

# Prostate-Specific Antigen Doubling Time as a Predictor of Gleason Grade in Prostate Cancer

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**Introduction:** Our aim was to evaluate the value of serum prostate-specific antigen doubling time (PSADT) to differentiate patients with high-grade prostate cancer who require more aggressive therapy from those with low-grade cancer.

**Materials and Methods:** Of 460 patients with extended 12-core transrectal ultrasonography-guided biopsy of the prostate, 59 with confirmed prostate cancer were selected. They had not received any previous treatment for prostate cancer and had at least 2 consecutive serum PSA tests with a rising trend. The PSADT was calculated in patients with 2 serum PSA levels measured with an interval more than 3 months.

**Results:** Of 59 patients with prostate cancer, 35 (59.3%) had low-grade and 24 (40.7%) had high-grade tumors. There was no difference in age between the two groups. The median PSADT in patients with high-grade and low-grade tumors were 12.70 months (range, 0.7 to 44.8 months) and 25.00 months (range, 1.65 to 41.2 months;  $P = .001$ ). A total of 21 patients with high-grade tumors (87.5%) had a PSADT less than 12 months, while only 9 of those with low-grade tumors (25.7%) had a PSADT less than 12 months. A PSADT cutoff of 12 months provided a sensitivity of 74% and a specificity of 87% for differentiation of high-grade from low-grade cancers.

**Conclusion:** We concluded that men with a short PSADT (< 12 months) were at a higher risk of harboring a high-grade prostate cancer. Our data suggests PSADT can identify patients with high-grade tumors who require more aggressive therapy.

Keywords: prostate-specific antigen, prognosis, prostatic neoplasms

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## INTRODUCTION

Serum prostate-specific antigen (PSA) measurement is widely used in the management of prostate cancer. The rate at which PSA is increasing has been shown to be valuable in determining prognosis of the patients in various settings, and therefore, may be a useful marker for mortality as a result of prostate cancer.<sup>(1-6)</sup> Prostate-specific antigen

velocity was originally described by Carter and Pearson.<sup>(7)</sup> Subsequently, serum PSA doubling time (PSADT) was described by Schmid and coworkers and was studied in the patients treated by radiotherapy for prostate cancer.<sup>(8)</sup> By increasing the PSA level in a linear fashion (with a constant increasing rate), PSA velocity can be estimated by this formula: change in PSA level

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divided by the interval between measurements. However, it seems that PSA increases in an exponential fashion (constant percentage increase) in prostate cancer,<sup>(8,9)</sup> in which case the PSADT is a more appropriate measure of PSA kinetics. In contrast to PSA velocity, the estimation of PSADT requires logarithmic analysis, and thus, it may be more difficult to be applied in the clinic. In this study we investigated the value of PSADT for differentiation of low-grade and high-grade prostate cancer in newly diagnosed patients

## MATERIALS AND METHODS

### Patients

Data of 460 patients who had been referred to our medical center for transrectal ultrasonography-guided biopsy of the prostate between April 2004 and December 2007 were collected. Biopsy indications were abnormal digital rectal examination or increased PSA (PSA more than the normal level for age). After obtaining informed consent from each patient, digital rectal examination was performed before transrectal ultrasonography-guided biopsy. Of 460 patients who underwent extended 12-core biopsy, 59 had a pathologic report of prostate cancer that had not received any previous treatment for prostate cancer and had at least 2 consecutive PSA tests with more than 3 months interval. Sequential PSA readings were obtained from the same laboratory using a well-calibrated assay.

### Pathologic Examination

All samples were examined by one expert pathologist in uropathology. Every positive sample was graded using the Gleason scoring system and the score was calculated from the sum of the primary and secondary grade. Gleason scores less than and greater than 7 were considered to be representative of a low-grade and high-grade tumor, respectively. In case of a Gleason score of 7, the total score was assigned as high grade if the primary grade was 4 or 5; otherwise, it was considered as low grade.

### Prostate-Specific Antigen

The PSADT was estimated in patients with rising

PSA before the onset of treatment according to the formula:

$$t \times \log_e(2) / (\log_e[\text{PSA2}] - \log_e[\text{PSA1}])$$

where  $t$  is the time between the two consecutive PSA determinations (PSA1 and PSA2).<sup>(10,11)</sup> This was made possible as all PSA assays for each patient were performed in a same laboratory.

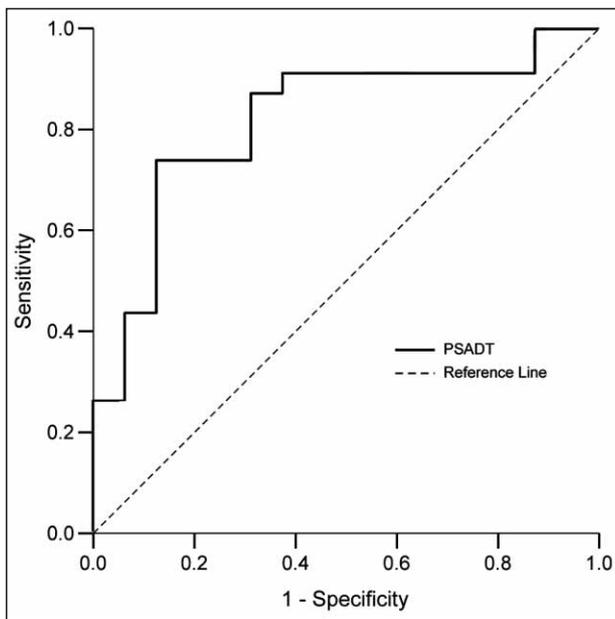
### Statistical Analyses

The 1-sample Kolmogorov-Smirnov test showed that PSADT and PSA values had nonparametric distributions and age had a parametric distribution; therefore, data were analyzed by the Mann-Whitney test and the  $t$  test, where appropriate. The receiver operating characteristic curve analysis was used for determination of a cutoff value for PSADT to differentiate low-grade and high-grade tumors. A  $P$  value less than .05 was considered significant.

## RESULTS

Of 59 patients with prostate cancer, 35 (59.3%) had low-grade and 24 (40.7%) had high-grade tumors. The mean age of the patients in low-grade and high-grade groups was  $70.0 \pm 10.9$  years (range, 47 to 86 years) and  $68.0 \pm 5.8$  years (range, 58 to 80 years), respectively ( $P = .47$ ).

The median time interval between the two consecutive PSA tests was 5.60 months (range, 3.8 to 11.0 months). The median PSADT in patients with high-grade and low-grade tumors were 12.70 months (range, 0.7 to 44.8 months) and 25.00 months (range, 1.65 to 41.2 months;  $P = .001$ ). A cutoff point of 12 months was considered for differentiation of high-grade tumors from low-grade ones based on PSADT. A total of 21 patients with high-grade tumors (87.5%) had a PSADT less than 12 months, while only 9 of those with low-grade tumors (25.7%) had a PSADT less than 12 months. The receiver operating characteristic curve showed that a PSADT cutoff of 12 months provided a sensitivity of 74% and a specificity of 87% for differentiation of high-grade from low-grade cancers. The area under the curve was 82% (Figure). The positive predictive value and negative predictive value were 70% and 73%, respectively.



The figure shows receiver operating characteristic curve for determining the prostate-specific antigen doubling time (PSADT) threshold value for differentiation of high-grade from low-grade prostate cancer.

## DISCUSSION

Because PSA velocity and PSADT are measures of the rate of PSA change with time, their estimation relies on the statistical technique of regression. Calculation of PSA velocity is based on the assumption that serum PSA increases in a linear fashion, and therefore, is implicated by linear regression analysis. In contrast for PSADT, an exponential increase in PSA is assumed, and therefore, it requires a complex analysis for estimation. Regression techniques for the estimation of PSADT require the logarithmic transformation of the available serum PSA values by a somewhat daunting formula. In practice, calculation of PSADT requires the use of statistical software. However, a recently published graphical tool allows the estimation of PSADT in practice settings without the need for electronic resources.<sup>(12)</sup>

Several previous studies have shown PSADT to be an appropriate tool for monitoring of prostate cancer at any step of the disease.<sup>(13)</sup> However, measurement of serum PSA may be accompanied by errors due to interassay and biological variations; therefore, some precautions are needed to minimize such errors on estimates

of PSA. As a result, sequential PSA tests should be obtained with longer intervals in order that the resulting estimate truly reflects cancer growth. On the other hand, there are some limitations in this approach including the need for expedient decision making, costs of repeating PSA test, and variation in PSA kinetics with time.<sup>(14)</sup> Two PSA tests with at least a 3-month interval appear to provide an accurate estimate of PSADT; however, when possible, a minimum of 3 tests during at least 6 months should be obtained. In the present study, our analysis showed that patients with a short PSADT (< 12 months) before the onset of therapy were at a higher risk of harboring a high-grade prostate cancer. Pound and colleagues showed that a PSADT of equal to or less than 10 months was predictive of development of metastatic disease, which was in accordance with the results reported by Pollack and associates after definitive radiotherapy.<sup>(15,16)</sup>

An increasing concern is the overtreatment of patients with “good-risk” prostate cancer, while undertreatment in patients with a more aggressive biological phenotype should be avoided. Various criteria have been proposed to identify patients with aggressive disease, but none has been validated.<sup>(17)</sup> A rapid PSADT (< 12 months) probably reflects a more aggressive phenotype. Choo and coworkers analyzed the distribution of PSADT in “good-risk” patients on surveillance.<sup>(18)</sup> The median PSADT was 7 years in their patients; 42% and 22% of the them had a PSADT more than 10 and less than 3 years, respectively, the latter of whom were at a high risk of progression and were treated radically. At 8 years, the mortality rate was less than 1% suggesting this approach to be safe. McLaren and associates showed that PSADT was significantly lower in patients with progressive disease and strongly correlated with the time to treatment. They concluded that PSADT was the most important indicator of disease activity.<sup>(4)</sup>

Our data confirms an acceptable level of accuracy for PSADT to identify patients with high-grade prostate cancer who require more aggressive therapy. This indicator appears to convey prognostic information that should be considered with conventional prognostic factors such as

absolute serum PSA concentration, clinical stage, and biopsy grade and can help in determining the prognosis years ahead.<sup>(19)</sup> The PSADT is probably useful in determining outcomes after treatment and suggesting experimental multimodal therapy protocols for those with aggressive disease. Finally, PSADT measures may be crucial for intervention; however, further investigation is needed to determine precise cutoff levels.

## CONCLUSION

It seems that PSADT provides useful information in the prediction of the pathological features of prostate cancer patients and selection of the patients who need more aggressive treatment.

## CONFLICT OF INTEREST

None declared.

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