Published in final edited form as:
J Urol. 2008 June ; 179(6): 2181–2186. doi:10.1016/j.juro.2008.01.099.

Prostate-Specific Antigen Working Group's Guidelines on PSA Doubling Time

Philip M. Arlen, **Fernando Bianco**, **William L. Dahut**, **Anthony D'Amico**, **William D. Figg***, **Stephen J. Freedland**, **James L. Gulley**, **Philip W. Kantoff**, **Michael W. Kattan**, **Andrew Lee**, **Meredith M. Regan**, and **Oliver Sartor**

From the Medical Oncology Branch, Center for Cancer Research, National Cancer Institute (PMA, WLD, WDF, JLG), Bethesda, Maryland; Urology Department, George Washington University (FB), Washington, DC; Brigham and Women's Hospital and Dana Farber Cancer Institute, Harvard University (AD'A, PWK, MMR, OS), Boston, Massachusetts; Division of Urology and Duke Prostate Center, Departments of Surgery and Pathology, Duke University (SJF), Durham, North Carolina; Cleveland Clinic (MWK), Cleveland, Ohio; and Department of Radiation Oncology, MD Anderson Cancer Center (AL), Houston, Texas. Authors are listed alphabetically

Abstract

Purpose—Prostate-specific antigen is a glycoprotein found almost exclusively in normal and neoplastic prostate cells. PSA doubling time, or the change in PSA level over time, has emerged as a useful predictive marker for assessing disease outcome in patients with prostate cancer. It is important to agree on definitions and values for the calculation of PSADT and to develop a common approach to outcome analysis and reporting.

Methods—In September 2006 a conference was held at the National Cancer Institute in Bethesda, Maryland to define these parameters and develop guidelines for their use.

Results—The PSA Working Group defined the following criteria regarding PSADT: (1) calculation of PSADT, (2) evidence to support PSADT as a predictive factor in the setting of biochemical recurrence, and (3) use of PSADT as a stratification factor in clinical trials.

Conclusions—We propose that investigators calculate PSADT prior to enrolling patients on clinical studies and calculate it as an additional measurement of therapeutic activity. We believe we have developed practical guidelines for the calculation of PSADT and its use as a measurement of prognosis and outcome. Furthermore, the use of common standards for PSADT in clinical trials is important as we determine which treatments should progress to randomized trials in which "hard" end points such as survival will be employed.

Keywords

prostate cancer; PSA; consensus; clinical trials; biomarkers

Prostate cancer is the most commonly diagnosed noncutaneous malignancy among males in the United States and the third leading cause of cancer-related mortality. It is estimated that

*Corresponding author: Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 10 Center Drive, Room 5A01, Bethesda, Maryland 20892 (telephone: 301-402-3622; FAX: 301-402-8606; e-mail: wdfigg@helix.nih.gov.

27,050 men will die of prostate cancer in 2007.[1] Changes in PSA, a 34 kD glycoprotein found almost exclusively in normal and neoplastic prostate cells and in seminal fluid, often antedate radiographic changes.[2] In 1989 Ferro et al.[3] first reported PSA changes as an indicator of response in patients with AIPC. Since then, the majority of phase II trials have used PSA as a marker. However, currently available data suggest that declining serum PSA concentration is not a reliable surrogate end point for prostate cancer-specific mortality.[4] Indeed, in some clinical settings, PSA changes and "hard" end points, such as survival, have shown no correspondence.[2]

PSADT is emerging as a useful marker for predicting outcomes in patients with prostate cancer. The concept of PSADT originated from the finding that temporal PSA trends in untreated patients conform to an exponential model, suggesting that prostate cancer has a typically slow log-linear growth rate.[5] D'Amico et al.[6] utilized linear regression analysis to calculate the PSADT of prostate cancers recurrent after external beam RT and found PSADT to be a constant that linearly correlated with the interval to clinical relapse after PSA failure. The slope of this correlation is equal to the number of PSADT (4.5 with 95% confidence interval [3–6]) required before clinical disease manifests after PSA failure, and as such can be a useful variable for grouping patients into those with aggressive (PSADT <3.8 months) and less aggressive (PSADT ≥3.8 months) tumor biology. This investigation led to subsequent studies evaluating the use of PSADT to guide treatment interventions.

Initial studies evaluating patients placed on watchful waiting identified PSADT as the strongest predictor of clinical progression.[7] Recently, PSADT has become well established as an important predictor of the risk of progression to metastatic disease after RP or RT.[8] A PSADT <3 months has also been found to be a useful surrogate marker for prostate cancer-specific and overall survival in patients with relapse after RP or RT,[9] and a predictor of duration of response to deferred ADT and metastasis-free survival in men with AIPC.[10] Moreover, Loberg et al.[11] reported that men with hormone-naive prostate cancer have a significantly longer PSADT than men with AIPC. Further studies by Semeniuk et al.[12] showed that PSADT serves as an independent prognostic marker for survival in patients with metastatic AIPC.

While PSADT may prove to be a useful predictor of disease outcome in all states of prostate cancer, a consensus has yet to be reached on either its universal usage or the exact method of calculation. One significant consideration is the methodology (such as time intervals and cut points) of appropriately calculating the PSADT and its ability to predict disease-specific survival. Both D'Amico et al.[8] and Freedland et al.[13] found that patients with a PSADT cut point of <3 months were at very high risk for prostate cancer-specific death. However, other studies describe different cut points for stratifying high, intermediate, and low risk, suggesting that larger prospective studies may be needed to optimize the use of PSADT.

METHOD

On September 28, 2006, 12 investigators actively engaged in prostate cancer research met at the National Cancer Institute to debate the specifics of PSADT and develop guidelines for uniform implementation. Investigators represented the specialties of urology, radiation oncology, biostatistics, pharmacology, and medical oncology.

Guidelines for calculating PSADT were developed using literature review, current patient monitoring, and available assay technology. The majority of the data in the literature reported is for the time of recurrent disease following primary local therapy.

RESULTS

Calculation of PSADT

PSADT is often calculated assuming an exponential rise in serum PSA and first-order kinetics. The formula takes into account the natural logarithm of 2 divided by the slope obtained from fitting a linear regression of the natural log of PSA on time.[14] All PSA values used in the calculation should be ≥0.20 ng/ml and follow a rising trend. PSA values need not be consecutively rising and all values obtained over a maximum period of 12 months should be included in the calculation. The maximum period of the past 12 months is recommended to reflect the patient's current disease activity, since in some men PSADT may change over time. Minimum requirements for the calculation are 3 PSA values obtained over 3 months with a minimum of 4 weeks between measurements. We recommend reporting PSADT in months; however in advanced disease states, weeks may be used where it is the appropriate time metric. On occasion, PSA values included in the calculation may result in a slope from the linear regression that is zero or negative, so that an estimate of PSADT would be nonexistent or negative.

Several other factors are important when reviewing PSA values used in the calculation:

- All PSA values must have been obtained using the same assay, preferably at the same laboratory. While it may be impractical, obtaining PSA values at approximately the same time of day may reduce variability resulting from circadian variations in PSA values.[15] PSA values should be recorded with a maximum of 2 significant digits after the decimal point.
- Serum testosterone concentration should be relatively stable over the period (ideally ≤10% variation). PSADT should not be calculated using PSA values obtained when testosterone is rebounding post-ADT. For example, one study found that after 6 months of GnRH agonists, testosterone did not return to normal for a median of 16.6 weeks.[16] For patients on testosterone-suppression therapy with no available historical testosterone concentrations, a history of continuous therapy and a testosterone measurement within the castrate range at any point during that treatment should suffice. Due to the relationship between PSA and serum testosterone levels, a measurement at diagnosis and at first recurrence may be clinically useful. However, there are no published trials to support this suggestion.
- Treatment that may affect PSA or prostate cancer (e.g., saw palmetto, 5-alpha reductase inhibitors) must be constant over the period of acquisition of PSA values.
- A patient's initial primary therapy will impact the absolute post-therapy PSA nadir.

Unlike the majority of patients treated surgically, patients treated with RT are unlikely to have undetectable PSA due to residual prostatic tissue, but may have a finite nadir PSA concentration after RT. The best approach to ensuring comparable PSADT estimates across therapies is not established, in part due to the difficulty of determining if the detectable PSA in radiation-treated patients is due to benign prostate tissue alone or a combination of malignant and benign tissue. One reasonable approach is nadir subtraction[8] wherein the nadir PSA concentration, defined by the lowest PSA value observed following RT, is subtracted from the post-RT PSA concentrations before calculating PSADT. This approach can also be considered for surgical patients who do not achieve an undetectable PSA level. In general, this correction need not be made in patients on ADT. The theory is that in order to get the same value of PSADT for a man managed using RP (where PSA generally starts at undetectable levels), the PSA for men undergoing RT should be normalized, otherwise the PSADT calculated for RT-managed men will be higher for the same changes in PSA level.

In Table 1, Example 1, each patient has an initial increase in PSA of 0.2 ng/ml. The magnitude of subsequent rises is the same in each patient; however, estimated PSADTs are 5.8 and 22.4 months based on PSA values. If the PSA nadir of 1.00 ng/ml is subtracted from each post-RT PSA value, then the PSADT for patients treated surgically and with RT are the same. In Example 2, again the magnitude of increases is the same in each patient. At these higher PSA concentrations the impact of the difference in PSA nadir is small but systematic, and therefore important for consistency.

- In nonsurgical patients with intact prostates, particularly post-brachytherapy, several factors may affect individual PSA measurements, including physical or sexual activity, prostatitis, radiation proctopathy, recent passage of a kidney stone, or instrumentation. Assuming a PSA half-life of 3.5 days, waiting at least 4 half-lives would suggest a wait period of at least 2 weeks; however, PSA bounces due to infection or inflammation can take 6 to 8 weeks to resolve.

PSADT calculations typically require more than 2 PSA measurements (see above) to yield accurate prognostic information. Time is an important variable as well. Recognizing that a very rare subset of patients with extremely rapid PSADT may have significant changes over very short periods, we suggest that the vast majority of patients should have repetitive PSAs determined at intervals ≥4 weeks over a period of ≥3 months. These guidelines are likely useful only for patients with early disease states.

PSADT as a Predictive Factor in Various Disease Recurrence Settings

The evidence upon which we base our considerations is exclusively level II, derived from cohort- or case-controlled analytic studies or controlled, nonrandomized trials.[13] However, data from this level II evidence are consistent and have been validated in multiple data sets, as demonstrated below. In the absence of level I evidence (derived from randomized controlled studies), this provides the best justification for considering PSADT in clinical management. We also acknowledge that we know more about the natural history than about the effects of therapeutic interventions in this setting.

Multiple studies have examined the association between post-surgical PSADT and risk of metastasis, prostate-cancer death, and all-cause mortality.[8, 13, 17] As seen in Table 2, a longer PSADT is associated with a longer time to metastasis, prostate-cancer death, and all-cause death. Moreover, as the PSADT increases, the time to metastasis or prostate-cancer death steadily increases. Importantly, these prior studies identified a small group of patients (6% to 20% of all men with PSA failure) with very rapid PSADT (<3 months) in which prostate-cancer mortality approaches 100%.[8, 13] These studies leave little doubt that men with a PSADT <3 months are at extremely high risk for adverse clinical outcomes. In contrast, men with a slow PSADT (>15 months) have an extremely low risk of prostate-cancer death. In one study, men with a PSADT >15 months who recurred >3 years after surgery (n = 82) had a 0% prostate-cancer mortality at 15 years after biochemical recurrence.[13] For the majority of patients, with an intermediate PSADT of 3 to 15 months, no best cut point is known and other clinical factors may play a larger role in determining risk.

A comprehensive study illustrating the continuous nature of PSADT was conducted by Johns Hopkins University.[18] The authors identified multiple cut points that stratified men into 4 categories based upon PSADT. Although these identified cut points, with the exception of PSADT <3 months,[8] have not been validated in other patient populations, they provided reasonable stratification of patients' risk of adverse clinical outcomes.

After definitive external beam RT, PSADT has been shown to be a prognostic factor, with results similar to post-RP (table 2). Longer PSADT is associated with longer time to metastasis[2] and prostate-cancer death.[8] Drawing on the analogy to surgically treated patients,

men with a PSADT <3 months (calculated after subtracting the nadir PSA value) are at extremely high risk, with prostate-cancer mortality approaching 100%.[8]

Studies have also found that among men who received RT plus hormonal therapy, or who underwent brachytherapy, a rapid PSADT is associated with increased risk of prostate-cancer death. However, in these settings, issues related to PSA bounce[4] or the slow return of testosterone to normal post-hormonal therapy can complicate the interpretation of PSADT (see above). More data are needed regarding the role of PSADT in risk stratification for men undergoing RT with hormonal therapy and, in particular, brachytherapy.

Finally, the concept that rapid PSADT correlates with poor prognosis has been shown even among men with nonmetastatic[17] or metastatic[19] AIPC. However, given the limited number of studies conducted in this disease setting, further study is needed to clarify the value of PSADT in predicting outcome in this patient population.

PSADT as a Stratification Factor in Clinical Trials

PSA Failure Only, Hormone Naïve—PSADT is an excellent predictor of clinical outcome, including clinical recurrence (in the absence of ADT) and survival.[13] It is therefore recommended that patients selected for novel cytotoxic trials should primarily be those with PSADT <15 months, which represents 58% of patients, 76% of all mortalities, and 89% of prostate-cancer deaths. Although these cut-offs have not been validated, stratification by PSADT (<3 months versus 3 to 9 months versus 9 to <15 months) should be considered in all randomized clinical trials in this patient population, along with factors such as Gleason score, on-study PSA, ECOG performance status, etc.

ADT Post-RT or Post-Surgery—There is some evidence of a link between post-treatment kinetics and outcome. D'Amico et al.[20] showed that in patients treated with ADT who have a PSADT of <3 months, a PSA nadir of >0.2 ng/ml following 8 months of ADT is associated with poor prognosis. Thus, patients in this subset should be considered for clinical trials.

Newly Diagnosed Metastases—Currently, there are no prognostic data for PSADT in this patient population.

AIPC with No Metastases, Rising PSA—Smith et al.[17] evaluated 201 nonmetastatic prostate cancer patients with rising PSA despite castrate testosterone levels. Median bone metastasis-free survival was 30 months. Median time to first bone metastasis and overall survival were not reached. Baseline PSA >10 ng/ml (relative risk, 3.18; 95% CI, 1.74 to 5.80; $p < 0.001$) and PSA velocity (4.34 for each 0.01 increase in PSA velocity; 95% CI, 2.30 to 8.21; $p < 0.001$) independently predicted shorter time to first bone metastasis. Thus, stratification by both PSA kinetics and PSA concentration is suggested in this subset of patients; however, no formal PSADT data are available.

AIPC with Metastasis—Vollmer et al.[19] demonstrated that both log (PSA) and average relative velocity of PSA were significantly correlated with survival time ($p = 0.0001$ and $p = 0.0008$, respectively) in patients with metastatic AIPC. The prognostic value of PSADT was corroborated in a study by Halabi et al. (personal communication). However, the effects of PSADT changes in this population have not been determined. Given the fact that patients with AIPC have such a poor prognosis, studies that include stratification by pretherapy PSADT should be considered.

Post-Taxane Hormone-Refractory—There are no current data supporting PSADT as a marker for patients with metastatic AIPC who have progressed through docetaxel therapy.

CONCLUSIONS

Measurement of PSADT can be problematic due to factors such as prior and current therapies, assay type, frequency of assays, and duration of measurements. PSADT can be used to risk-stratify patients into those with aggressive or indolent disease, but PSADT is only one of many variables in the clinical setting. Diagnostic and therapeutic intensity may vary in accordance with the risk of progressive disease. Clinical trials or aggressive therapies are encouraged for patients with rapid PSADT. Observation or less aggressive therapies are warranted for those with slow PSADT as these patients have a prolonged natural history in the absence of intervention.

Acknowledgements

The authors thank Kathy Compton, Dr. Cindy Chau, and Bonnie L. Casey for their editorial assistance in the preparation of this manuscript. The September 2006 conference was supported by the intramural program of the National Cancer Institute #Z01 BC 010453.

Abbreviations and Acronyms

ADT
androgen-deprivation therapy

AIPC
androgen-independent prostate cancer

GnRH
gonadotropin-releasing hormone

PSA
prostate-specific antigen

PSADT
prostate-specific antigen doubling time

RP
radical prostatectomy

RT
radiotherapy

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. Cancer statistics, 2006. CA Cancer J Clin 2006;56:106. [PubMed: 16514137]
2. Lee WR, Hanks GE, Hanlon A. Increasing prostate-specific antigen profile following definitive radiation therapy for localized prostate cancer: clinical observations. J Clin Oncol 1997;15:230. [PubMed: 8996147]
3. Ferro MA, Gillatt D, Symes MO, Smith PJ. High-dose intravenous estrogen therapy in advanced prostatic carcinoma. Use of serum prostate-specific antigen to monitor response. Urology 1989;34:134. [PubMed: 2476882]
4. Ciezki JP, Reddy CA, Garcia J, Angermeier K, Ulchaker J, Mahadevan A, et al. PSA kinetics after prostate brachytherapy: PSA bounce phenomenon and its implications for PSA doubling time. Int J Radiat Oncol Biol Phys 2006;64:512. [PubMed: 16213667]
5. Schmid HP, McNeal JE, Stamey TA. Observations on the doubling time of prostate cancer. The use of serial prostate-specific antigen in patients with untreated disease as a measure of increasing cancer volume. Cancer 1993;71:2031. [PubMed: 7680277]

6. D'Amico AV, Hanks GE. Linear regressive analysis using prostate-specific antigen doubling time for predicting tumor biology and clinical outcome in prostate cancer. Cancer 1993;72:2638. [PubMed: 7691393]
7. McLaren DB, McKenzie M, Duncan G, Pickles T. Watchful waiting or watchful progression?: Prostate specific antigen doubling times and clinical behavior in patients with early untreated prostate carcinoma. Cancer 1998;82:342. [PubMed: 9445192]
8. D'Amico AV, Moul JW, Carroll PR, Sun L, Lubeck D, Chen MH. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. J Natl Cancer Inst 2003;95:1376. [PubMed: 13130113]
9. Sandler HM, Dunn RL, McLaughlin PW, Hayman JA, Sullivan MA, Taylor JM. Overall survival after prostate-specific-antigen-detected recurrence following conformal radiation therapy. Int J Radiat Oncol Biol Phys 2000;48:629. [PubMed: 11020557]
10. Shulman MJ, Karam JA, Benaim EA. Prostate-specific antigen doubling time predicts response to deferred antiandrogen therapy in men with androgen-independent prostate cancer. Urology 2004;63:732. [PubMed: 15072890]
11. Loberg RD, Fielhauer JR, Pienta BA, Dresden S, Christmas P, Kalikin LM, et al. Prostate-specific antigen doubling time and survival in patients with advanced metastatic prostate cancer. Urology 2003;62 (Suppl 1):128. [PubMed: 14747050]
12. Semeniuk RC, Venner PM, North S. Prostate-specific antigen doubling time is associated with survival in men with hormone-refractory prostate cancer. Urology 2006;68:565. [PubMed: 17010728]
13. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. Jama 2005;294:433. [PubMed: 16046649]
14. Memorial Sloan-Kettering Cancer Center cancer information: prostate nomogram. [Accessed December 2007]. Available at: http://www.mskcc.org/mskcc/html/10088.cfm
15. Mermall H, Sothern RB, Kanabrocki EL, Quadri SF, Bremner FW, Nemchausky BA, et al. Temporal (circadian) and functional relationship between prostate-specific antigen and testosterone in healthy men. Urology 1995;46:45. [PubMed: 7541585]
16. Gulley JL, Figg WD, Steinberg SM, Carter J, Sartor O, Higano CS, et al. A prospective analysis of the time to normalization of serum androgens following 6 months of androgen deprivation therapy in patients on a randomized phase III clinical trial using limited hormonal therapy. J Urol 2005;173:1567. [PubMed: 15821487]
17. Smith MR, Kabbinavar F, Saad F, Hussain A, Gittelman MC, Bilhartz DL, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol 2005;23:2918. [PubMed: 15860850]
18. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, et al. Death in patients with recurrent prostate cancer after radical prostatectomy: prostate-specific antigen doubling time subgroups and their associated contributions to all-cause mortality. J Clin Oncol 2007;25:1765. [PubMed: 17470867]
19. Vollmer RT, Kantoff PW, Dawson NA, Vogelzang NJ. A prognostic score for hormone-refractory prostate cancer: analysis of two cancer and leukemia group B studies. Clin Cancer Res 1999;5:831. [PubMed: 10213219]
20. Stewart AJ, Scher HI, Chen MH, McLeod DG, Carroll PR, Moul JW, et al. Prostate-specific antigen nadir and cancer-specific mortality following hormonal therapy for prostate-specific antigen failure. J Clin Oncol 2005;23:6556. [PubMed: 16170163]

Table 1

Four scenarios of serial PSA values and PSA nadirs following primary local therapy and the corresponding PSADT

	Example 1			Example 2		
	Surgery		RT	Surgery		RT
	PSA	PSA	Nadir-subtracted PSA	PSA	PSA	Nadir-subtracted PSA
Nadir	0	1.00		0	1.00	
1/1/2006	0.20	1.20	0.20	10.00	11.00	10.00
4/1/2006	0.30	1.30	0.30	15.00	16.00	15.00
7/1/2006	0.40	1.40	0.40	20.00	21.00	20.00
10/1/2006	0.60	1.60	0.60	30.00	31.00	30.00
PSADT (mos)	5.8	22.1	5.8	5.8	6.1	5.8

Table 2

Review of literature linking PSADT and time to metastasis, prostate cancer-specific mortality, and all-cause mortality

PSADT cut point	Ref. #	Median time to distant metastasis (yrs)	Median time to prostate cancer-specific mortality (yrs)	Median time to all-cause mortality (yrs)
Surgery				
<3	3 (n=23/329)		5–6 (n=9)	5–6
3–9	3 (n=119/379)		10 (n=38)	10
<10	9 (n=1997)	5		
>15	3 (n=158/379)		Not reached after >16 (n=7)	15
Radiation				
<3	4 (n=8669)		5–6	5–6
<8	7 (n=381)	4		
<12	24*		5*	5*
Nonmetastatic AIPC				
<6	38 (n=201)	1		
6–19	38	2.5		
>19	38	Not reached after >3		

* Most men in this study with a PSADT <12 months had a PSADT <3 months, thus explaining the more rapid disease course than would be typically expected among men with a PSADT <12 months.