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# The Continuing Role of PSA in the Detection and Management of Prostate Cancer

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## Abstract

Despite being used extensively for the diagnosis and management of prostate cancer, prostate-specific antigen (PSA) testing remains controversial. Doubts have been raised over the continued use of PSA in the detection of clinically significant prostate cancer because many men now present with early-stage, small-volume tumours. This article examines the limitations of using a single PSA value in diagnosis and discusses alternative approaches to PSA testing, in particular PSA velocity and PSA doubling time, which are now emerging as valuable pretreatment disease predictors. A clinical scenario is also presented to illustrate the use of PSA kinetics in identifying candidates for biopsy.

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## 1. Introduction

Prostate-specific antigen (PSA) testing was introduced in the 1980s and is now used widely for screening and early detection of prostate cancer, monitoring the evolution of established disease, making treatment decisions, and assessing patient outcomes. Although PSA is considered to be the best tumour marker available for prostate cancer, the PSA test has several shortcomings including the overdetection of early disease. Here we examine some of the issues associated with PSA testing and relate these to clinical practice by reflecting on a clinical scenario.

## 2. Limitations of absolute PSA values in diagnosis

Because PSA is expressed by both normal and malignant prostate cells, it is not a specific marker for prostate cancer. Serum PSA levels may, therefore, be influenced by factors other than the presence of cancerous cells, including benign
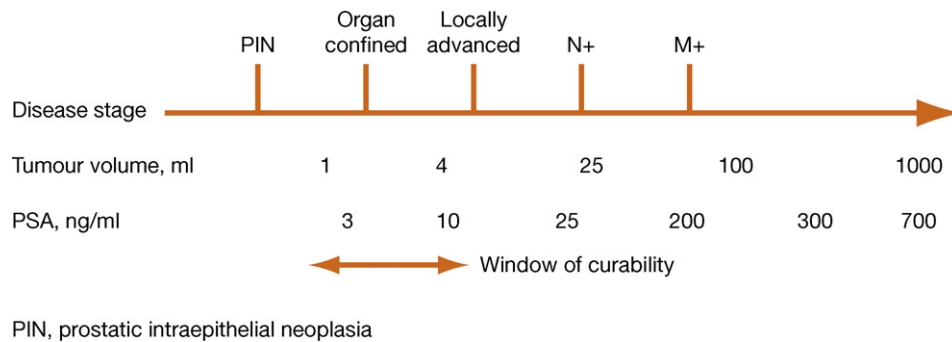
Fig. 1 – Relationship between the early detection of prostate cancer and the possibility of cure.

prostatic hyperplasia [1] and prostate inflammation [2]; both of these conditions can cause more PSA to enter the blood. Furthermore, PSA levels fluctuate naturally within individuals, rendering results of single tests unreliable in some patients [3,4].

In most of Europe and the United States, a serum PSA level of ≥4 ng/ml is considered abnormal, leading to the recommendation of prostate biopsy. Patients with organ-confined and, therefore, potentially curable prostate cancer would be expected to have serum PSA levels between 4 and 10 ng/ml (Fig. 1); however, the specificity of the PSA test is relatively poor in this range. Only 20–30% of men with PSA levels between 4 and 10 ng/ml will actually have prostate cancer, meaning that the remaining 70–80% will undergo unnecessary biopsies [5]. Conversely, PSA levels within the normal range of 0–4 ng/ml do not exclude the possibility of prostate cancer. One study has reported that as many as 15% of men with a PSA level ≤4 ng/ml had biopsy-detectable prostate cancer; moreover, approximately 15% of these cancers were aggressive (Gleason score ≥7) [6]. In contrast to previous thinking, it now seems that there is no single PSA cut-off value at which to recommend biopsy, and a continuum of prostate cancer risk exists across a spectrum of PSA values [7]; however, there is as yet no consensus regarding how this should translate to clinical practice. The National Comprehensive Cancer Network guidelines, for example, currently advise biopsy in men with a PSA level of ≥2.5 ng/ml [8]; this cut-off point has also been advocated in a recent independent editorial [9]. In contrast, the European Association of Urology guidelines state that more data from which to make a recommendation are required [10].

### 2.1. The continued role of PSA testing

In 2004, Stamey and colleagues questioned the continued role of PSA testing following analysis of

the correlation between PSA levels and the pathology of prostate cancer samples collected over 20 yr at Stanford University Medical Center in the United States [11]. During the earliest period studied (1983–1988), PSA correlated well with the volume of the index cancer (Pearson correlation coefficient = 0.659; $p < 0.0005$); however, in more recent years (1999–2003), this correlation had decreased (Pearson correlation coefficient = 0.148; $p < 0.045$). The authors concluded that PSA screening is currently detecting only benign prostatic hyperplasia rather than prostate cancer. The observed decrease in the correlation coefficient over time is not unexpected because in the pre-PSA era men were more likely to present with palpable, advanced tumours; today, however, as a result of PSA screening, most men present with a nonpalpable tumour (stage T1c). It is interesting to note that although PSA had a stronger correlation with tumour volume in the past, it was not necessarily a marker for curable cancer at that time [12]. Furthermore, the percentage of the index tumour that was composed of Gleason grades 4 and 5 remained stable over the 20 yr studied [11].

Evidence from contemporary studies clearly suggests that PSA remains a useful marker for prostate cancer. For example, the PSA level has subsequently been shown to correlate more closely with the percentage and volume of cancer in radical prostatectomy specimens than with prostate size [13], and a linear relationship between PSA level and prostate cancer detection rate has been demonstrated [6] (Table 1).

### 2.2. Refinements in PSA testing

Ideally, a biomarker for prostate cancer would be capable of differentiating aggressive tumours from slow-growing or latent disease at a stage when they are still curable. Until such biomarkers are discovered, the key is to refine PSA testing to overcome its current limitations. Repeat PSA measurements

**Table 1 – Relationship between prostate-specific antigen (PSA) level and the prevalence of prostate cancer and high-grade disease**

| PSA level, ng/ml | No. men | No. (%) men with prostate cancer | No. (%) prostate cancers with Gleason score ≥7 |
|---|---|---|---|
| ≤0.5 | 486 | 32 (6.6) | 4 (12.5) |
| 0.6–1.0 | 791 | 80 (10.1) | 8 (10.0) |
| 1.1–2.0 | 998 | 170 (17.0) | 20 (11.8) |
| 2.1–3.0 | 482 | 115 (23.9) | 22 (19.1) |
| 3.1–4.0 | 193 | 52 (26.9) | 13 (25.0) |
| Total | 2950 | 449 (15.2) | 67 (14.9) |

should be performed and the evaluation and treatment of prostate inflammation considered. Several variations of PSA testing may be used to increase specificity compared with the use of absolute PSA values alone. A meta-analysis has shown that measurements of the free-to-total PSA ratio (f/t PSA) or complexed PSA (cPSA) in men with PSA levels between 2 and 10 ng/ml can reduce the number of false-positive results [14]. For example, at a sensitivity of 95% (allowing 5% of cancers to be missed), use of the f/t PSA test would avoid 6% and 18% of unnecessary biopsies in the PSA ranges of 2–4 ng/ml and 4–10 ng/ml, respectively. Similar results were obtained when the diagnostic performance of cPSA was examined. At present, these approaches are not universally endorsed as screening modalities; rather, they may help to determine the need for repeat prostate biopsy after an initially negative one.

PSA velocity (PSA-V), which is defined as the absolute rate of change in PSA level over time, may also be helpful in improving the specificity of PSA for cancer detection. Based on data from several studies [15–17], the National Comprehensive Cancer Network guidelines recommend that PSA-Vs of ≥0.5 ng/ml/yr and ≥0.75 ng/ml/yr are an indication for biopsy in men with PSA levels of <4 ng/ml and 4–10 ng/ml, respectively [8]. It should be noted that conflicting data on the value of PSA-V have recently been reported from 588 men in the European Randomized Study of Screening for Prostate Cancer Rotterdam [18]. In these men, whose PSA levels had increased from <4.0 ng/ml at presentation to >4.0 ng/ml after 4 yr, PSA-V was no better at detecting prostate cancer than a PSA cut-off of 4.0 ng/ml. These data are, however, limited in that there were only two PSA values separated by 4 yr [18,19]; it is currently recommended that PSA levels be measured over a period of no less than 18 mo and that multiple values (minimum of three) be used to perform the calculation [8].

Other refinements of the PSA test include the measurement of PSA density (the relationship of PSA level to the volume of the prostate) [20], pro-PSA (the inactive precursor of PSA) [21], and human kallikrein 2 (hK2; a prostate-specific protein similar to PSA) [22,23]. PSA density may help to differentiate between prostate cancer and benign conditions that cause prostate enlargement [20], but it is not widely used in clinical practice because of the need for accurate prostate volume determination using transrectal ultrasound. Pro-PSA has been shown to be superior to f/t PSA and cPSA for detecting prostate cancer in the PSA range of 2–10 ng/ml [21] and is particularly useful in the 2–4 ng/ml range [24]. hK2 has also demonstrated improved specificity compared with total and f/t PSA measurements [22,25]. These refinements are not, however, presently incorporated into any official guidelines for the early detection of prostate cancer.

### 2.3. Can PSA be used for predicting tumour stage and aggressive disease?

Although PSA levels increase with advancing disease, there is no direct relationship between PSA levels and pathologic stage [1]. To date, there is no convincing evidence that any of the molecular forms of PSA or hK2 can be used as a single modality for staging [26–28].

PSA-V and PSA doubling time (PSADT; defined as the time required for the serum PSA concentration to double in value) are, however, emerging as valuable pretreatment predictors of the risk of death from prostate cancer, and the use of PSA kinetics for this purpose will be discussed in detail in the next section. Some studies also suggest that a low f/t PSA may be a predictor of aggressive disease; among men with a PSA level of 2.0–3.9 ng/ml, unfavourable tumour characteristics were found in 90% of those with an f/t PSA of <10% and in 54% of those with an f/t PSA of

between 10% and 15% [29]. The proportion of men with unfavourable tumour characteristics continued to decrease steadily as the f/t PSA increased. Similarly, in a recent study of men treated with radical prostatectomy for clinically localised disease who had a pretreatment PSA level of >10 ng/ml, a low pretreatment f/t PSA was associated with advanced pathologic features, biochemical progression, and development of metastases [30].

## 3. PSA kinetics: the future of PSA testing

### 3.1. PSA-V

A preliminary report from the Baltimore Longitudinal Study of Aging has recently suggested that an increased pretreatment PSA-V may be predictive of an increased long-term risk of death from prostate cancer [31]. The analysis included 502 men, 114 of whom had prostate cancer. At a median follow-up of 15.4 yr between the first and final PSA measurement, 11 men had died from prostate cancer and 120 men had died from other causes. Stratification of PSA-V (ng/ml/yr) into four groups (<0.01, 0.01–0.06, >0.06–0.16, and >0.16) revealed that 9 of the 11 men who died from prostate cancer had a PSA-V of >0.16 ng/ml/yr and that increasing PSA-V was associated with an increased risk of prostate cancer death.

Pretreatment PSA-V has also been significantly associated with time to prostate cancer death following definitive therapy. D'Amico and colleagues analysed data from 1095 men with localised prostate cancer who participated in a prospective screening study and subsequently underwent radical prostatectomy [32]. They found that a >2.0 ng/ml increase in PSA level during the year prior to diagnosis was significantly associated with a shorter time to biochemical recurrence (relative risk 1.5; 95% confidence interval [CI] 1.1–1.9; $p = 0.003$), death from prostate cancer (relative risk 9.8; 95%CI 2.8–34.3; $p < 0.001$), and death from any cause (relative risk 1.9; 95%CI 1.2–3.2; $p = 0.01$; Fig. 2) compared with an increase of ≤2.0 ng/ml. Similar results have been reported from a second analysis of 358 men who received radiotherapy for localised prostate cancer [33]. PSA-V may, therefore, be a valid indicator for those patients at high risk of prostate cancer death, for whom aggressive therapy may be the most appropriate strategy. However, the interval and level of PSA increase >2.0 ng/ml that should prompt intervention remains to be defined.
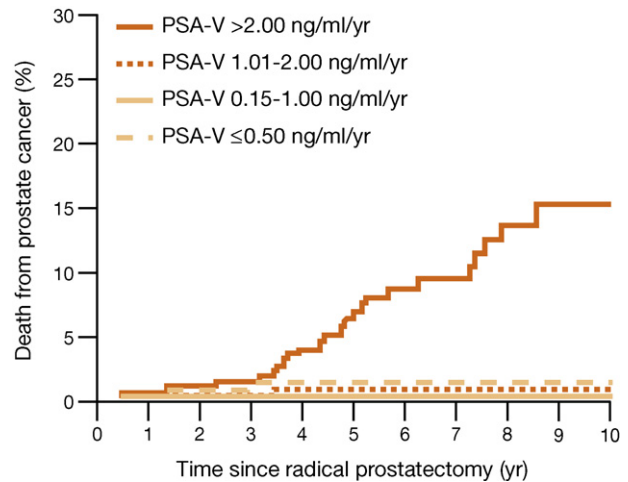


Fig. 2 – Prostate-specific antigen velocity (PSA-V) may be used to predict patients at higher risk of death from prostate cancer. Cumulative incidence of prostate cancer death in 1095 men who underwent radical prostatectomy for localised prostate cancer, stratified according to PSA-V. Reproduced with kind permission from D'Amico AV, et al. N Engl J Med 2004;351:125–35 [32]. Copyright © 2004, Massachusetts Medical Society. All rights reserved.

### 3.2. PSADT

When measured prior to treatment, PSADT appears to predict more aggressive phenotypes. Klotz and colleagues conducted a study in 299 patients with good-risk prostate cancer defined as PSA level <15 ng/ml, Gleason score ≤7, and tumour stage ≤2b at study entry [34]. The choice between continued active surveillance or definitive therapy was determined by the PSADT or the development of early, rapid disease progression. At a median follow-up of 64 mo, only two patients had died from prostate cancer, both of whom had a PSADT of <2 yr. Final pathology results for the 24 patients who underwent radical prostatectomy for a PSADT of <2 yr showed a high rate of locally advanced disease.

Data from this study suggest that the determination of an aggressive phenotype can be made at approximately 2 yr after initiating surveillance, based on eight or nine PSA data points (every 3 mo) and two sets of 8–12 core biopsies [35]. The authors concluded that the appropriate PSADT threshold for intervention is likely to be <3 yr; approximately 20% of patients in the series fell into this category. PSADT is, therefore, a useful predictor for those high-risk patients who should be regularly tested and monitored by the clinician.

## 3.3. PSA-V versus PSADT

PSA-V and PSADT have been compared as predictors of outcome following radical prostatectomy in a cohort of 2290 patients who had at least two PSA measurements recorded in the 2 yr prior to surgery [36]. At 7.1 yr median follow-up, 42 patients had died from prostate cancer. A PSA-V of >3.4 ng/ml/yr (hazard ratio [HR] 6.54; 95%CI 3.51–12.19; $p < 0.0001$) and a PSADT of <18 mo (HR 6.22; 95%CI 3.33–11.61; $p < 0.0001$) were both significant predictors of an increased risk of death from prostate cancer. In a multivariate analysis, PSADT appeared to be a stronger predictor of prostate cancer death compared with PSA-V. However, PSA-V is easier to use in clinical practice and provides a good approximation in the short term.

## 4. Clinical role of PSA in detecting prostate cancer

A clinical scenario involving a 60-yr-old man was discussed in a meeting of 746 specialists [37]. The patient, who visited his physician to request information about the early detection of prostate cancer, made an informed decision to undergo testing in September 2004 (Box 1).

### 4.1. PSA testing

Audience polls at the meeting revealed that only around one-third (37%) of respondent urologists and oncologists would take the time to explain the nature of PSA testing to their patients, suggesting that this is often overlooked in clinical practice. This conflicts with current recommendations, which typically stress the importance of counselling the patient on the benefits and limitations of PSA testing so that he can make an informed decision [38].

Almost all of the respondents (98%) indicated that they would offer PSA testing to the patient, who was 60 yr old at presentation. However, when asked to consider their recommendations if the patient were 40 yr old, approximately two-thirds (63%) of the respondents indicated that they would perform PSA testing only if the man had a family history of prostate cancer, whereas one-third (31%) would take a PSA reading as a baseline value. In the United States, it has generally been accepted that annual PSA testing should be offered to men >50 yr old who have a life expectancy of at least 10 yr [39], and PSA testing beginning at the age of 40 yr has typically been restricted to men who are in high-risk groups, such as those having a family history of prostate cancer [40]. However, a recent report based on follow-up data from men with a median age of 34 yr has suggested that increased PSA levels in early adulthood may be predictive of an increased risk of prostate cancer later in life [41]. Given that benign prostatic disease, which can reduce the value of PSA screening, is rare in men younger than 50 yr, there is a now a reasonable case for obtaining a baseline PSA value when the patient is approximately 40 yr of age.

### 4.2. Biopsy

The clinical scenario described illustrates how PSA kinetics can be used to help identify when a biopsy should be performed. When tested in September 2004, the patient had an absolute PSA level within the normal range, but his f/t PSA was relatively low at 15%, suggesting the possibility of prostate cancer with unfavourable tumour characteristics [29]. Eighty-nine percent of the respondents in the audience polls agreed that such a patient should be followed with active surveillance, although opinion was divided on whether to repeat the PSA measurement after 3 mo (49%) or 1 yr (38%). By

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**Box 1. Presentation of a 60-yr-old man**

|  | September 2004 | October 2004 | December 2004 | March 2005 | June 2005 | December 2005 |
|---|---|---|---|---|---|---|
| PSA, ng/ml | 2.7 | 2.8 | 3.1 | 3.7 | 3.7 | 4.9 |
| f/t PSA, % | 15 | 15 | 16 | 14 | 15 | 14 |
| PSADT, mo | — | — | 20.4 | 15.4 | 20.4 | 19.3 |
| PSA-V, ng/ml/yr | — | — | 1.2 | 1.3 | 1.3 | 1.6 |
| Other | No suspicious findings on DRE | Active surveillance | Active surveillance | 10-core biopsy negative for PIN and ASAP | Active surveillance | Rebiopsy in January 2006 revealed prostate cancer in 15% of 1 of 10 cores (Gleason score 6) |

ASAP = atypical small acinar proliferation; DRE = digital rectal examination; f/t PSA = free-to-total PSA; PIN = prostatic intraepithelial neoplasia; PSA = prostate-specific antigen; PSADT = PSA doubling time; PSA-V = PSA velocity.

March 2005, the majority of the respondents (73%) would have recommended a biopsy because the patient's PSA level had continued to rise to 3.7 ng/ml and his PSADT was 15.4 mo, suggesting that he was at risk of aggressive disease. The patient had an initial negative biopsy, leaving the clinician with the difficult decision of whether to perform a repeat biopsy. Opinion was divided over this decision, with 41% of respondents voting for a rebiopsy and the rest (59%) opting for a further PSA check after an interval of 3 mo (17%), 6 mo (35%), or 1 yr (7%). The probability that this patient would have a positive repeat biopsy was estimated at approximately 9% using a nomogram [42]. Taking into account the PSA kinetics, the general consensus (77% of the respondents) was that the patient remained at risk of harbouring prostate cancer and that a repeat biopsy should be performed. Because the PSA level was unchanged at June 2005, the previous rise could have been due to natural variation, and the PSADT was recalculated as 20.4 mo. However, by December 2005, the patient's PSA level had again increased and the PSADT was revised to 19.3 mo. At this point, a rebiopsy was performed, and the patient was found to have prostate cancer in 15% of 1 of 10 cores (Gleason score 6). It is, therefore, possible that while PSA levels alone may, due to natural variations over time, result in unnecessary biopsies, their use in combination with kinetic data can facilitate a more accurate assessment of risk to the patient.

## 5.    Conclusions

PSA remains a useful marker in the early detection and diagnosis of prostate cancer, although PSA kinetics are more important than absolute values in predicting disease. Monitoring PSA levels over time can help clinicians to decide when best to perform a biopsy and, more importantly, to identify which patients are at risk of prostate cancer death before definitive therapy is undertaken. At present, however, no consensus has been reached on the application of PSA kinetics in routine practice [10] and this is reflected in the variability of the poll responses. Given that the PSA test is easy to perform, relatively inexpensive, and readily available for use in most countries, regular monitoring should be incorporated into clinical decision-making.

## Conflicts of interest

Professor Kurt Miller has worked as a paid consultant and attended advisory boards for AstraZeneca.

Professor Per-Anders Abrahamsson has no commercial association that might pose a conflict in connection with the submitted article. Dr Koichiro Akakura has received financial support from AstraZeneca. Dr Frans DeBruyne and Dr Christopher P Evans have no conflicts of interest with respect to this article. Professor Laurence Klotz has received honoraria from AstraZeneca, Abbott and Sanofi-Aventis.

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