a man aged ≤ 50 PSAD is 0.32 prostate biopsy should be strongly recommended to confirm the presence of clinically significant PCa. We believe that future guidelines for PCa screening should incorporate a measurement of PSAD.

This study had some limitations, including its lack of prognostic data because follow-up periods were short. Another limitation was that men in their 40 s were indiscriminately ordered a standard battery of laboratory tests, so our results cannot be extrapolated to the general population.

Although no significant parameter should be used in clinical practice to increase the ability to predict the presence of clinically significant PCa, PSAD can be a useful and very effective predictor in a man aged ≤ 50 and we can counsel patients with discretion regarding the likelihood of significant PCa. Serial PSA data and P vol increase the accuracy of the diagnosis based on the PSAD value. These data can help determine when to recommend biopsy.

Disclosure of conflict of interest

None of the authors has any conflict of interest.

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