Review – Prostate Cancer

Current Applications for Prostate-Specific Antigen Doubling Time

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Abstract

Objective: To review the current status of prostate-specific antigen doubling time (PSADT) as it pertains to the evolution of prostate cancer (PCa), specifically assessing its role in the following four stages: before diagnosis, prior to definitive treatment, following treatment including salvage therapy after recurrence, and lastly, after onset of androgen-insensitive PCa.

Methods: We searched PubMed literature for current articles on PSADT using the key words listed for this review and, where possible, selected those with significant levels of evidence that were deemed relevant, seminal, or controversial. We summarized the data regarding PSADT as a marker for diagnosis and disease characterization, as well as a predictor of progression, response to treatment, and mortality.

Results: PSADT may offer an advantage in providing a more dynamic picture of tumor behavior, providing clues regarding the relative aggressiveness of the underlying pathology. Evidence points toward a role for PSADT in the management of PCa, specifically in active surveillance, disease recurrence after treatment, and in androgen-independent PCa. PSADT is an important prognostic factor that may serve as an auxiliary end point for cancer-specific survival; however, optimal cut-off points denoting risk remain debatable.

Conclusions: PCa management requires risk stratification with a combination of variables, PSADT being one of the most reliable predictors. It is now a parameter included in many predictive nomograms and in treatment guidelines for expectant management and salvage therapy.

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1. Introduction

Because prostate cancer (PCa) remains a significant cause of cancer deaths, means of improving detection and management continue to develop in an effort to overcome inadequacies of current methods. Specific tumor markers that not only detect PCa but also differentiate indolent from clinically significant disease are needed. To more accurately define the risk of progression and better tailor management throughout the course of disease, improvements in biomarkers must be exploited. Current nomograms using Gleason grade, clinical stage, and prostate-specific antigen (PSA) require modification to provide useful stratification for today’s evolving patient population.

Among the many disease markers under investigation, PSA doubling time (PSADT) has emerged as a potentially useful tool. Derived from the same data as PSA velocity (PSAV), which measures the absolute rate of change and is calculated as the slope of a linear regression of PSA measurements over time (ng/ml × yr), PSADT represents the relative rate of PSA change over time and is defined as the time needed for the PSA value to double. As opposed to PSAV, which is related to tumor volume, PSADT takes into account the exponential nature of neoplastic growth and requires logarithmic analysis. It is independent of the baseline PSA value and should therefore be used when comparing different patient populations [1]. Despite these differences, the diagnostic and prognostic value of PSADT compared with PSAV is uncertain, and the relative merits of these variables deserve further assessment.

Notably, PSADT is still limited by fluctuations in PSA values, which can be considerable depending on the timing of measurements. Early determinations of PSADT in the active surveillance population may not necessarily be representative of overall PSADT calculations [2]. Although a question remains as to the optimal number and timing of measurements, a currently accepted approach is to use three or more values separated by at least 3 mo each with a minimum increase of 0.2 ng/ml [3]. However additional values separated by longer intervals may yield more reliable results during expectant management [2]. Furthermore, multiple studies demonstrate significant discrepancies in PSA measurements among different detection assays despite current efforts to standardize PSA assays [4]. The inadequacies in interchangeability between assays may seriously weaken the reliability of PSADT calculations; thus, PSA values should be measured using the same assay.

Multiple methods have been described for calculating PSADT. The simplest involves dividing the natural log of 2 (0.693) by the slope of the line described by two log-transformed PSA values, or all log PSA values may be used to create the best fit line by least squares regression (Fig. 1). When calculating PSADT following radiation therapy, subtracting PSA nadir from subsequent values may increase accuracy [3]. More complex methods involving splines or quadratic equations to correct for baseline PSA and benign prostatic hyperplasia have been demonstrated but are not yet commonly applied. Conveniently, online prediction tools that calculate PSADT are available for use in clinical practice through, for example, the Memorial Sloan-Kettering Cancer Center Prostate Nomogram Web site [5].

Using PSADT as opposed to individual or absolute PSA values may more closely approximate the biologic behavior of the cancer, that is, tumor progression. Pruthi et al showed that a short PSADT following radical prostatectomy (RP) correlated with the aggressiveness of operative pathology including capsular penetration, percent Gleason 4–5 disease, and lymphatic involvement [6]. In the initial paper suggesting prognostic value to PSADT, D’Amico and Hanks observed a relationship between shorter PSADT and more rapid clinical progression in 22 patients with biochemical recurrence following external-beam radiation therapy (EBRT) [7]. Additional evidence that PSADT reflects tumor biology derives from the fact that, following initial differences related to therapy, patients with biochemical relapse after RP compared to EBRT have similar doubling times [8]. Since then, the possible prog-
nostic value of PSADT has been explored in detail and expanded significantly.

Here, we summarize existing data to clarify when during the course of PCa management PSADT is a reliable biomarker and can therefore be useful in clinical practice. This review of PSADT will be organized chronologically around the natural history of PCa and its treatment. Four sections will be described: first, the value of PSADT before diagnosis; second, following diagnosis but prior to definitive treatment; third, following definitive treatment, and including salvage therapy, androgen-insensitive PCa (AIPCa); and finally, after AIPCa, including secondary androgen-deprivation therapy (ADT) and chemotherapy.

Fig. 2 presents the possible uses of PSADT along a PCa timeline and takes into account the level of evidence according to American Society of Clinical Oncology (ASCO) guidelines [9].

Fig. 2 – Overall use of prostate-specific antigen doubling time along the prostate cancer timeline. (1–5) Level of evidence according to American Society of Clinical Oncology (ASCO) guidelines [9]. Evidence from (1) meta-analysis of multiple, well-designed, controlled studies or high-powered randomized trials; (2) at least one well-designed, experimental study or low-powered randomized trials, (3) well-designed, quasi-experimental studies including nonrandomized, controlled, single-group, cohort, or case-controlled studies; (4) non-experimental studies including descriptive and case studies; and (5) case reports and clinical examples. PCa = prostate cancer.

2. **PSADT before diagnosis**

The usefulness of PSADT prior to diagnosis is probably limited because assessment involves the binary decision regarding whether or not to perform biopsy rather than extracting prognostic data. A few studies have evaluated the diagnostic ability of PSADT and confer that although PSADT can predict the presence of disease, it offers little improvement beyond current methods in determining the need for initial biopsy.

Raaijmakers et al examined 1689 men undergoing biopsy in the screening arm of the European Randomized Study of Screening for Prostate Cancer [10]. PSADT was significantly different between those with and without PCa (5.1 vs. 6.1 yr, \( p = 0.002 \)). However, further analysis revealed PSA kinetics conveyed little additional data in predicting biopsy results. PSADT was marginally superior to PSAV with an area under the curve of 0.573 compared to 0.549, but neither was significant on multivariate analysis.

Spurgeon et al support these conclusions in a study examining 1699 men with a PSA level of <10 ng/ml undergoing biopsy, the majority of which consisted of only six cores [11]. PSADT of 2–5 yr was very weakly associated with a positive biopsy and high-grade PCa (Gleason \( \geq 7 \)) and was not significant when other variables were considered. The authors cite data suggesting that biologic variation of PSA in the treatment-naïve prostate may reduce the accuracy of PSADT prior to definitive therapy.

On the other hand, PSADT may play a more useful role following initial negative biopsy. Garzotto et al
retrospectively examined 373 patients undergoing repeat biopsy and found that PSADT was the best independent predictor for positive results among other well-characterized predictors. The authors suggest using PSADT to stratify patients into risk groups predicting for high-risk disease (Gleason ≥7), which should then ascertain the need for repeat biopsy. Kaplan-Meier analysis demonstrated that four risk groups could be characterized using PSADT, PSA density, and the presence or absence of high-grade prostatic intraepithelial neoplasia (PIN) [12]. An update of these data with longer follow-up indicates PSADT (>5 yr, 2–5 yr, and <2 yr) alone is sufficient to categorize patients into low-, intermediate-, and high-risk groups, respectively [13].

3. Prior to definitive treatment

Prior to definitive treatment, PSADT has been sought to provide information on the aggressiveness of PCa in order to predict treatment outcomes and aid in treatment selection, but data are controversial and inadequate for supporting its use in patients requiring definitive therapy. Studies examining the potential correlation between pretreatment PSADT and pathologic features have yielded mixed results regarding Gleason score, extracapsular extension, and surgical margins status (Table 1) [14–17]. Although most of these studies support a correlation between PSADT and pathologic stage, incorporating pretreatment PSADT into current methods of clinical staging has not been reported to increase the accuracy of predictive models.

In addition, investigators have hypothesized that pretreatment PSADT can predict biochemical recurrence following definitive therapy; however, these results are also conflicting and cannot confirm that PSADT is a reliable prognostic factor, most likely because outcomes are strongly influenced by the treatment given (Table 1). Unfortunately, these investigations are limited by their retrospective nature, small study populations, short follow-up time, interassay variability, and inconsistency in operator techniques. Discrepancies in patient populations, progression criteria, and PSADT calculations may account for varied results.

Alternatively, active surveillance has emerged as a reasonable option for many patients with clinically insignificant disease, and PSADT may play a pivotal role in identifying tumor progression, that is, an increase in Gleason grade or in the extent of disease, while these cancers still remain curable. In an investigation by McLaren et al, a cohort of 113 patients with mostly T1–T2 disease were

| Series | n | Clinical stage | No. of PSA determinations per patient (median) | Median time between PSA determinations, mo (range) | PSADT significantly correlated with | Gleason score | Pathologic stage | Extracapsular extension | Seminal vesicle involvement | Surgical margin status | Biochemical recurrence | Surgical margin status | Seminal vesicle involvement | Surgical margin status | Biochemical recurrence |
|--------|---|----------------|-----------------------------------------------|-----------------------------------------------|-------------------------------------|--------------|------------------|--------------------------|-----------------------------|---------------------------|------------------|------------------|------------------|-----------------------------|------------------|------------------|
| Hanks et al [14] | 99 | T1–T3NXMX | ≥3 | 9 (2–48) | No | No | No | No | Yes (≤ 12 mo) | No |
| Goloboff et al [15] | 56 | T1–T2N0MX | ≥3 | 25 (2–83) | No | Yes | No | Yes | Yes | No | Yes | No | No | No |
| Egawa et al [16] | 62 | T1–T3N1MX | ≥4 | 17 (6–74) | No | Yes | Yes | Yes | No | No | Yes | No | No |
| Freedland et al [17] | 86 | T1–T2N0MX | ≥3 | 33 (12–96) | No | No | No | No | No | No | No | No | No | No |

PSADT = prostate-specific antigen doubling time; na = not applicable (no pathologic specimen for evaluation).

* Significance denotes $p < 0.05$.
followed with active surveillance for a median of 21 mo [18]. Analysis of PSA progression revealed that PSADT predicted for clinical progression (p < 0.0001), stage progression (p = 0.01), and time to treatment (p = 0.0001). In fact, 50% of patients with a PSADT < 18 mo progressed within 6 mo. Overall survival rates at 2 and 5 yr were 92% and 68%, respectively, with no recorded cancer-specific deaths.

In a prospective study conducted by Klotz et al, 299 patients with a PSA level < 15 ng/ml, Gleason ≤ 3 + 4, and T ≤ 2b were followed with active surveillance [19]. Selective delayed intervention was initiated if the cancer progressed clinically, histologically, or by PSA analysis: PSADT < 2 yr, final PSA > 8 ng/ml, and an increase in PSA over time yielding p < 0.05 on regression analysis. At 8 yr, overall survival was 85% and disease-specific survival was 99.3%. Notably, the two patients who died of PCa did so within 5 yr and had a PSADT < 2 yr, suggesting the presence of occult metastasis at the time of diagnosis. Moreover, of the 24 patients who underwent RP for PSADT < 2 yr, 66% had stage > T3 disease.

Although studies conclude PSADT is useful in determining which patients on active surveillance are at high risk for progression, the indication for treatment remains controversial. Definitions of rapid versus slow doubling times differ among studies, and PSADT levels can vary considerably [20]. As opposed to the common 2-yr cut-off, others, including the European Randomized Study of Screening for Prostate Cancer, have found pretreatment PSADT < 4 yr to be associated with a higher risk of disease progression [21]. Notably, a recent abstract revealed that although PSADT > 18 mo predicted for 10-yr systemic progression-free survival in a cohort of 2296 men, it had less predictive power as Gleason score increased [22]. Moreover, others have revealed that an accurate PSADT calculation may depend on the number and timing of PSA measurements and can therefore be of consequence in obtaining significant results [2].

Despite these uncertainties, the clinical use of PSADT has become more common [23], and is, to date, one of the best markers for advancing disease in the active surveillance population. Certainly, in weighing options for intervention one must consider the entire picture of progression, as well as patient preferences and risks associated with treatment. Clinically, National Comprehensive Cancer Network (NCCN) guidelines for active surveillance, which suggest PSADT < 3 yr to indicate cancer progression, can give practitioners additional information for counseling patients and deciding on further treatment [24].

4. Following PSA relapse

4.1. Before salvage therapy

Approximately one third of patients who undergo definitive therapy for PCa will have a detectable increase in PSA within 10 yr [25]. However, PSA values vary markedly, as does the rate of clinical progression, and biochemical recurrence may not exactly reflect PCa mortality. Recently, PSADT has been shown to facilitate the evaluation of treatment modalities, type of tumor relapse, and cancer-specific survival (CSS) by allowing comparison at an earlier end point than observable disease manifestation.

In the early 1990s, PSADT was recognized by numerous authors to correlate with the time to develop clinical failure [7,14], and subsequent data described PSADT as a predictor for disease relapse, as well as type of disease relapse, after definitive radiotherapy failed [26–28]. Considerable retrospective data reveal that a significantly greater number of patients with PSADT > 6 mo experience local failure as opposed to metastatic failure, whereas those with PSADT < 6 mo are more likely to exhibit metastatic failure. Likewise, multiple large studies have found PSADT to be a significant risk factor for clinical progression on multivariate analysis and indicative of the pattern of clinical recurrence after RP (Table 2) [29,30]. Furthermore, Okotie et al demonstrated that men with PSADT < 6 mo were at increased risk of having a positive bone scan (p = 0.007) or computed tomography scan (p = 0.017) compared to men with longer PSADT and recommend incorporating PSADT as a factor determining the need for bone scintigraphy after PSA recurrence [31].

These data suggest those with a shorter PSADT harbor existing distant metastases best suited to systemic treatment, whereas a longer PSADT may represent another source or a slow-growing process to which delayed or local therapy may be more appropriate. Recent studies add substantial evidence in favor of this hypothesis [28,32,33]. Pinover demonstrated that post-EBRT patients treated with ADT developed distant failure later than untreated patients if PSADT was < 12 mo (p = 0.02), but in corresponding treatment groups with longer PSADT there was no difference in the 5-yr freedom from distant metastasis rate (p = 0.74) [28]. Leventis et al examined predictors of response to salvage EBRT after RP in 49 men with local recurrence [32]. In multivariate analysis, they found PSADT to be a significant independent predictor, with values < 11.8 mo reflecting poor response to radiation (p = 0.025). In a multicenter analysis of 501 patients,
Stephenson et al found similar results using a cut-off of 10 mo; however, some men with rapid PSADT or high-grade disease (or both), specifically those with positive surgical margins, benefited from salvage radiotherapy [33]. In these patients, PSADT may not directly reflect metastatic disease as in patients with negative surgical margins, but rather aggressive residual pelvic disease where early local salvage therapy may prevent future metastases.

Although it is important to note that not all men with rapid PSADT will progress, PSADT may be specific enough to effectively predict patient outcome. Several recent studies have characterized PSADT < 12 mo as an unfavorable prognostic variable for mortality [34]. Furthermore, stratification of 1064 patients following RP into high-, intermediate-, and low-risk groups according to PSADT has yielded significant differences in clinical progression and mortality among those with PSADTs of < 1.0 yr, 1.0–9.9 yr, and ≥ 10 yr [35]. Specifically, those at high risk had a higher incidence of local and systemic progression as well as death compared to both the intermediate- and low-risk groups.

In addition, PSADT was the strongest predictor of PCa mortality after biochemical failure in a preliminary study of 379 patients by Freedland et al [36]. They established PSADT < 15 mo was significantly associated with mortality, with PSADT < 3 mo indicating a very high risk of death, similar to other data [3]. In a follow-up study of the same cohort, shorter PSADT remained correlated to cancer-specific and all-cause mortality (p < 0.001), and PSADT subdivided risk groups of < 3 mo, 3–8.9 mo, and 9.0–14.9 mo paralleled the prior analysis [37]. After PSADT stratification, 100% of deaths were due to PCa in those with PSADT < 3 mo, 92% of deaths in those with PSADT < 9 mo, and 78% of deaths with PSADT 9.0–14.9 mo, but PCa accounted for only 35% of deaths in patients with PSADT ≥ 15 mo.

Despite the prognostic power of PSADT following definitive treatment, a question remains as to whether PSADT is valuable as a surrogate end point for CSS. Valid assessment, according to Prentice’s criteria, must meet four specific conditions (Table 3). Although D’Amico et al claim posttreatment PSADT < 3 mo satisfies these criteria [3], an analysis of a phase 3 clinical trial of 1514 men with locally advanced PCa determined PSADT supports, but is not completely consistent with, a true end point [38]. In this investigation Valicenti et al evaluated prospective, randomized data from patients treated with radiation and ADT and demonstrated that treatment was not prognostic for PSADT < 3 mo. A possible explanation may be the relatively small number of patients in this subgroup in whom

<table>
<thead>
<tr>
<th>Series</th>
<th>Treatment type</th>
<th>n</th>
<th>Follow-up, yr (range)</th>
<th>No. of PSA determinations per patient</th>
<th>Time interval between PSA determinations (every 3 mo, semiannually, annually thereafter)</th>
<th>PSADT, mo</th>
<th>Type of failure</th>
<th>p</th>
<th>Mean value</th>
<th>Mean value</th>
<th>Mean value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pound et al [29]</td>
<td>RP</td>
<td>315</td>
<td>5.3 (0.5–15)</td>
<td>≥ 2</td>
<td>Every 3 mo (year 1), semiannually (year 2), annually thereafter</td>
<td>&lt; 10</td>
<td>Distant</td>
<td>&lt; 0.001</td>
<td>5.2</td>
<td>(0.5–15)</td>
<td>(0.5–15)</td>
</tr>
<tr>
<td>Roberts et al [30]</td>
<td>RP</td>
<td>879</td>
<td>4.7 (0.5–11)</td>
<td>≥ 2</td>
<td>(1.59/yr)</td>
<td>≤ 6.0</td>
<td>Local</td>
<td>&lt; 0.001</td>
<td>5.2</td>
<td>(0.5–11)</td>
<td>(1.59/yr)</td>
</tr>
<tr>
<td>Sartor et al [26]</td>
<td>EBRT</td>
<td>400</td>
<td>3 (0.9–7.3)</td>
<td>≥ 4</td>
<td>Every 2 mo (year 1), every 4 mo (year 2), semiannually (years 3–5), and annually thereafter</td>
<td>≤ 6.0</td>
<td>(median 12)</td>
<td>&lt; 0.001</td>
<td>5.2</td>
<td>(0.9–7.3)</td>
<td>(every 2 mo, year 1)</td>
</tr>
<tr>
<td>Crook et al [27]</td>
<td>EBRT</td>
<td>118</td>
<td>5.7 (4–9)</td>
<td>≥ 6–18 (median 12)</td>
<td>Every 2 mo (year 1), every 4 mo (year 2), semiannually (years 3–5), and annually thereafter</td>
<td>≤ 6.0</td>
<td>(median 12)</td>
<td>&lt; 0.001</td>
<td>5.2</td>
<td>(4–9)</td>
<td>(every 2 mo, year 1)</td>
</tr>
</tbody>
</table>

PSADT = prostate-specific antigen doubling time; RP = radical prostatectomy; EBRT = external-beam radiation therapy.

* Mean value.

1. All values taken within a 15-mo period.
treatment failed; however, it may be that such a short PSADT is associated with uncompromising disease, which necessitates more aggressive therapy to detect a significant difference. Nevertheless, the fact that three criteria were met with PSADTs of <6 mo, <9 mo, and <12 mo and that the fourth criteria was not met by only a narrow margin substantiates the predictive power of PSADT. Recently, Stephenson et al developed an internally validated nomogram that may be clinically useful to predict progression-free survival at 6 yr in patients undergoing salvage radiotherapy for biochemical recurrence after RP [39]. Using Cox regression analysis, they determined significant predictors of disease progression in a multi-institutional cohort of 1540 patients and used these parameters (including PSADT < 10 mo) to provide a more accurate model of cancer relapse (c-index = 0.69). Finally, NCCN treatment guidelines for salvage radiation suggest patients with a relapse PSADT of >10 mo are more likely to benefit from therapy.

4.2. Following salvage therapy, but before AIPCa

PSADT may also have a role in determining the timing of hormonal therapy after biochemical progression. In a large observational study, Moul et al revealed that there is a delay in the development of clinical metastasis if ADT is initiated early in patients with high-grade disease (Gleason > 7) or rapid PSADT (<12 mo) following RP [40]. However, in the overall cohort, early ADT did not affect clinical outcome suggesting its use for high-risk patients only. Longer follow-up and a randomized, controlled study incorporating survival benefit are needed to substantiate these data. In patients treated with EBRT and subsequent short-term ADT, PSADT has been found to be a significant independent predictor of freedom from distant metastasis rates, CSS, and overall survival [41]. Sengupta et al expanded PSA stratification to 463 post-RP patients treated with adjuvant hormonal therapy and identified PSADT as a significant independent predictor of recurrence-free survival and CSS in both N+ and N0 disease [42]. Stewart et al demonstrated 72% cancer-specific mortality by 7 yr in patients with a pre-ADT PSADT of <3 mo and a post-ADT PSA nadir >0.2 ng/ml, regardless of the type of prior treatment and the use of ADT [43]. Notably, in a follow-up study of selected patients with PSADTs of <6 mo, no significant difference in the estimated time to cancer-specific mortality was found between PSADTs of <3 mo and 3–6 mo [44]. These high-risk patients may harbor hormone-insensitive micrometastases and would therefore be ideal candidates for future therapeutic clinical trials.

5. PSADT after AIPCa

In the initial study of PSADT in patients with AIPCa, Loberg et al found that PSADT had no independent predictive value in AIPCa. However, the onset of AI disease significantly shortened PSADT, suggesting the emergence of more aggressive disease [45]. Subsequent investigations found PSADT may continue to have predictive value for counseling patients with AIPCa regarding survival. In a large retrospective study by Oudard et al, data from 250 patients treated with chemotherapy revealed stratification by 45 d was a significant predictor of death on multivariate analysis [46]. Patients with a PSADT of ≥45 d had a 26.4-mo median survival compared to 16.5 mo in those with shorter PSADTs. Daskivich et al calculated PSADTs at the emergence of AIPCa and found PSADTs of ≤12 wk predicted for decreased overall survival in multivariate analysis [47]. Multiple articles have confirmed these results although the optimal cut-off point for PSADT varies among different patient populations. In addition, Svatek et al developed a nomogram to estimate the risk of mortality in patients with AIPCa not yet exposed to chemotherapy [48]. PSADT is the first stratifying variable in their model because it was found to be the strongest prognostic predictor in their cohort of 129 patients. Most at risk were men with a PSADT of <6 mo; however, the nomogram allows for evaluation on a continuous PSADT axis with additional statistical analysis demonstrating 80.9% accuracy.

PSADT may also predict response to therapy and therefore serve as a convenient tool for risk stratification during clinical trial design [49]. Shulman et al studied 36 patients with AIPCa treated with deferred antiandrogens [49]. Twelve responded with an average pretreatment PSADT of 12.7 mo compared to 7.5 mo in non-responders. PSADT was the only significant predictor of response (p = 0.037).

### Table 3 – Prentice’s criteria for the use of PSADT as a surrogate end point

<table>
<thead>
<tr>
<th>Treatment is prognostic for prostate cancer-specific survival (true end point)</th>
<th>PSADT is prognostic for prostate cancer-specific survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment is prognostic for PSADT (surrogate end point)</td>
<td>The full effect of treatment on prostate cancer-specific survival is explained by PSADT</td>
</tr>
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</table>

PSADT = prostate-specific antigen doubling time.

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An analysis by Schmid et al. of men with AIPCa subsequently treated with chemotherapy revealed significant differences in PSADT between those who had partial remission or stable disease and those experiencing progressive disease \( (p = 0.002) \) [50]. Although PSADT did not strictly meet criteria for a surrogate end point, this study promotes its use as a potential auxiliary end point until a prospective trial with survival as a primary end point is conducted.

6. Conclusions

Many of the limitations of PSA measurement are due to the unreliability of a single measurement to provide useful data. In contrast, PSA kinetics provides a more dynamic picture of PCa activity. There is increasing emphasis on using multiple PSA measurements over time for PCa detection and in monitoring progression, and NCCN treatment guidelines for expectant management and salvage therapy now incorporate PSADT [24].

Before diagnosis, PSADT has not been shown to be of additional value to current screening and diagnostic methods. However, it may be helpful in determining which patients with initial negative biopsy actually harbor prostate cancer.

Prior to definitive therapy, PSADT usefulness is limited by the inherent biologic variability of PSA from the intact prostate. Alternate methods for calculating PSADT may partially compensate, but this has yet to be demonstrated. Only until pre-treatment PSADT is proven to have a greater predictive power than PSA alone should it be implemented in clinical practice. Nevertheless, accumulating evidence indicates that men who have a continual rise in PSA are more likely to have disease progression, and if the rise is rapid, prognosis is more ominous. Therefore, PSADT, in combination with other variables, may be useful in risk stratification, although parameters for observation and intervention are the subject of controversy.

After definitive therapy, PSADT is an important determinant of the presence and pattern of disease recurrence, but optimal thresholds are still to be established. Certainly those with a short PSADT represent clinically important disease that should be treated aggressively, but for the majority of patients, those with longer doubling times, the benefits of therapy need to be better defined. Most likely, levels reflect a continuum of degree of risk without exact cut-off points. Given the heterogeneity that exists within each stage of PCa, management should be dictated by a combination of variables, PSADT being a highly reliable predictor.

Following ADT, PSADT maintains its value as a significant prognostic indicator and is now being included in nomograms for this patient subset. It is possible that PSADT is also a predictor for certain therapies in the AI setting, as well as a suitable criterion in selecting patients for new therapeutic clinical trials.

Finally, the use of PSADT as a surrogate for CSS has not yet been confirmed, but because data are promising and other applicable end points are lacking to evaluate the often extended course of PCa, many short-term trials are alternatively using PSADT. Prospective, randomized trials and meta-analysis to determine optimal cut-off points in the above-listed categories could improve validity and bring clarity to conflicting data in the literature.

Conflicts of interest

The authors have nothing to disclose.

References


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**Editorial Comment on: Current Applications for Prostate-Specific Antigen Doubling Time**

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The search for new and better prostate cancer biomarkers is ongoing. Prostate-specific antigen (PSA) remains the best marker for detection, prognostication, and monitoring of prostate cancer. This report by Ramírez et al [1] reviews the literature pertaining to the use of PSA Doubling Time (PSADT) across the disease spectrum of prostate cancer.

PSADT has been demonstrated to be associated with outcome in the post radical prostatectomy setting [2] but the role of PSADT in a patient with a prostate in situ has still to be clarified. The authors state in their conclusion that “Only when pretreatment PSADT has been demonstrated to add significantly to the predictive ability of PSA alone should it be incorporated into clinical practice.” This is a very important statement because only when the prostate has been removed and there is no contribution of PSA by benign tissue may PSADT truly have a significant contribution.

The method of calculation of PSADT remains controversial, and this paper reports that although PSADT and PSA velocity are derived from the same data, PSADT is independent of baseline PSA. However, Riffenburgh et al [3] demonstrate by simple mathematics that PSADT is a simple manipulation of PSA velocity and is dependent on all PSA measurements used in the calculation. Hence, the use of PSA kinetics in active surveillance as a trigger point for intervention is questionable, unless the absolute PSA value is not also a trigger point because they both contain the same information. Furthermore, the timing and numbers of PSA measurements used may affect study results.

The role of PSADT across the spectrum of prostate cancer has yet to be defined completely. The take home message from this paper should be that PSADT may well have a role in predicting...
outcome. However, PSADT must improve the predictive ability of a current outcome prediction model for it to be incorporated into clinical practice.

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Editorial Comment on: Current Applications for Prostate-Specific Antigen Doubling Time

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Ramírez et al’s review paper has been well researched and clearly documents the advantages and disadvantages of prostate-specific antigen (PSA) doubling time [1].

Prostate cancer is found in a significant number of men with PSA levels lower than the traditional cutoff, which has led to recommendations for decision points much lower than 4 ng/ml [2]. The number of indolent cancers found using lower decision points may increase, but this result could possibly be avoided with the use of PSA doubling time or PSA velocity.

It should be considered that a short period of monitoring for calculation of PSA doubling time or velocity may not generate reliable information because of factors such as biological intraindividual variability or differences in the assays used. Biological variability has been reported to be approximately 20% if only one PSA measurement is taken into consideration. In addition, analytical variability of modern PSA assays accounts for another 5% of variability [3]. Using different PSA assays, variation in a sample can be greater than the reported velocity change for diagnosing prostate cancer of 0.5 or 0.75 ng/ml per year [4,5].

There have been many reports of the active surveillance of prostate cancer patients that depend on PSA dynamics; therefore, treatment decisions will be subject to the same issues mentioned above.

A method is urgently needed to safely identify patients with prostate cancer who could avoid radical intervention.

References


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Editorial Comment on: Current Applications for Prostate-Specific Antigen Doubling Time
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Prostate-specific antigen doubling time (PSADT) holds great promise for the prediction of cancer characteristics, such as stage and probability of progression before the delivery of definitive therapy [1–4]. Similarly, PSADT appears to have the ability to predict the probability of prostate cancer (PCa) diagnosis, especially after a previously negative biopsy. Moreover, PSADT was shown to predict progression towards lethal PCa phenotypes after radiation or surgery. Finally, PSADT represents one of the most powerful predictors of PCa-specific mortality in men with androgen-insensitive prostate cancer (AIPC) [5]. PSADT calculators are available at several PCa-oriented Web sites, such as the MSKCC site (www.nomograms.org) or the University of Montreal site (www.nomogram.org). The PSADT calculators allow the clinician to define the PSADT value of the individual patient at a given time. This metric showed promise as an independent predictor of cancer outcomes at different stages of the natural history of treated prostate cancer. Unfortunately, the current reports which showcase the value of PSADT might at times be difficult to interpret and even more difficult to implement. The problem relates to different PSADT cut-offs that are suggested as “ideal” predictors of unfavorable outcome. As a result, the clinician might not be able to derive the full benefit of the information contained within this powerful marker. Svatek et al circumvented the problem related to the interpretation of various PSADT cut-offs and integrated PSADT within a prognostic nomogram for men with AIPC [5]. Of all predictors, PSADT was the most informative, and accomplished its prognostic role for prediction of PCa-specific mortality in noncategorized format. Svatek et al demonstrated that this powerful predictor can result in most accurate predictions and can yield the best calibration, when it was combined with three other informative and significant variables [5]. Most importantly, these researchers proved that PSADT can be used to provide individualized predictions, which can be easily interpreted (prognosis expressed as a probability from 0–100% of dying from PCa at different time points) and can be equally easily accessed by patients and/or physicians (www.nomogram.org). Hopefully, more researchers will reexamine their valuable findings and will attempt to integrate PSADT within prognostic models capable of providing evidence-based, individualized prognostic information. Such measures would certainly result in much wider use of PSADT and would possibly improve patient care.

References


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