Review – Prostate Cancer

Implications of Prostate-Specific Antigen Doubling Time as Indicator of Failure after Surgery or Radiation Therapy for Prostate Cancer

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Abstract

Objectives: To review the methodology of PSA doubling time (PSA DT) calculations and the implications of PSA DT for the follow-up of prostate cancer patients curatively treated with surgery or radiation therapy.

Methods: A literature search of the most recent articles on PSA DT (those published after 2000) led to the selection of six studies with the largest and best-documented cohorts of patients treated with surgery or irradiation with curative intent.

Results: PSA kinetics, in the form of PSA DT, is the most effective parameter for identifying patients at significant risk for mortality specific to prostate cancer. Thresholds of 3, 6, and 12 mo have shown prognostic significance both in surgical and radiation series, notwithstanding differences in treatment selection, definition of biochemical recurrence, and methods of DT calculation.

Conclusions: In retrospective studies, PSA DT is a reliable predictor of prognosis; however, prospective validation studies are needed to determine the cut points of PSA DT. Optimal time intervals for calculation and optimal thresholds are still to be determined.

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1. Introduction

Radical retropubic prostatectomy (RRP) and external beam radiation therapy (EBRT) are the most widely used definitive treatments for clinically significant intracapsular prostatic cancer [1–3]. Both treatments are associated with good long-term overall survival; nevertheless, within 5–10 yr after treatment, more than one third of men experience an increase in prostate-specific antigen (PSA) (ie, biochemical
The likelihood of developing biochemical relapse can double in patients whose primary tumour had intermediate- and poor-risk prognostic features [4–7].

The clinical significance of biochemical recurrence is not straightforward; some men develop either local recurrence or distant progression, whereas others live many years without significant risk of clinical recurrence. This phenomenon makes the natural history of biochemical recurrence difficult to predict. Moreover, once the PSA increase is observed, 8 yr may pass before clinically detectable metastatic (M+) disease develops [8,9].

Predictors of prognosis have been investigated so that patients who have undergone definitive treatment might be stratified in terms of possible biochemical recurrence. PSA kinetics, in the form of PSA doubling time (PSA DT), was identified as a reliable predictor of prognosis, either alone or in association with primary tumour features (pretreatment PSA levels, tumour stage, Gleason score) and duration of first remission [2,9,10].

The present review focuses on PSA DT as a measure of PSA kinetics and its implications for follow-up of prostate cancer patients after RRP or EBRT with curative intent.

There is a well-established relationship between prostate cancer cells and serum PSA levels—specifically, PSA levels preceding the diagnosis of prostate cancer and PSA levels in untreated prostate cancer, which we discuss briefly.

1.1. **PSA before diagnosis of prostate cancer**

Men with prostate cancer have significantly greater rates of change in PSA over time, compared with men with known benign prostatic disease or men with normal glands (controls). Such an accelerated PSA increase could precede the diagnosis of prostate cancer by 5–10 yr. After an initial observation in a longitudinal case-control study in the United States [11], the same findings were also confirmed by independent concurrent studies in Europe [12]. In addition, PSA increases appeared to be independent of age, one of the most important confounding factors, as androgen levels are known to modulate PSA secretion and to evolve with age [11].

The relationship between PSA levels in young adult age and the detection of prostate cancer several decades later has also been investigated. In longitudinal case-control studies, strong trends toward increased prostate cancer risk with increasing PSA levels in young adults were identified among black men (odds ratio [OR]: 4.4) and white men (OR: 3.5) with a median age of 34 yr at the time of blood sampling. Furthermore, an increase of similar magnitude was also found for aggressive cancers (ie, those diagnosed at locoregional or distant stages, or those of poorly differentiated or undifferentiated grades), compared with nonaggressive cancers, in black men and white men [13].

An association between baseline PSA values and subsequent prostate cancer detection also became evident in studies screening for prostate cancer with long-term follow-up. From 1991 to 2001, 13,943 men younger than 60 yr participated in a study screening for prostate cancer [14]. Of those subjects, more than 2000 men in their 50s underwent biopsy during the study period (10 yr). The median baseline PSA value was significantly higher among men in whom prostate cancer was diagnosed during the study (2.4 ng/ml vs. 0.9 ng/ml; \( p < 0.0001 \)). Interestingly, PSA velocity (PSAV) was significantly greater in men with baseline PSA levels greater than the median.

Such studies in men of relatively young age (50 yr or younger) are of particular interest given the rare incidence of benign prostatic disease and its confounding effect on PSA in that subgroup. In addition, these men might represent a subset worth being subjected to screening programs.

1.2. **PSA in patients with untreated prostate cancer**

Patients with untreated prostate cancer were followed with repeated serum PSA level determinations to assess whether the growth rate was constant and to estimate the shape of the growth curve [15]. On the basis of two or more PSA determinations at least 2 mo apart, it appeared that PSA values closely followed a straight line on a logarithmic scale over time. The increase in serum PSA fitted an exponential, log-linear curve throughout all the measurements considered. DTs varied from less than 12 mo to more than 24 mo. More specifically, DTs of more than 24 mo were expressed by almost all the men with organ-confined cancer and by only one half of the men with non-organ-confined disease. On the other hand, men harbouring distant metastases expressed DTs of less than 12 mo. Such observations led the authors to conclude that PSA levels display a log-linear increase over time [15].

2. **PSA kinetics**

In men without clinical evidence of prostate cancer, sequential PSA measurements have been defined as PSAV. PSAV measures the absolute increase in PSA over time and is calculated as the slope of a linear regression of PSA measurements over the span of
time during which they were obtained, usually 1 yr [16]. PSAV is commonly used as a diagnostic tool and is related to tumour volume.

In the calculation of PSAV as a linear regression, PSA values are modelled as increasing linearly at a constant rate. There is no accepted definition of the number and time intervals of PSA readings needed to accurately estimate velocity. In addition, if PSA increase reflects tumour growth patterns that are known to follow an exponential growth model, this growth pattern is likely to be best represented exponentially [17]. If the PSA growth pattern is truly exponential, the measure of PSAV, when obtained over a different time period, may vary (Fig. 1). Thus, PSA changes are best expressed with the use of the exponential model (ie, after logarithmic transformation of the PSA value). PSA DT (Fig. 2) is defined as the time needed for the PSA value to double, according to the first-order kinetics exponential model:

$$\text{PSA}(t) = \text{PSA}(0) \exp(\lambda t), \quad (1)$$

where $t$ represents the time from diagnosis ($t = 0$).

Thus, defining the doubling time $T$ as the time needed for PSA to double—ie, PSA$(T) = 2\times$PSA$(0)$—it immediately follows from equation (1) that $\exp(\lambda T) = 2$, and thus the PSA DT is the natural log of 2 (= 0.693) divided by the slope ($\lambda$) of a linear regression of the log(PSA) over time (Fig. 3). The PSA slope can be estimated with the use of linear least squares when three or more PSA values are available, or, when only two measurements are available, with the use of the following simplified formula:

$$\text{PSA-DT} = \frac{\log 2 \times (T2 - T1)}{\log \text{PSA2} - \log \text{PSA1}}, \quad (2)$$

with PSA1 and PSA2 obtained at times T1 and T2, respectively; T2 > T1.

In contrast to estimating PSAV, estimating PSA DT requires logarithmic analysis. For easier, more rapid calculations of PSA DT, graphic methods have been developed [18], and PSA electronic calculators are now available on the Internet, together with nomograms that help patients and clinicians decide on the best treatment option by PSA measurements, disease features, and patient characteristics [19].

Some debate remains regarding the minimum number of PSA measurements needed [20], the optimal time interval between measurements [21], and whether a more complex mathematical model than a first-order exponential model is needed [22]. Obtaining three PSA measurements (each separated by 3 mo and showing a minimum increase of 0.2 ng/ml) and discarding all PSA measurements obtained after further intervention is currently considered the appropriate approach for computing PSA DT [23]. After retropubic prostatectomy, the starting point for calculating PSA DT is the first time a detectable PSA level is measured, whereas after radiation therapy the starting point is the first postnadir elevation [21]. This approach is known to introduce bias (ie, artificial inflation in dating PSA recurrence, vide infra).
<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>Treatment period</th>
<th>Median follow-up (yr)</th>
<th>PSA DT analysis (n)</th>
<th>RRP (n)</th>
<th>EBRT (n)</th>
<th>BF definition</th>
<th>End point (events)</th>
<th>PSA DT definition</th>
<th>PSA DT cutoff (mo)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou et al [26], Dana Farber, Boston, 2005</td>
<td>8669</td>
<td>1998–2002</td>
<td>6.8</td>
<td>1159</td>
<td>498</td>
<td>661</td>
<td>ASTRO criteria</td>
<td>D’Amico¹, last three PSA values closest to salvage HT. For EBRT, subtraction of nadir value. “Late PSA DT.”</td>
<td>PCSM (102)</td>
<td>3 (variable initially treated as continuous, cut-point suggested by earlier studies)</td>
<td>PSA DT is significantly associated with PCSM after BF.</td>
</tr>
<tr>
<td>Albertsen et al [27], University of Connecticut, Framingham, 2004</td>
<td>3739</td>
<td>1990–1992</td>
<td>Not stated</td>
<td>1136</td>
<td>613</td>
<td>523</td>
<td>—</td>
<td>PCSM (98)</td>
<td>After RRP: all PSA values &gt;0.25 ng/ml. After EBRT: all values after yr 2 or nadir. “All values PSA DT.”</td>
<td>12 (cut point that yielded maximum separation)</td>
<td>PCSM is directly correlated to number of posttreatment PSA doublings per year. PSA DT, GS ≥ 8, and time to BF are independent risk factors for PCSM.</td>
</tr>
<tr>
<td>Freedland et al [8], Johns Hopkins, Baltimore, 2005</td>
<td>5096</td>
<td>1982–2000</td>
<td>6</td>
<td>379</td>
<td>379</td>
<td>—</td>
<td>PSA &gt; 0.2 ng/ml</td>
<td>PCSM (66)</td>
<td>≥2 PSA values separated by ≥3 mo within 2 yr after BF. “Early PSA DT.”</td>
<td>3, 9, 15 (some validation of the model by bootstrap resampling, yielding a concordance index of 0.84)</td>
<td>PSA DT is the only variable that independently predicts time to CF.</td>
</tr>
<tr>
<td>Ward et al [29], Mayo Clinic, Rochester, MN, 2003</td>
<td>3903</td>
<td>1987–1995</td>
<td>8.8</td>
<td>1289</td>
<td>1289</td>
<td>—</td>
<td>PSA &gt; 0.4 ng/ml</td>
<td>CF (368)</td>
<td>≥2 PSA values, using all values from BF to salvage treatment or to 15 mo after BF. “All values PSA DT.”</td>
<td>12 (no details on method of selection of the cut point)</td>
<td>PSA DT is the only variable that independently predicts time to CF.</td>
</tr>
<tr>
<td>Zelefsky et al [30], Memorial Sloan-Kettering, New York, 2005</td>
<td>1650</td>
<td>1989–2001</td>
<td>7.7</td>
<td>381</td>
<td>—</td>
<td>381</td>
<td>ASTRO criteria</td>
<td>DM (98)</td>
<td>First 3 PSA values used to determine PSA relapse. No subtraction of nadir value. “Early PSA DT.”</td>
<td>3, 6, 12 (the variable is initially treated on a continuum; cut points are arbitrarily selected for display)</td>
<td>PSA DT, clinical tumour stage, and GS are the only independent variables that predict DM. PSA DT is highly predictive of DM.</td>
</tr>
<tr>
<td>Hanlon et al [31], Fox Chase, Philadelphia, 2002</td>
<td>615</td>
<td>1989–1995</td>
<td>5.3</td>
<td>136</td>
<td>—</td>
<td>136</td>
<td>ASTRO criteria</td>
<td>DM (17)</td>
<td>≥2 PSA values after BF, at least 60 d apart. “All values PSA DT.”</td>
<td>12 (cut point arbitrarily selected)</td>
<td></td>
</tr>
</tbody>
</table>

ASTRO = American Society for Therapeutic Radiology and Oncology; BF = biochemical failure; CF = clinical failure; DM = distant metastasis; DT = doubling time; EBRT = external beam radiation therapy; GS = Gleason score; HT = hormonal therapy; PCSM = prostate cancer-specific mortality; PSA = prostate-specific antigen; RRP = radical retropubic prostatectomy.


¹ D’Amico’s definition, the first-order kinetics exponential model, requires at least three values (each separated by 3 mo and showing a minimum increase of 0.2 ng/ml).
3. Available data on PSA DT

After a search of the available English-language literature related to PSA DT, we selected studies with the most recent data (published after 2000) on the largest and best-documented (in terms of number of patients treated, uniformity of treatment plans, adherence and length of follow-up) cohorts of patients treated with surgery or radiation therapy with curative intent at major referral centres. In cases of multiple publications on the same or similar patient cohorts, the most recent reports were considered. Some studies were excluded from analysis because they referred to clinical settings of the disease not addressed in this review, because there were potentially confounding factors other than tumour biology [24,25], or because findings were affected by the PSA “bounce” after brachytherapy prostate implantation, an effect that frequently occurs earlier than biochemical relapse [26].

Table 1 summarises the data available from the studies selected. Altogether, in some 4000 prostate cancer patients treated primarily at different institutions, PSA DT, either alone or in association with tumour parameters, and with the time interval to recurrence, was a reliable predictor of disease failure (both local and distant) and disease-specific mortality.

There were close similarities in PSA kinetics in both the surgical and the radiation series. The studies arrived at parallel conclusions even when analysing populations of patients with different treatments and despite discrepancies in the definition of biochemical recurrence. In fact, American Society for Therapeutic Radiology and Oncology (ASTRO) criteria were adopted in most of the EBRT series, whereas two PSA cutoffs (0.2 and 0.4 ng/ml) were used in the RRP series [27]. This discrepancy between the radiation and surgical literature is known to have introduced a time bias in favour of EBRT series [21,23].

In the study published by Zhou et al [28], follow-up data from patients who underwent surgery or irradiation were evaluated in parallel. To avoid potential bias, the ASTRO criteria for biochemical recurrence were applied to both treatment groups, although this approach may be subject to criticism [29]. PSA DTs were calculated as suggested by D’Amico et al [23], with the use of a minimum of three PSA values, each showing a \( \geq 0.2 \) ng/ml increase and obtained a minimum of 3 mo apart, with only the values closest to initiation of salvage treatment being computed. On multivariate analysis, PSA DT was a statistically significant independent predictor of time to prostate cancer-specific mortality (PCSM), both as a continuous and as a categoric variable, resulting in a hazard ratio of 12.8 for patients with a PSA DT of less than 3 mo, in comparison with 3 mo, or longer. In addition, 13% of RRP-treated patients and 30% of EBRT-treated patients with a PSA DT of less than 3 mo were still at high risk for PCSM, despite the use of hormonal treatment after PSA failure (namely, at a PSA level of 10 ng/ml).

Albertsen and coauthors [30] applied a less usual definition of biochemical recurrence. They included in the PSA DT analysis all men with two or more PSA values spanning 3 mo and all men with three or more PSA values 2 yr after radiation therapy (under the assumption that nadirs typically occurred within 2 yr) or, alternatively, 2 consecutive values after the nadir (in the case of patients in whom the nadir occurred within 2 yr). The investigators observed that once the disease recurred after surgery or radiation therapy, the total PSA readings at recurrence showed the same wide distribution of values and followed a log-linear pattern in both treatment groups. In addition, PSA DTs were independent of treatment selection. The authors found that among patients with recurrence, the number of PSA doublings per year was predictive of the probability of dying of prostate cancer. In patients who had posttreatment PSA increases exceeding two doublings per year (ie, when DT was less than 1 yr), the probability of PCSM was 40–50% within 10 yr after treatment. In EBRT-treated patients, PSA DTs were estimated to be approximately 20% longer than after surgery. Slight PSA production by normal prostatic tissue may cause this discrepancy, as the authors pointed out. Nevertheless, the discrepancy might also reflect differences in the definition of recurrence.

The natural history of biochemical relapse has been found to be long both in surgery and in radiotherapy series [7,8]. In a study by Freedland et al [9], median survival among the cohort of men with biochemical relapse after radical prostatectomy was not reached after 16 yr of follow-up [9]. However, after a median follow-up of 5 yr from biochemical relapse, patients with PSA DTs of less than 3 mo, time to biochemical recurrence of 3 yr or less, and pathologic Gleason scores of 8–10 had a reduction in median survival (3 yr). Conversely, patients with PSA DTs of 15 mo or more and time to biochemical recurrence of more than 3 yr had 100% cause-specific survival.

Ward and coauthors [31] found that once a PSA event occurred, the distinction between patients in whom indolent biochemical recurrence was
detected and those at risk for clinically significant disease progression was related to PSA DT, and not to the time to biochemical recurrence, nor to the absolute level of PSA measured in single, isolated observations. They suggested, therefore, that a threshold involving PSA kinetics is a more efficient tool in decisions about the use of salvage therapy than absolute PSA values during follow-up (eg, 0.2 or 0.4 ng/ml). Finally, the prognostic significance of PSA DT was independent from time to recurrence, although a “late” increase in PSA, defined as occurring 5 yr or more after surgery, can be expected in one of four patients experiencing biochemical recurrence.

Zelefsky and coworkers [32] analysed the Memorial Sloan-Kettering Cancer Center database and found that patients with a PSA DT between 0 and 6 mo experienced a 35% incidence of distant metastasis within 2 yr after biochemical recurrence. In comparison with traditional pretreatment variables, PSA trends were the most reliable predictor of distant metastasis. This observation was also confirmed within the subset of patients treated with neoadjuvant hormonal therapy. To avoid the lead-time bias that artificially inflates survival time when PSA relapse is backdated to the midpoint between the nadir PSA and the first increase, the investigators applied the ASTRO criteria for biochemical recurrence without backdating the date of relapse. In addition, PSA DTs were calculated with the use of only the three consecutive increases in PSA that provided the definition of relapse. This approach reduces the variability in PSA DT that occurs as more PSA measurements are collected. In contrast to the suggestion by D’Amico et al [23], the nadir value was not subtracted before calculating PSA DT, to preserve the logarithmic relationship modelled by PSA DT and to retain the natural definition of PSA DT.

Hanlon and coworkers [33] calculated PSA DT using at least two postfailure PSA values, obtained 60 d apart, in a group of 136 patients in biochemical failure after EBRT. The authors reached the similar conclusion that a PSA DT < 12 mo, in conjunction with a PSA nadir > 2.0 ng/ml, can be used to guide timing of androgen deprivation therapy in this setting.

Table 1 gives an overview of additional information obtained by including PSA DT calculations in the follow-up of RRP- and EBRT-treated patients. PSA kinetics, in the form of PSA DT, appears to be the most effective parameter for identifying patients at significantly high risk for PCSM—those in need of timely and aggressive systemic treatment (hormonal therapy, chemotherapy). Differences in methods of calculation, influenced by the definition of biochemical recurrence, do not affect the prognostic significance of PSA kinetics, which appears to be consistently independent of treatment selection in the studies.

4. Interpretation

The rate of change in PSA levels, and more specifically PSA DT, gives a close representation of tumour biology in a disease with a natural history known to be remarkably long. PSA DT consistently showed a strong association with the development and evolution of prostate cancer. Incremental changes in PSA levels appear to herald meaningful events in the disease process: They can precede prostate cancer diagnosis by years, and, at the opposite end of the spectrum, they can announce prostate cancer-specific death (PCSD) after (biochemical) failure of curative treatment. A short PSA DT—in particular, less than 12 mo—is the most reliable predictor of PCSD. This observation is particularly relevant because, within this population of patients, the overall risk of PCSD is relatively low, and mortality from causes not related to prostate cancer represents a serious competing event. Some points, however, deserve attention.

The first point is the number and timing of tests. Most reports on the prognostic value of PSA DT were retrospective, and correlations with clinical parameters were made only after PSA relapse occurred. Prospective validation studies are needed to determine the optimal time interval for calculating PSA DT and to determine the best threshold value. With regard to the frequency of PSA measurements, there is probably little clinical advantage in reducing the interval of follow-up visits given that the natural history of biochemical recurrence has consistently been described as long. Similarly, to facilitate DT calculation and interpretation, the time intervals between PSA tests should preferably remain constant during the follow-up period. PSAV, or slope, is influenced by the number of PSA measurements, the PSA sampling interval, and by both. The existence of an inverse relationship between PSAV and the PSA sampling interval has been known for a long time [34]. As a consequence, the rate of change in PSA appears steeper, with shortening sampling intervals. Some degree of anxiety may incite patients, and physicians, to test PSA more and more frequently; hence, the number of PSA readings obtained after a diagnosis of biochemical recurrence is frequently higher than that obtained through routine follow-up visits up to that point in time. Inclusion of all final PSA values in DT calculations
might skew the curve artificially upward. In other words, taking into account the last PSA values retrospectively, as described in some studies [28,30,31,33], is likely to yield the “worst prognostic” PSA DT. If it is to be as useful prospectively as it has been shown to be retrospectively, PSA DT should enable clinicians to predict an event early on. It therefore would seem more appropriate to accumulate a PSA history—for example, comparing three consecutive measurements at a constant time interval. The optimal number of PSA values needed to derive a patient’s PSA DT is still unknown. Because several PSA readings taken at irregular time intervals introduce variation into PSA DT estimates, use of a given constant time interval should be encouraged in future prospective studies. The time intervals could be at a midpoint (6 mo) within the range of PSA DT thresholds (3–15 mo) found to be significant prognosticators for PCSM.

The second point to be discussed is PSA variability. Total PSA has shown day-to-day variations of up to 30%; in addition, PSA levels may decrease after an initial increase in a significant percentage of men [35–37]. This phenomenon is known to occur in men with an intact prostate, without clinical evidence of prostate cancer, and has not yet been studied in the posttreatment setting. Such a large variability evidently reduces the value of events defined on the basis of PSA values above a fixed threshold, or “static” measures. However, PSA variability will be less burdensome when “dynamic” PSA testing is considered. For example, if a growth curve is built with DT calculations based on three serial measurements over fixed time intervals, random fluctuations that might falsely be interpreted as biochemical recurrence would average out to a null slope and thus to infinite PSA DT.

The third point to be discussed is the PSA DT threshold. As shown in Table 1, most studies initially assessed the PSA DT on a continuous scale, and cut points were fixed arbitrarily or referred to those maximising the observed differences in predicted survival time. Although the body of evidence seems convincing that PSA DT is a strong predictor of future disease evolution, prospective validation studies are needed to confirm the PSA DT thresholds currently in use, or to identify alternatives, to serve for risk stratification.

The fourth point is PSA DT as a surrogate end point. Although a rapid PSA DT in patients who achieved a first cure by irradiation or surgery has been convincingly shown to have prognostic value, this finding is insufficient for a conclusion to be made that PSA DT, or other measures of changes in PSA, can reliably be used as an end point in assessing new treatments in this setting. D'Amico and colleagues [23] studied a PSA DT of less than 3 mo as a surrogate end point for prostate cancer mortality in a nonrandomised cohort of 5918 men treated with surgery and 2751 men treated with radiation. They demonstrated that the Prentice conditions for surrogacy [38] were fulfilled. However, major issues of concern remain, the most important of which can be summarized as follows: the absence of randomisation, the inclusion of patients receiving salvage hormonal treatments, and the calculations of PSA-DT for the radiation treatment arm that was not exempt from the artificial inflation bias (vide supra). In addition, relatively few patients have a PSA DT shorter than 3 mo (74 [12%] of 611 patients relapsed after radical prostatectomy); hence, the practical applicability of their results remains questionable. Conclusively, for the time being, generalisation of their results is unwarranted.

The fifth point is graphic representation. The calculation of PSA DT in a given patient requires the use of logarithmic formulas that might be cumbersome to apply in every day, busy, clinical practice, whereas a graphic representation might produce instant comprehension.

In the near future, additional data on PSA DT, especially from studies on active surveillance with delayed specific intervention [39], as well as implementation of newer forms of PSA (ie, early PSA [40]), are also likely to further clarify the clinical relevance of PSA kinetics.

5. Conclusions

Incremental changes in PSA levels appear to herald meaningful events in the disease process: They can precede prostate cancer diagnosis by years, and, at the opposite end of the spectrum, they can announce PCSD after (biochemical) failure of curative treatment. DT calculations may appear somehow cumbersome; however, electronic calculators and graphic methods have been developed that are of substantial help. Despite some discrepancies in patient populations and treatment, a review of the most recent studies of PSA kinetics from the surgical and the radiation literature led to similar conclusions. PSA DT is the most effective parameter for identifying patients at significantly high risk for PCSM—those in need of timely and aggressive systemic treatment. Data on PSA DT are not sufficient for PSA DT to be used as a reliable surrogate end point in assessing new treatments.
Conflicts of interest

No author has any commercial interest related to the present article to be disclosed.

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References


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**Editorial Comment**

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The authors are to be congratulated on a timely and concise synthesis of the rich literature on prostate-specific antigen doubling time (PSA DT), which without doubt represents one of the most important markers of disease progression. PSA DT offers several advantages over isolated PSA readings or even PSA trends. For example, after definitive therapy the use of PSA DT circumvents problems related to the lack of standardization of biochemical recurrence cut-off points. PSA DT characteristics after failed radical prostatectomy represent a valuable predictor of the likelihood of response to salvage radiotherapy.

Moreover, PSA DT accurately predicts the probability of distant progression and prostate cancer-specific survival. Based on these considerations, PSA DT certainly holds great promise in prostate cancer prognostics. Despite its qualities, several limitations remain. As the authors have emphasized, the standardization of PSA DT recording and calculation methods should represent a priority. Once this obstacle is overcome, data derived from standardized PSA assessments may be used to define the most bias-free definition of PSA DT values indicative of failed cancer control.