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INVITED EDITORIAL

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The rise and fall of PSA: clinical implications of prostate specific antigen kinetics

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The investigation of the kinetics of tumour markers has a long tradition in urology. As early as 1949, Gastineau et al. [9] reported the time course for the decay of human chorionic gonadotropin (HCG) in a single individual following the ablation of a testicular tumour. Since then many publications have focused on half-life determinations of HCG in molar pregnancy or the follow-up of chemotherapy for testicular tumours [13], but to our knowledge no subsequent investigations have considered the half-life of testicular tumour markers after the removal of the primary tumour.

In this editorial we explore the multiple kinetic parameters of prostate specific antigen (PSA) before diagnosis and after treatment of prostate cancer. The essential clinical utility of these analyses may not yet be fully realised.

The rise of PSA

An increase of PSA over time can either be expressed as PSA velocity (PSAV) or PSA doubling time (PSADT). Carter and colleagues at Johns Hopkins Hospital inaugurated PSAV as a means to enhance the specificity of PSA for prostate cancer detection [6]. PSAV has been defined as an *absolute* annual increase in serum PSA (ng/ml×year). PSADT was established in untreated patients with known prostate cancer who were followed by investigators from Stanford University [27]. PSADT takes into account the exponential increase of serum PSA over time and reflects a *relative* change. It can easily be calculated according to the original formula [27]:

$$\mathrm{PSADT} = \frac{\log\ 2 \times \mathrm{t}}{\log\ (\text{second PSA}) - \log\ (\text{first PSA})}$$

where t is the time between the two PSA determinations.

The difference between these two concepts has not yet been fully appreciated. The example in the table may illustrate why PSAV and PSADT are conceptually different:

Variable	Unit	Patient A	Patient B
PSA increase within 1 year	ng/ml	3.6→4.4	7.6→8.4
PSA velocity	ng/ml×year	0.8	0.8
PSA doubling time	years	3.5	6.9

PSADT has two major advantages when compared to PSAV. First, it is independent of the baseline PSA value. In the example, patient A is more likely to harbour cancer than patient B based on his shorter PSADT. Note that PSAV is identical in both patients. Second, PSADT is also independent of the assay, although the *same* assay should be used for a given patient [30]. Thus, comparisons of serial PSA measurements in men from different study populations using different assays should be done by PSADT rather than by PSAV.

In screening programs, the dynamic parameter PSADT is potentially suitable for discriminating prostate cancer from benign prostatic hyperplasia (BPH) based on the following observations: the median doubling time of localised prostate cancer is 3–4 years [27], whereas Berry et al. have demonstrated that the doubling time for BPH in men from 51 to 70 years old is 10 years [2]. Furthermore, prostate cancer elevates serum PSA levels about 12 times more per unit volume of tissue than BPH [33]. Thus, in the most important age group for the early detection of prostate cancer, BPH contributes only marginally to any rapid rise in serum PSA. Since the current data for PSAV and PSADT are not yet conclusive, the clinical usefulness of both concepts should be

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further evaluated in large prospective trials such as the European Randomised Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colon, and Ovarian Cancer Screening Project (PLCO).

In addition to their use in the early diagnosis of prostate cancer, PSAV and PSADT may also be used for the monitoring and follow-up of patients with an established diagnosis of prostate cancer. Patients who relapse after radical prostatectomy or external beam irradiation could be assigned to adjuvant therapy based on their PSADT [8, 14]. In radiation and anti-androgen treated patients, PSADT is related to prognosis [1]. Recently, PSADT has been suggested as a surrogate end point in hormone-refractory prostate cancer [28]. This is most important as novel chemotherapeutic agents are urgently needed, but their evaluation is severely hampered by the fact that most patients only have non-measurable (bone) metastases [29].

In summary, both dynamic concepts of PSAV and PSADT certainly hold promise in screening for and monitoring of prostate cancer patients. The results from large multicenter trials are eagerly awaited in the urological community.

The fall of PSA

The use of serial post-therapeutic total prostate specific antigen (t-PSA) measurements for the prognosis and monitoring of patients with prostate cancer is well established in clinical practice. Blood samples from patients undergoing radical prostatectomy should show a pattern of declining PSA concentrations. Failure to reach undetectable concentrations following radical prostatectomy is evidence for residual disease and therefore probably a poor prognostic indicator. Likewise, the reappearance of PSA in patients, months or years after an initial decline to undetectable levels, indicates cancer recurrence. When the source of PSA is removed by radical prostatectomy, the PSA half-life can be estimated. This subject was recently reviewed comprehensively [3, 10].

The first investigation calculating the half-life of t-PSA was published in 1987 by Stamey et al. [33]. In 14 patients the mean t-PSA half-life was calculated to be 2.2 days, starting the half-life calculation with the t-PSA concentration 5 min after removal of the prostate (t_0). One year later, Oesterling et al. [21] found a mean half-life of 3.2 days in 30 patients, but used a t_0 as late as the third day after radical prostatectomy. In 1990, Pontes et al. [22] found a mean half-life of 1.9 days, which is similar to that reported by Stamey et al., using a t_0 of 2 to 4 h after the removal of the prostate. In general, this type of calculation reveals longer half-lives the later the serum sample which is utilised as t_0 is drawn after the removal of the prostate.

It is noteworthy that Pontes et al. [22] reported two patients who showed no regular PSA decline and developed metastases within 6 months of surgery. In one patient, PSA did not decline to 50% within 9 days while the other patient showed a half-life of 2.7 days but did not reach undetectable PSA concentrations. Unfortunately no follow-up of the patients with a ''regular'' PSA decline was reported in this study.

More recently, t-PSA half-life has been calculated by several investigators employing a variety of sampling intervals, assuming mono- or bi-exponential elimination kinetics. In studies without long-term follow-up, mean half-lives of 1.9–3.4 days were reported for t-PSA. Two investigators calculated t-PSA half-life in patients after more than 10 months of follow-up post surgery and found significantly longer half-lives for patients with recurring or persistent cancer (3.0 and 3.1 days [31]; 2.9 and 3.1 days [7] respectively) than for patients without evidence of disease in the follow-up (1.5 days [31] and 1.6 days [7]).

In our investigation [31], the mean t-PSA half-life in patients who reached persistently undetectable PSA concentrations was significantly shorter (1.5 days) than the mean half-life of patients who initially reached undetectable t-PSA concentrations but showed rising t-PSA concentrations during the follow-up (3.0 days). Extended follow-up of the same patient population [32] and additional patients [11] confirmed the original conclusions. A simplified procedure that calculates the ratio of the PSA concentration 5 min after the removal of the prostate and the PSA concentration on postoperative day 7 was introduced by Hamm et al. This showed the equivalent prognostic information when compared to the more complicated half-life calculation utilising multiple postoperative PSA concentrations [11].

Brändle et al. [4, 5] focussed their work on the methodological problem of blood loss and fluid substitution during radical prostatectomy and proposed a way to correct for the volume shift to minimise its impact on half-life determinations. The influence of prostatic manipulations on various forms of PSA has been studied by several groups and was recently reviewed extensively [23]. The more rigorous manipulations during radical prostatectomy induce significant elevations in t-PSA and in free, uncomplexed PSA (f-PSA). Post-manipulatory peaks are markedly higher for f-PSA than for t-PSA. Mean maximal f-PSA levels showed a 4.3-fold increase, followed by a rapid decline after prostate removal, reaching preoperative ranges after 60–90 min, while t-PSA only increased 1.2-fold and declined more slowly [20].

A question raised by Schifman [26] is still unanswered: how can residual cancer be capable of prolonging half-life, without preventing PSA from reaching undetectably low concentrations? Knowledge of different molecular forms of PSA prompted recent investigations to consider different elimination kinetics for f-PSA and for PSA complexed to α1-antichymotrypsin [35]. The very short half-life of f-PSA found in these studies may aid in the understanding of a bi-phasic elimination pattern of t-PSA. In addition, bi-phasic elimination patterns have also been described for f-PSA [15, 16]. A possible answer to Schifman's question could

be found by looking at the different forms of f-PSA. An excellent review of PSA forms was recently published by Rittenhouse et al. [25]. Together with the findings of Ravery et al. [24], who found a shorter half-life of f-PSA in patients with benign prostatic hyperplasia (1.4 days) than in patients with prostate cancer (2.1 days), the recent reports of two different forms of f-PSA, BPSA [19] and proPSA [17,18] may explain the differences in the elimination kinetics of f-PSA originating from benign prostatic tissue or from prostate cancer, since proPSA is reported to be preferentially localised in cancerous tissue and BPSA is found predominantly in the transition zone where BPH originates.

The disappearance rate in the early postoperative period may be caused by a rapid extracellular redistribution of f-PSA [12, 34]. Whether the elimination of f-PSA in the second, slower phase is caused by renal glomerular filtration [16] seems to be debatable since the PSA concentration in the urine of men with normal renal function decreases immediately after the removal of the prostate despite persistent high concentrations of PSA in the serum [32].

Future investigations on the elimination route and kinetics of these f-PSA forms and the role of α2–macroglobulin, forming a complex with f-PSA molecules that can not be detected with conventional immunoassays, may contribute to our understanding of the prognostic relevance of PSA elimination kinetics after radical prostatectomy.

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