PSA doubling time and its calculation

A. Ruffion, X. Rebillard, S. Oudard
In addition to the various published nomograms for treatment decision-making in prostate cancer, the prostate specific antigen doubling time (PSADT) provides a dynamic parameter which may help further refine the management and monitoring of patients. Numerous data have been published on the subject, and the PSADT is currently considered as an independent prognosis marker in many situations of prostate cancer management, even though its value has not yet been confirmed in prospective studies.\(^\text{1}\)

Most kinetic analyses of PSA reported in the literature are based on two measurements: the velocity of total PSA (PSAV) and the PSA doubling time (PSADT). As it is very easy to calculate, PSAV was the first to be used. However, it quickly became apparent that this method of calculation is not adapted to situations where PSA levels rise exponentially, as in prostate cancer.\(^\text{1-3}\) The use of PSADT thus appears as more logical in this indication. The main pitfall of PSADT is the need to use complex mathematical formulas,\(^\text{4-8}\) which require specific software equipment.
Clinical use of PSA doubling time in prostate cancer

PSADT and simple monitoring:

PSADT may help monitor more progressive cancers and guide the treatment: the shorter the PSADT, the more aggressive the treatment needs to be.\(^9\) However, some cancers may progress despite a stable PSA level.\(^{10}\) Prospective studies on this issue may cause patients and surgeons to rush into a curative treatment based on PSADT values, but caution is required until prolonged follow-up periods provide sufficiently reliable data.\(^{11}\)

The use of PSADT as a prognosis factor prior to a curative treatment:

PSADT may be a pre-treatment prognosis factor able to evaluate the tumour’s aggressivity.\(^{12}\) A short PSADT may suggest an aggressive tumour, except in certain moderately differentiated cancers with low PSA secretion.\(^{13}\) Short PSADTs are associated with a high Gleason score, a high pre-treatment PSA level, or a high TNM stage.\(^{14}\) Short PSADTs appear to be significantly associated with the onset of a biological recurrence\(^{3,4}\), and may predict a higher mortality risk specific to prostate cancer following a curative treatment.\(^{13}\)
Evaluation of the prognosis in curative treatment failure in prostate cancer:

Several retrospective series analysed the prognosis value of PSADT following a curative treatment. PSADTs appear to have an independent prognosis value, like the time to biological recurrence and the tumour’s Gleason score.\(^{(4, 14,23)}\) For certain authors\(^{(18)}\), the PSADT is the most important factor to take into account. PSADTs between 3 and 12 months may indicate a poor prognosis for the specific prostate cancer survival.\(^{(15,16,20)}\) Certain authors consider that PSADTs below 12 months are indicative of occult metastases, and would then justify early hormone therapy.\(^{(19,22,24,25)}\)

The role of PSADT as a marker of local or general recurrence has raised numerous discussions and polemics on the necessary interval before an interpretable PSADT is obtained (see below). No currently available series has yet been able to provide conclusive evidence.\(^{(26,27)}\)

Following curietherapy, a nadir at 1 year may be indicative of the treatment’s efficacy, whereas there is few data available on patients in whom this treatment has failed.\(^{(28,29)}\) However, it is possible that, given the frequency of the PSA “paradoxical rebound” in these patients, PSADT may be more difficult to use following this type of treatment.\(^{(30)}\)

PSADT and hormone therapy:

As seen in the previous chapter, a short PSADT may be an element in favour of early initiation of hormone therapy, to increase survival without metastatic symptoms.\(^{(24)}\)

Certain authors suggest that PSADTs may be useful after the initiation of hormone therapy. A low PSADT (\(< 12\) months) has recently been reported as still indicative of a poor prognosis in terms of specific and metastasis-free survival in patients with prostate cancer.\(^{(23)}\) As expected, the PSADT is longer in localised disease (7.5 months) than in metastatic disease (2.5 months).\(^{(31)}\) PSADTs under 70 days may be a mortality risk factor, specific of prostate cancer in patients with a hormone dependent disease.\(^{(32,33)}\)
Precautions to take when using PSADT

**Physiological, inflammatory, or iatrogenic variations of PSA:**

In disease-free patients, PSA levels rise on a linear pattern\(^2\) with physiological fluctuations. Following an acute bacterial prostatitis, urinary retention, prostate biopsy or endourethral prostate resection, total blood PSA rises exponentially for at least 2 to 4 weeks.\(^{28}\) The literature reports a half-life of PSA following acute prostatitis of 14 to 16 days.\(^{34,35}\)

**PSA variations in benign prostate hypertrophy:**

In benign prostate hypertrophy, PSA levels follow a curvilinear pattern.\(^2\) The expected PSADT is very long, around 25 years.\(^{36}\) The half-life of PSA following an adenomectomy is 3.4 days, versus 2.4 days after a radical prostatectomy.\(^{37}\) The shorter PSA half-life after radical prostatectomy is explained by the fact that the whole prostatic tissue has been removed, thus preventing any residual PSA synthesis.\(^{37}\)

**What are the optimum timing and minimal number of PSA tests to calculate the PSADT?**

There are no “good practice” rules available to calculate the PSADT, as this prognosis factor is still under evaluation, as mentioned above. However, most of the published articles recommend calculating the PSADT with at least three successive values of PSA, each separated by at least three months. It is also important to know that the accumulation of too many PSA tests too close to one another may artificially reduce the PSADT.\(^{11}\)
References


