

# Current role of prostate-specific antigen kinetics in managing patients with prostate cancer

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## INTRODUCTION

PSA is the most widely used tumour marker in clinical practice, but the value of PSA in identifying patients at increased risk of prostate cancer is controversial. PSA screening has resulted in a dramatic stage migration towards small-volume cancer. Stamey *et al.* [1] therefore questioned the utility of an isolated PSA level reading in the context of prostate cancer diagnosis. The ongoing debate over PSA measurement has only recently begun to incorporate the additional value derived from using PSA kinetics for patient decision-making, which is the focus of this review.

## PSA VELOCITY (PSAV)

PSAV is the absolute rate of change in PSA over time. The original description, by Carter *et al.* [2], differentiated between men subsequently diagnosed with prostate cancer who had a PSAV of  $\geq 0.75$  ng/mL/year, and those who had BPH or no appreciable prostatic disease (PSAV  $< 0.75$  ng/mL/year). This threshold of 0.75 ng/mL/year was 95% specific and 72% sensitive for a subsequent diagnosis of prostate cancer. These differences were demonstrable for up to 5 years before diagnosis. Data from the National Prostate Cancer Detection Project confirmed the specificity of a PSAV of 0.75 ng/mL/year in detecting prostate cancer (96%), albeit with a somewhat reduced sensitivity of 55% [3]. Subsequently this value became widely accepted as a trigger for biopsy in those men who had sufficient PSA data to assess PSAV.

A more recent analysis (AUA, 2005) of the Baltimore Longitudinal Studies of

Aging cohort, reported that a PSAV of  $> 0.16$  ng/mL/year identified men at considerably higher risk of death from prostate cancer. In that series, 8% of men in this group went on to die from prostate cancer 15–20 years later, compared to 0–1% of men with a PSAV of  $< 0.16$  ng/mL/year.

The difficulty with this approach is the confounding effect of the biological variability of PSA. In the absence of disease, day-to-day variation in PSA has been estimated at 34%. Indeed, an increase between consecutive PSA levels that is  $< 20$ –46% may be due to biological and analytical variation alone [4]. Infection and prostatic manipulation can also affect PSA levels [5]. It follows that the variation is often substantially greater than 0.75 ng/mL/year (much less 0.2 ng/mL/year) and may result in the identification of many patients as having a 'rapid rise', when what is being observed is biological variation. In undiagnosed men, a minimum of three measurements acquired over a 1.5–2 year interval should be used to minimize the effects of 'normal' variation and causes unrelated to cancer [6]. More recent data from the Polyp Prevention Trial reaffirm the importance of confirming an isolated increase in PSA level before proceeding with further testing [7]. Among those with an elevated age-specific PSA level in that study, values returned to normal in 55% of men at one or more subsequent visits during 4 years of follow-up.

In North America, the population characteristics of prostate cancer and PSA have changed drastically. Patients now have smaller volume cancers, lower PSA levels and lower stage disease. Therefore, data based on populations studied before the mid-1990s may not be generally applicable. Nonetheless, the evidence consistently shows that there is a significant difference in PSA kinetics between populations with and without prostate cancer.

## PSAV AND SCREENING

Two studies address the use of PSAV as a screening tool in men with a PSA level of  $\leq 4$  ng/mL. Using a PSAV threshold of 0.1 ng/mL/year, 81% and 85% of cancers were correctly identified in the Baltimore Longitudinal Study of Aging and the European Research Study of Prostate Cancer [8,9]. However, using this value, the specificity decreased to 50% and 18%, respectively. The disparity in the specificity rates in these two studies probably reflects design differences. The Baltimore Longitudinal Study of Aging was an observational study and the data presented here refer to results obtained over two decades. Many of the cancers were detected before the use of PSA testing (and hence were more likely to be advanced). The European screening study analysed data collected over a 4-year period only. It is possible that men currently thought to be cancer-free in this cohort will develop prostate cancer with a longer follow-up.

When analysing PSAV data three or more PSA values should preferably be used. However, clinicians often encounter situations where a suboptimal number of measurements are available. Riffenberg and Amling [10] have described 'early PSAV' (defined as the change from the first to second PSA reading standardized as PSA change per year), which can be used in such situations. In this large single-centre retrospective study, there was a highly significant difference in early PSAV between those patients whose PSA level subsequently increased to  $> 4$  ng/mL and those who had a positive biopsy result and those who had neither an increase in PSA level or positive biopsy.

## PSAV: A MARKER OF DISEASE BIOLOGY?

The role of preoperative PSAV in determining the subsequent risk of death from prostate cancer has been analysed in a recent publication on 1095 men with clinically

localized prostate cancer. D'Amico *et al.* [11] reported that a preoperative PSAV of  $>2$  ng/mL/year, calculated by linear regression, was associated with lymph-node metastases, an advanced pathological stage and high-grade disease. This threshold level in PSAV was also associated with a significantly shorter time to recurrence, death from prostate cancer, and death from any cause. Strikingly, men with a PSA increase of  $>2.0$  ng/mL had prostate cancer-specific mortality rates nine times greater than those with a PSAV of  $<2$  ng/mL. Nonetheless, with a mean follow-up of 5 years,  $<10\%$  of patients with a rapid PSAV actually died from prostate cancer in that series.

These findings are in stark contrast to those presented by Freedland *et al.* [12], who found that the preoperative PSAV did not predict biochemical recurrence or adverse pathological features after radical prostatectomy (RP). From a cohort of 331 patients who had undergone RP, 86 were identified who had sufficient PSA data to allow an estimation of preoperative PSAV; the PSAV was not predictive of margin positivity, seminal vesicle involvement or capsular penetration ( $P = 0.30$ ). Neither was there an association between preoperative PSAV and surgical Gleason score ( $P > 0.36$ ). This later study was lacking in power, and direct comparisons between these studies are problematic.

The data of D'Amico *et al.* [11], if confirmed, should change clinical practice. Of men with high-grade disease and a PSAV of  $>2$  ng/mL, 28% died from their disease within 7 years of surgery. This means that: (i) these patients are candidates for aggressive therapy, even if they have 'unfavourable' clinical values or significant comorbidity; and (ii), as surgery alone is insufficient for a considerable proportion adjuvant therapies need to be considered in this group.

### PSA DOUBLING TIME (PSADT)

The PSADT is the time required for the PSA level to double in value. Pearson and Carter [13] reported that, in patients with prostate cancer, PSA levels increase initially linearly, followed by an exponential phase. If it is assumed that PSA is increasing exponentially at the time of diagnosis then the doubling time can be expressed as the natural log  $2(0.693)/\lambda$ , where  $\lambda$  is the slope of

log PSA vs time [14]. This method uses all PSA values available to determine the PSADT.

A short PSADT is a surrogate for rapid tumour growth and a longer PSADT implies a more indolent tumour. DeKernion [15,16] was the first to correlate PSADT with clinical behaviour in patients with biochemical failure after RP, in whom he found that PSADTs of 4.3 and 11.7 months were associated with metastatic and locally recurrent disease, respectively. In a similar setting Pound *et al.* [14] reported that a PSADT of  $\leq 10$  months was predictive of the probability and time to the development of metastatic disease. Similar data were also reported after definitive radiotherapy [17].

An increasing volume of data, from Stamey, the Prostate Cancer Prevention Trial and the Medical Therapy of Prostatic Symptoms trials, indicate prostatic volume rather than prostate cancer as the cause of mild elevation of PSA levels in many men with early cancer [1,18,19]. Therefore, a high baseline PSA level may delay identification of a rapid PSA rise. One proposed solution to this problem is the use of subtracted PSA values, where baseline PSA is subtracted from all subsequent PSA determinations in calculating PSADT. This is based on a three-variable model, i.e.  $A + Bt + Ce^{\lambda t}$ , where A is the baseline PSA from BPH, B is the linear increase of PSA from BPH over time (assumed to be minimal), and C is the exponential increase of PSA from prostate cancer over time [20]. The concept of correcting for baseline PSA level is also attractive when comparing follow-up data in patients treated definitively with surgery or with radiation. After RP, PSA values usually fall to undetectable levels; after radiation therapy, viable benign prostatic epithelium results in some persistence of PSA. It has been suggested that the nadir PSA be subtracted from the post-radiation PSA level before the PSADT is determined (subtraction PSADT) [21]. This ensures equal PSADTs are calculated for patients with the same absolute increase in PSA.

Recently a novel method of determining changes in PSADT using spline functions was described [22]. This technique uses a best-fitting spline (i.e. a broken-line approximation) to a graph of log PSA vs time, to estimate PSADT before and after treatment. The putative advantages of such a technique are its relative simplicity and ability to show statistically significant responses to

treatment for individual patients. However, at present, the calculations are too cumbersome for routine clinical use.

### PSADT: A PREDICTOR OF THERAPEUTIC OUTCOME

There have been many attempts to use PSADT to predict treatment outcome before definitive therapy. D'Amico and Hanks [23] found that, after radiation therapy for prostate cancer, PSADT was linearly correlated with the interval to clinical relapse after PSA failure. They suggested that those patients with a PSADT of  $>18$  months could be managed expectantly, as their cancers were likely to remain latent. Hanks *et al.* [24] also found that pre-treatment PSADT significantly correlated with biochemical recurrence. Egawa *et al.* [25] also showed a significant correlation between preoperative PSADT and postoperative biochemical failure. In that study a PSADT of  $<36$  months significantly predicted extracapsular disease ( $P = 0.02$ ).

By contrast, Freedland *et al.* [12] found that preoperative PSADT did not correlate with adverse pathological findings or biochemical recurrence. These differences may reflect the effects of stage migration seen over the last 15 years.

### PSADT AND DISEASE PROGRESSION

About a third of patients who undergo radical therapy for prostate cancer will have biochemical recurrence within 10 years of surgery [26]. Patients thought to have local recurrence are treated with salvage radiotherapy, whereas those thought to have metastatic disease are treated with hormones. However, the ability to make this crucial distinction accurately is limited.

In patients with biochemical failure after RP, a third of those with systemic disease will have a PSA level of  $<10$  ng/mL at the time of diagnosis [27]. On this basis, Partin *et al.* [28] recommended bone scans in all patients with PSA recurrence. However, there is a very low yield from such studies unless the PSA level is high or the PSADT is short [29]. Okotie *et al.* [30] recently reported that the likelihood of a positive bone scan, in men with a PSA level of  $<10$  ng/mL, increases from 3% if the PSADT was  $>6$  months to 26% if the PSADT was  $<6$  months. Similarly, positive CT scans were

noted in 24% of men with PSADTs of <6 months vs 0% if the PSADT was >6 months. The probability of either a positive bone scan or CT scan increased even further if the total PSA level was >10 ng/mL and the PSADT was <6 months.

The reported success rates for salvage radiotherapy for clinically localized prostate cancer are 10–50%. This implies that most of these patients harbour unrecognized metastatic disease before starting treatment, and thus will not benefit from salvage radiation therapy. Stephenson *et al.* [31] attempted to identify those patients with prostate cancer who may benefit from salvage radiotherapy, by defining prognostic indicators for these patients; those who are unlikely to benefit may be spared toxicity associated with unsuccessful therapy, or possibly enrolled in randomized trials of novel systemically active agents. In their study, of 501 patients who received salvage radiotherapy for biochemical recurrence, a PSADT of  $\leq 10$  months before radiotherapy was a significant predictor of disease progression. Importantly, a PSADT of >10 months also helped to identify a subset of men with high-grade disease who were likely to have a durable response to treatment.

### PSADT AND ACTIVE SURVEILLANCE

There is an increasing concern that patients with 'good' risk prostate cancer are being over-treated. Ideally, those with clinically insignificant prostate cancer should be managed with surveillance. The challenge is to correctly identify such patients, and avoid under-treatment in those with a more aggressive biological phenotype. The key to such strategies is regular observation, so those patients who manifest disease that is more aggressive are identified when curative treatment is still feasible. Various criteria to identify patients with aggressive disease have been proposed; however, to date none of these have been validated [32]. Insofar as the PSA kinetics reflect tumour growth, a rapid PSADT in a patient on a watchful-waiting protocol probably reflects a more aggressive phenotype.

Several studies have explored the utility of PSADT in such a setting. Klotz *et al.* [33] analysed the distribution of PSADTs in a large prospective phase 2 cohort of 'good' risk patients on surveillance. The median PSADT in

this group was 7.0 years; 42% of patients had a PSADT of >10 years. By contrast, 22% had a PSADT of <3 years. This group is thought to be at high risk of progression, and was treated radically. At 8 years, this cohort has had a <1% prostate cancer mortality rate, suggesting that this approach is feasible and safe.

McClaren *et al.* [34] reported that the PSADT was significantly lower in patients with progressive disease ( $P < 0.001$ ) and strongly correlated with time to treatment ( $P < 0.001$ ). That study concluded that PSADT rather than histopathological criteria of the tumour were the most important indicator of disease activity.

Stephenson *et al.* [35] reported that a PSADT of <120 months correlated with disease progression on DRE and on repeat biopsy. The limitation of this variable is lack of specificity; a threshold of 120 months will identify 60% of men as having 'aggressive disease'. Based on well established incidence to mortality ratios, this is considerably higher than the proportion of patients in this group who are likely to require treatment.

El-Geneidy *et al.* [36] found that a PSADT of <3 years was a significant predictor of intervention on multivariate analysis. Meg *et al.* [37] found that amongst patients in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database, the mean PSA increase in those progressing to treatment was 7.2 ng/mL. Treatment was instigated at a median of 1.7 years from diagnosis in these patients. By contrast, over the same period the mean PSA level decreased by 0.4 ng/mL in those patients electing to continue with watchful waiting ( $P < 0.001$ ).

These data confirm the ability of PSADT in conjunction with other indicators of disease progression (PSAV, clinical and pathological changes) to identify patients who require definitive therapy amongst watchful-waiting cohorts.

There are several potential pitfalls when analysing PSADT data from patients on active surveillance protocols; there is significant variability in PSADT in such groups [33]. Such patients should have PSA estimates on a 3-monthly basis and therefore have relatively many data points for analysis. Given the short-term physiological variability in PSA measurements, it is not surprising that such

variability exists. Therefore the interval on which the determination of PSADT is based must be long enough (6–12 months) to avoid decisions based on random variation in PSA levels [38].

### PSADT AS A MARKER OF CANCER-SPECIFIC MORTALITY

Patients with a short PSADT (<12 months) after radiation therapy have almost identical estimates of prostate cancer-specific and all-cause mortality [39]. In other words, almost all deaths in this subset of patients were secondary to prostate cancer. Therefore, this implies that such patients should be considered candidates for adjuvant trials to prevent an otherwise inevitable prostate cancer-related death. In keeping with these data, Sandler *et al.* [40] reported that in patients with biochemical recurrence after conformal external-beam radiation therapy, the 5-year prostate cancer-specific mortality rates decreased from 52% to 10% in patients with a PSADT of <1 year vs >1 year ( $P = 0.007$ ).

It is possible to stratify prostate cancer-specific mortality into high- or low-risk categories based on PSADT after local therapy. In a retrospective analysis of the CaPSURE and the Center for Prostate Disease Research databases, the risk of prostate cancer-specific mortality was 20 times more in men with a PSADT of <3 months (high-risk, median survival 6 months) than in men with a PSADT of >18 months (median survival >10 years) [39].

### UTILITY OF PSADT IN CLINICAL TRIALS

If a short PSADT is a predictor of negative outcome then a prolonged PSADT implies a prostate cancer-specific survival advantage. PSADT may also predict the response to secondary hormonal intervention in men with androgen-independent prostate cancer. About a third of men with androgen-independent prostate cancer experience a clinical response to secondary hormonal manipulation. The ability to predict response could avoid the toxicity associated with such treatment in those patients who are unlikely to respond. Shulman *et al.* [41] analysed pretreatment variables in patients with androgen-independent prostate cancer to determine the effect on PSA response after

instigating maximum androgen blockade. PSADT was the only significant predictor of response (12.7 months in responders vs 7.5 months in nonresponders;  $P=0.037$ ). The study also addressed an interesting question as to which patients may benefit from secondary hormonal manipulation and which from cytotoxic chemotherapy.

PSADT also has a role in determining the timing of androgen deprivation in patients with PSA progression after surgery. Moul *et al.* [42] reported the effect of early vs delayed hormonal therapy on disease-free survival in patients with PSA-only recurrence after RP. In all, 355 men received early hormonal therapy (hormonal therapy instigated based on PSA recurrence alone with no clinical evidence of metastatic disease) and 997 men were either treated hormonally at the time of diagnosis of systemic disease or to date have not been treated hormonally. Strikingly, the timing of therapy had no overall impact in the time to androgen-independent progression. However, in those patients with a rapid PSADT (<12 months) or high-grade disease, early hormonal therapy (for a PSA level of <10 ng/mL) was associated with a delay in the time to androgen-independent progression. This important study suggests that patients with PSA recurrence should only be treated if their PSADT is <1 year, or they have Gleason 8–10 cancer; otherwise, androgen-deprivation therapy should be withheld until clinical progression or a rapid PSADT develops. It also supports a PSA threshold of 5–10 ng/mL for initiating treatment in the high-risk patient.

Clinical trials of new mechanistic agents in prostate cancer face several difficulties. The assessment of novel agents used in solid-organ cancer therapy is based on the radiological and pathological response of indicator lesions. Men with biochemical recurrence after definitive therapy frequently have unmeasurable disease. The use of time to progression and survival as endpoints pose problems, given the prolonged natural history and variable clinical course of the disease. PSADT appears to be sufficiently robust as a surrogate marker of prostate cancer survival that it might serve as a valid endpoint in trials of patients with hormone-refractory disease [43].

## CONCLUSIONS

The limitations of PSA in screening and early detection, predicting outcome, and

identifying patients at risk of death after radical therapy are largely based on the use of a single PSA determination. By contrast, increasing evidence supports the use of PSA kinetics (PSAV, DT, acceleration, etc.) as a powerful indicator of tumour biology.

Preoperative PSAV appears to be one of the most important predictors of death in patients with localized prostate cancer. It can be used as a means to stratify high-risk patients who might benefit from adjuvant therapy from 'good-risk' patients who are likely to require standard therapy only.

PSAV and PSADT are useful in monitoring disease recurrence and progression after failure of definitive therapy. PSADT in particular can be used to identify patients at high risk of rapidly progressive disease. This information should guide treatment decisions about radiation vs androgen-deprivation therapy for biochemical recurrence, the timing of androgen-deprivation therapy, and the use of second-line androgen deprivation.

The protracted natural history of prostate cancer necessitates very prolonged gathering of data in clinical trials. Proof of a survival advantage associated with novel treatment is therefore very difficult to establish, particularly given the advanced age of many patients with prostate cancer. Determining PSA kinetics in such a setting may allow for a more rapid and meaningful evaluation of novel therapeutic strategies. The analysis of PSA kinetics should play a major role in managing localized and advanced prostate cancer.

## CONFLICT OF INTEREST

None declared.

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**Abbreviations:** PSAV, PSA velocity; PSADT, PSA doubling time; CaPSURE, Cancer of the Prostate Strategic Urologic Research Endeavor; RP, radical prostatectomy.