Velocity and doubling time of prostate-specific antigen: mathematics can matter

Edward Uchio,[1] Mihaela Aslan,[2,3] John Ko,[2] Carolyn K Wells,[2,3] Krishnan Radhakrishnan,[2] John Concato[2,3]

[1]University of California (Irvine), Irvine, California, USA
[2]Department of Veterans Affairs Connecticut Healthcare System, Clinical Epidemiology Research Center, West Haven Veterans Affairs Medical Center (VAMC), West Haven, Connecticut, USA
[3]Department of Medicine, Yale University School of Medicine, New Haven, Connecticut, USA

Correspondence to
Dr John Concato, VA Connecticut Healthcare System, Clinical Epidemiology Research Center, 950 Campbell Avenue—151B, West Haven, CT 06516, USA; john.concato@yale.edu

Accepted 8 December 2015

ABSTRACT

Changes in prostate-specific antigen (PSA) values are often reported as velocity or doubling time. We compared the association of these two calculations —at the time of PSA failure after primary treatment for prostate cancer—with prostate cancer mortality. From a source population of 1313 US Veterans with prostate cancer, including 623 treated with curative intent, the study population included 242 men experiencing biochemical failure, 81 after surgery and 161 after radiation therapy. Clinically relevant calculations of PSA velocity (linear slope) and PSA doubling time (logarithmic slope) were assessed for their association with 11–16 years of mortality from prostate cancer. Death due to prostate cancer occurred in 52/242 (21.5%) men. Among men receiving surgery, PSA velocity ≥1.0 ng/mL/year was associated with increased prostate cancer mortality (HR=4.2, p value=0.037), whereas doubling time ≤12 months did not confer risk (HR=1.0, p value=0.95). Conversely, among patients receiving radiation therapy, doubling time ≤12 months was associated with increased prostate cancer mortality (HR=2.4, p value=0.049), but velocity did not confer a statistically significant risk (HR=3.8, p value=0.19). When assessing risk of prostate cancer mortality, PSA velocity can be more predictive after surgery and PSA doubling time can be more predictive after radiation therapy.

INTRODUCTION

The effectiveness of prostate-specific antigen (PSA) as a screening test for prostate cancer is controversial,[1–3] yet PSA is regarded as a useful tumor marker[4] after a diagnosis of prostate cancer and during subsequent treatment. Specifically, PSA levels in a patient with prostate cancer would be expected to decrease as tumor burden is reduced or eliminated after primary treatment with surgery or radiation therapy. Conversely, subsequent increases in PSA are often a harbinger of relapse of disease.

After treatment for prostate cancer with curative intent, PSA values can be judged against threshold values used to determine biochemical recurrence, also known as 'PSA failure,' with negative implications regarding prognosis.[4 5] Importantly, the specific threshold values differ, based on whether surgery removes the entire prostate gland, or radiation therapy is directed at the prostate tumor. In clinical care, PSA failure often triggers secondary therapy for prostate cancer, including androgen deprivation or salvage treatment, although such approaches are either not considered curative or have a modest impact on mortality. In research, PSA failure is often used as a surrogate outcome, implying a progression from PSA-defined recurrence to prostate cancer mortality. This sequence of events may not occur, however, for older men with competing causes of mortality.[6]

Rates of change or the 'kinetics' of PSA—including velocity or doubling time—are used as mathematical models to characterize PSA trajectory.[7 8] Such measures can be calculated either before or after the diagnosis of, or treatment for, prostate cancer. In the current research, we examined clinical and methodological issues affecting PSA velocity and doubling time, when determined at the time of PSA failure among men who had received surgery or radiation therapy as primary treatment, and using prostate cancer mortality as the end point of interest.

METHODS

Patients and clinical information

Among 64,545 male Veterans aged ≥50 years receiving care in 1990 at any of nine Department of Veterans Affairs (VA) facilities in New England, 1313 had incident prostate cancer during 1991–1995. Medical records were available for 1270 men (96.7%), and a comprehensive review of these records was combined with a search of death registries. Complete data were available for 1156 (91.0%) men regarding date of treatment ('zero-time'),[9] type of treatment, and date/cause of death (if applicable). The source population included patients who used the VA as their primary site for healthcare (minimizing non-VA testing of PSA).[10] For the current analyses, and from among 623 men treated for curative intent, the study population included the subset of 242 men with PSA failure (see below for definitions) —including 81/225 (36.0%) men with failure after surgery, combined with 161/398 (40.5%) men with failure after radiation therapy. Mortality was assessed from a minimum of 11 years to a maximum of 16 years, based on data from the VA Patient Treatment File, the VA Beneficiary Identifier Locator System, and the National Death Index.[10] Cause of death was assessed and validated by a comprehensive medical record review.[10]

To cite: Uchio E, Aslan M, Ko J, *et al*. *J Investig Med* Published Online First: [*please include* Day Month Year] doi:10.1136/jim-2015-000008

PSA in assessing prognosis

PSA usually becomes undetectable within 6 weeks after prostatectomy, with the major source of PSA (the prostate gland) having been removed. Detectable PSA following prostatectomy most likely implies residual or recurrent prostate cancer. A PSA cut-point of ≥0.2 ng/mL was the most commonly used criterion among 53 definitions reviewed by the American Urological Association (AUA) guideline panel in 2007,[11] but this value can identify PSA failure that is clinically insignificant.[12] Accordingly, a cut-point for failure of ≥0.4 ng/mL has been recommended after radical prostatectomy,[13 14] and this value was used in the current analyses.

After radiation therapy, with prostatic epithelium affected by treatment, a gradual decline in PSA occurs before reaching a post-treatment nadir. Owing to concerns with a prior definition,[15 16] the American Society for Therapeutic Radiation Oncology (ASTRO) now recommends a definition of PSA failure among patients treated with radiation therapy of PSA greater than 'absolute nadir plus 2 ng/mL'[17]; this threshold value was used for the current analyses.

Pragmatic considerations

Several decisions were made, related to pertinent clinical issues, in evaluating the associations of interest. For example, if a research infrastructure had been in place to schedule PSA testing, then measurements might have been spaced regularly in time. Instead, for the current study, 'real-world' PSA values obtained at any point during routine clinical care were assessed. In particular, the PSA values of interest for each patient had to have been obtained between primary treatment and (as applicable) failure time, secondary treatment, or the end of follow-up.

In this context, and to replicate clinical decision-making, calculations were based on two consecutive PSA values at the time of PSA failure. To avoid unstable mathematical results, however, calculations were obtained only when PSA tests were separated by more than 14 days; shorter intervals were considered retesting, with the value closest to failure time used. Each patient's PSA velocity at failure time was then determined as the change in PSA, in units of ng/mL/year. Similarly, PSA doubling time at failure time was determined as the calculated interval for PSA to double in value, in units of months. (Of note, PSA doubling time corresponds to velocity when calculated using the natural logarithm of PSA values over time).

Conceptual considerations

For a given increase in PSA over a fixed time interval (ie, constant velocity), the PSA doubling time is shorter (smaller) with lower initial PSA values, because of the smaller absolute change required for PSA to double in magnitude (eg, a velocity of 1 ng/mL/year corresponds to a doubling time of 12 months when initial PSA=1 ng/mL, vs 24 months when initial PSA=2 ng/mL). Accordingly, after prostatectomy, when the PSA level is typically very low, the predictive utility of a doubling time threshold can be reduced. Conversely, for a given doubling time, the PSA velocity is higher (larger) with larger initial PSA values, because of the larger absolute change in PSA per unit of time (eg, a doubling time of 12 months corresponds to a velocity of 4 ng/mL/year when initial PSA=4 ng/mL, vs 2 ng/mL/year when initial PSA=2 ng/mL). Accordingly, after radiation therapy, when the PSA level is usually relatively high, the predictive utility of a velocity threshold can be reduced. Also of note, the current analysis assumes a therapeutic nil hypothesis[9] for the secondary treatment of prostate cancer. This approach includes a clinical assumption that any (potential) impact of hormonal therapy on prostate cancer mortality would not be affected by the modality of primary treatment.

Statistical analysis

Each patient's values for PSA velocity and doubling time at failure time were compared to thresholds for velocity of ≥1 ng/mL/year, and for doubling time of ≤12 months, as trajectories that implied a worse ('poor') prognosis. In subsequent analyses, and separately for men receiving surgery or radiation therapy, the association of PSA velocity or doubling time with prostate cancer mortality (up to 16 years) was assessed using proportional hazard analysis;

Table 1 Baseline characteristics among men receiving surgery or radiation therapy for curative intent and with complete data (N=623)

Characteristic	Surgery (N=225) n (%)	Radiation (N=398) n (%)	p Value*	Both groups (N=623) n (%)
Age (years)			<0.001	
50–59	19 (8.4)	8 (2.0)		27 (4.3)
60–69	143 (63.6)	134 (33.7)		277 (44.5)
70–79	63 (28.0)	242 (60.8)		305 (49.0)
≥80	0 (0)	14 (3.5)		14 (2.2)
Race/ethnicity			0.83	
African-American	25 (11.1)	42 (10.6)		67 (10.8)
All other	200 (88.9)	356 (89.4)		556 (89.2)
Comorbidity (Charlson score)			<0.001	
0 (none)	91 (40.4)	103 (25.9)		194 (31.1)
1 (mild)	70 (31.1)	131 (32.9)		201 (32.3)
2 (moderate)	47 (20.9)	93 (23.4)		140 (22.5)
≥3 (severe)	17 (7.6)	71 (17.8)		88 (14.1)
Anatomic stage			0.04	
Localized (T1, T2)	221 (98.2)	374 (94.0)		595 (95.5)
Regional (≥T3)	4 (1.8)	24 (6.0)		28 (4.5)
Differentiation (Gleason score)			0.046	
Well (2–4)	57 (25.3)	81 (20.4)		138 (22.2)
Moderate (5–7)	147 (65.3)	254 (63.8)		401 (64.4)
Poor (8–10)	21 (9.4)	63 (15.8)		84 (13.5)
Baseline PSA† (ng/mL)			<0.001	
0 to <4.0	39 (17.3)	38 (9.5)		77 (12.4)
4.0 to <10.0	105 (46.7)	157 (39.5)		262 (42.1)
10.0 to <20.0	49 (21.8)	118 (29.6)		167 (26.8)
≥20.0	29 (12.9)	84 (21.1)		113 (18.1)
Unknown	3 (1.3)	1 (0.3)		4 (0.6)

*p Value is for the χ^2 test comparing patients receiving surgery versus radiation therapy.
†Of note, each patient had an average of 8.2 PSA tests done from zero-time to failure.
PSA, prostate-specific antigen.

Table 2 Association of velocity* or doubling time† with prostate cancer mortality among men with PSA failure and pertinent data (N=233; see text for details)

	HR	p Value	95% CI
Surgery patients (N=78)			
High velocity	4.2	0.037	1.1 to 16.4
Fast doubling time	1.0	0.95	0.27 to 4.0
Radiation therapy patients (N=155)			
High velocity	3.8	0.19	0.52 to 27.7
Fast doubling time	2.4	0.049	1.0 to 5.8

*Calculation of ≥1.0 ng/mL/year used to define high velocity.
†Calculation of ≤12 months used to define fast doubling time.
PSA, prostate-specific antigen.

HRs, p values, and 95% CIs were reported. As sensitivity analyses, other common thresholds for PSA velocity and doubling time were also evaluated.

RESULTS

As reported in earlier research,[18] among 623 men receiving primary treatment with curative intent, those receiving surgery tended to be younger and have less comorbidity and less extensive disease (anatomic stage, histological grade, and baseline PSA values) compared with men receiving radiation therapy (table 1). Data from the medical record review indicated that secondary treatment after PSA failure was initiated in 40/81 (49.4%) men after surgery and in 75/161 (46.6%) men after radiation therapy.

The associations of velocity and doubling time with prostate cancer mortality are shown in table 2. Of note, the sample size was reduced from N=242 to 233 participants, after excluding three men after surgery, and six men after radiation therapy, without two PSA values at the time of failure. During follow-up, cause-specific mortality was documented in 52/242 (21.5%) men, 10/81 (12.3%) after surgery and 42/161 (26.1%) after radiation therapy. The median time to death was 7.3 years after surgery and 5.6 after radiation therapy.

Among patients receiving surgery, men with a PSA velocity greater than or equal to, versus less than, 1.0 ng/mL/year were more than four times more likely to die of prostate cancer (HR=4.2, p value=0.037, 95% CI 1.1 to 16.4), whereas doubling time less than or equal to, versus greater than, the threshold of 12 months did not confer risk of death (HR=1.0, p value=0.95, 95% CI 0.27 to 4.0).

Among patients receiving radiation therapy, men with a PSA doubling time less than or equal to, versus greater than, 12 months were almost 2½ times more likely to die of prostate cancer (HR=2.4, p value=0.049, 95% CI 1.0 to 5.8), whereas increased velocity did not confer a statistically significant impact (HR=3.8, p value=0.19, 95% CI 0.52 to 27.7).

Figure 1 shows results for representative patients in the study. After surgery, although patients A and B both have

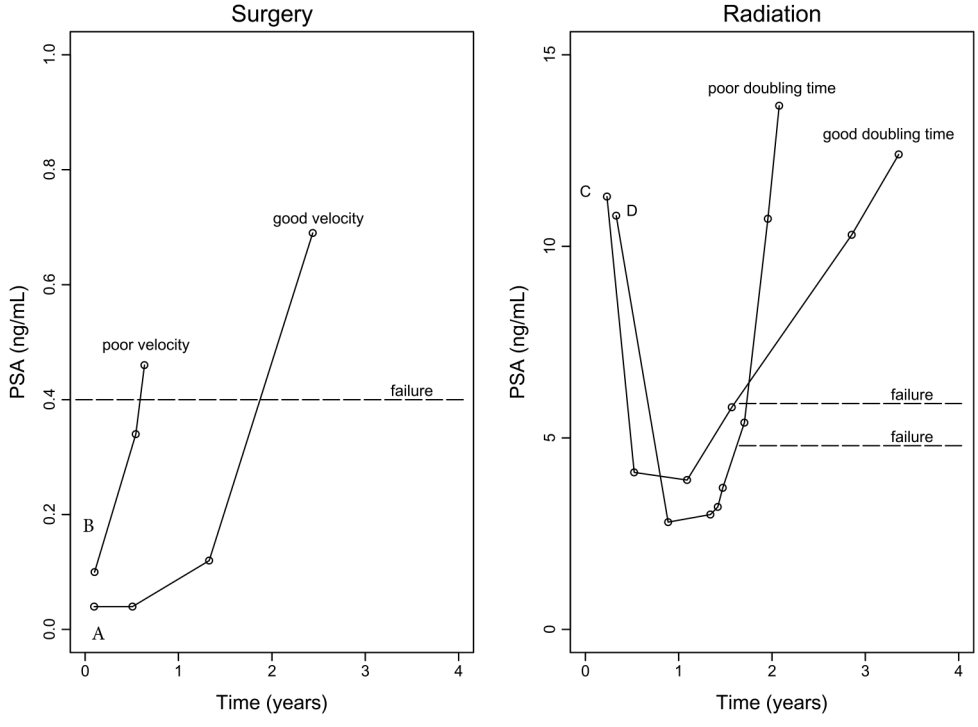

Figure 1 Prostate-specific antigen (PSA) velocity and doubling time in representative situations after primary treatment. Surgical scenarios include (A) 'good' velocity=0.51 ng/mL/year (and 'poor' doubling time=5.3 months) in a patient who lived and (B) 'poor' velocity=1.3 ng/mL/year (and 'poor' doubling time=2.6 months) in a patient who died. Radiation scenarios include (C) 'good' doubling time=18.3 months (and 'poor' velocity=3.5 ng/mL/year) in a patient who lived and (D) 'poor' doubling time=5.1 months (and 'poor' velocity=7.3 ng/mL/year) in a patient who died. Horizontal dashed lines indicate treatment-based and patient-specific (as appropriate) thresholds for biochemical failure; 'died' refers to death due to prostate cancer.

'poor' doubling times, the velocity threshold of ≥1 ng/mL/year (patient B) was linked with prostate cancer mortality. After radiation therapy, although patients C and D both have 'poor' velocity, the doubling time threshold of ≤12 months (patient D) was linked with prostate cancer mortality.

Sensitivity analyses using threshold velocities of 0.75, 1.5, and 2.0 ng/mL/year, and threshold doubling times of 3, 6, and 24 months, found a similar pattern (data not shown). Results were also comparable when secondary treatment was added to the model (data not shown).

DISCUSSION

On the basis of patterns of PSA change, definitions of PSA failure, and calculations of velocity and doubling time, our study suggests that post-treatment associations of PSA kinetics with prostate cancer mortality can vary considerably. We found (see table 2) that velocity was more predictive than doubling time among men after surgery, and doubling time outperformed velocity among men after radiation therapy. Any given patient may deviate from these patterns for various reasons, but mathematical properties have been demonstrated to affect results obtained in a real-world clinical setting.

The differing mathematical properties of velocity and doubling time provide the opportunity for calculations with discordant prognostic implications. As shown by representative patients (figure 1), the predictive value of a doubling time threshold can be reduced in post-prostatectomy situations, when low PSA values are typically observed. Conversely, the predictive value of a velocity threshold can be reduced in postradiation situations, when higher PSA values are typically observed.

Evaluating the literature on PSA kinetics is beyond the scope of this work. As an overview, however, articles can be subdivided conceptually into studies evaluating changes in PSA over various time periods: prior to diagnosis; after diagnosis but before treatment; after initiating active surveillance; after primary treatment; after biochemical failure; or after secondary treatment. In addition, studies can employ various mathematical calculations of PSA kinetics, but not necessarily comparing velocity and doubling time. The study population may include men postsurgery or postradiation therapy or both—with or without comparing results across treatment groups. Thresholds for abnormal values can be established in advance, or identified during analyses (with a risk of overfitting the data such that the results are not reproducible).

Various review articles address aspects of our research topic, such as one stating that 'the calculation of PSA velocity and doubling time is far from straightforward'[19]—a point of emphasis we noted in the Methods section. Challenges include the particular mathematical construct selected, as well as the decision of how to select among numerous PSA values when tests are obtained at irregular intervals. Although our focus differs from prior research articles, some reports provide specific insight on the topic we studied. For example, and consistent with our findings, one study[20] of men after radical prostatectomy found that PSA velocity, but not doubling time, was associated with a positive bone scan as the outcome of interest.

Limitations of the current research include a modest number of prostate cancer deaths, and selecting the two most common (among various) options for assessing PSA kinetics (ie, we did not compare numerous definitions of velocity and doubling time).[19] Also, from a broad perspective, the impact of PSA trajectory should be considered along with other clinical and laboratory factors, and our analysis recognizes that hormonal treatment is not considered to be curative. Among strengths of the current work, the study included multiple sites and real-world data collection, as well as 'expected' rates of surgery, radiation, secondary treatment, and mortality. Importantly, we assessed popular calculations of velocity and doubling time simultaneously. As another methodological strength, most prior studies had not simultaneously assessed patient groups receiving surgery and radiation therapy, whereas we did. Finally, the outcome of interest was cause-specific mortality, as confirmed by chart review.

Our findings provide insight on how biology affects clinical inferences that are made on the basis of mathematical calculations of PSA kinetics. In the setting of patients being followed after primary treatment for prostate cancer, the current results inform clinicians that PSA velocity and doubling time are not interchangeable. When assessed at the time of biochemical failure, and when evaluated for a relationship with prostate cancer mortality, PSA velocity can be more predictive after surgery and PSA doubling time can be more predictive after radiation therapy.

Funding This research was supported by the VA Office of Research and Development. MA, JC, JK, and KR are supported by the VA Cooperative Studies Program.

Competing interests None declared.

Ethics approval VA Connecticut Human Studies Subcommittee.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Andriole GL, Crawford ED, Grubb RL III, *et al*. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360:1310–9.
2 Schroder FH, Hugosson J, Roobol MJ, *et al*. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320–8.
3 Guide to Clinical Preventive Services, 2014. June 2014. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/guide/index.html.
4 Lange PH, Ercole CJ, Lightner DJ, *et al*. The value of serum prostate specific antigen determinations before and after radical prostatectomy. *J Urol* 1989;141:873–9.
5 American Society for Therapeutic Radiology and Oncology Consensus Panel. Consensus statement: guidelines for PSA following radiation therapy. *Int J Radiat Oncol Biol Phys* 1997;37:1035–41.
6 Albertsen PC, Hanley JA, Gleason DF, *et al*. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. *JAMA* 1998;280:975–80.
7 Carter HB, Pearson JD, Metter EJ, *et al*. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA* 1992;267:2215–20.
8 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;71:2031–40.
9 Concato J. Challenges in prognostic analysis. *Cancer* 2001;91:1607–14.
10 Concato J, Jain D, Uchio E, *et al*. Molecular markers and death from prostate cancer. *Ann Intern Med* 2009;150:595–603.
11 Cookson MS, Aus G, Burnett AL, *et al*. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the

American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. *J Urol* 2007;177:540–5.
12 Jhaveri FM, Zippe CD, Klein EA, *et al*. Biochemical failure does not predict overall survival after radical prostatectomy for localized prostate cancer: 10-year results. *Urology* 1999;54:884–90.
13 Amling CL, Bergstralh EJ, Blute ML, *et al*. Defining prostate specific antigen progression after radical prostatectomy: what is the most appropriate cut point?. *J Urol* 2001;165:1146–51.
14 Stephenson AJ, Kattan MW, Eastham JA, *et al*. Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. *J Clin Oncol* 2006;24:3973–8.
15 Kuban D, Thames H, Levy L, *et al*. Failure definition-dependent differences in outcome following radiation for localized prostate cancer: can one size fit all? *Int J Radiat Oncol Biol Phys* 2005;61:409–14.
16 Gretzer MB, Trock BJ, Han M, *et al*. A critical analysis of the interpretation of biochemical failure in surgically treated patients using the American Society for Therapeutic Radiation and Oncology criteria. *J Urol* 2002;168:1419–22.
17 Roach M III, Hanks G, Thames H Jr, *et al*. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006;65:965–74.
18 Uchio EM, Aslan M, Wells CK, *et al*. Impact of biochemical recurrence in prostate cancer among US veterans. *Arch Intern Med* 2010;170:1390–5.
19 Vickers AJ, Brewster SF. PSA velocity and doubling time in diagnosis and prognosis of prostate cancer. *Br J Med Surg Urol* 2012;5:162–8.
20 Dotan Z, Bianco FJ, Rabbani F, *et al*. Pattern of prostate-specific antigen (PSA) failure dictates the pattern of a positive bone scan in patients with an increasing PSA after radical prostatectomy. *J Clin Oncol* 2005;23:1962–8.