Pretreatment Prostate-Specific Antigen (PSA) Velocity and Doubling Time Are Associated With Outcome but Neither Improves Prediction of Outcome Beyond Pretreatment PSA Alone in Patients Treated With Radical Prostatectomy

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ABSTRACT

Purpose

Controversy exists as to whether current pretreatment prostate-specific antigen (PSA) dynamics enhance outcome prediction in patients undergoing treatment for prostate cancer. We assessed whether pretreatment PSA velocity (PSAV) or doubling time (PSADT) predicted outcome in men undergoing radical prostatectomy and whether any definition enhanced accuracy of an outcome prediction model.

Patients and Methods

The cohort included 2,938 patients with two or more PSA values before radical prostatectomy. Biochemical recurrence (BCR) occurred in 384 patients, and metastases occurred in 63 patients. Median follow-up for patients without BCR was 2.1 years. We used univariate Cox proportional hazards regression to evaluate associations between published definitions of PSADT and PSAV with BCR and metastasis. Predictive accuracy was assessed using the concordance index.

Results

On univariate analysis, two of 12 PSADT and four of 10 PSAV definitions were univariately associated with both BCR and metastasis ($P < .05$). One PSADT and one PSAV definition had a higher predictive accuracy for BCR over PSA alone, and four PSAV definitions improved prediction of metastasis. However, the improvements in predictive accuracy were small, associated with wide CIs, and markedly reduced if additional predictors of stage and grade were included alongside PSA. Modeling with random variables suggests that similar results would be expected by chance.

Conclusion

We found no clear evidence that any definition of PSA dynamics substantially enhances the predictive accuracy of a single pretreatment PSA alone.

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INTRODUCTION

Changes in prostate-specific antigen (PSA) over time, PSA dynamics, have been advocated for risk stratification of prostate cancer across the spectrum of the disease, including prediction of response to curative therapy.^{1,2} Recently, several studies have investigated the best mathematical method to calculate PSA dynamics, whether PSA doubling time (PSADT) or PSA velocity (PSAV).³⁻⁵ However, no study has compared the various published definitions for calculating PSAV and PSADT on the same cohort of patients. Moreover, although many authors have investigated whether there is a statistical association between outcome and either PSAV or PSADT, studies are lacking as to whether dynamics

improve our ability to predict outcome over and above either a single PSA measurement or a multivariable model including stage, grade, and PSA.^{6,7}

In this study, our aims were three-fold. First, we aimed to assess which pretreatment definitions of PSAV and PSADT are associated with outcome after radical prostatectomy. Second, we aimed to determine whether any PSA dynamic definition improves predictive accuracy beyond that of a single preoperative PSA measurement. Third, we aimed to determine whether any PSA dynamic definition improves the accuracy of the established clinical predictors of outcome (ie, tumor grade assessed by biopsy Gleason score, clinical staged assessed by digital rectal examination, and pretreatment PSA).

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PATIENTS AND METHODS

Patients

Using data prospectively collected in our database, we identified 3,112 patients with clinically localized prostate cancer who underwent radical prostatectomy at our institution between January 1989 and October 2006 and who had two or more PSA values 2 or more months apart recorded before intervention. Intervention was defined as the earliest treatment modality that would affect PSA, including hormone manipulation, 5 α -reductase inhibitors, transurethral resection of prostate, and radical prostatectomy. PSA values within 4 weeks after prostate biopsy were excluded. Patients who had received neoadjuvant chemotherapy ($n = 65$) or who underwent salvage prostatectomy ($n = 109$) were excluded from the analysis. However, 240 patients who received neoadjuvant hormone manipulation were included because this treatment has been shown not to change the 5-year biochemical recurrence (BCR) rate.⁸ For such patients, only PSA values up to the commencement of hormonal manipulation were used. The single PSA value used in the predictive model was the final PSA value before intervention used in the dynamic calculation, which was not necessarily the last PSA before diagnosis or treatment.

Patients were generally observed for disease recurrence with serum PSA determinations and clinical assessments every 3 months for 3 years, semiannually during the next 2 years, and annually thereafter. BCR was defined as either postoperative PSA value ≥ 0.10 ng/mL and a confirmatory increase or postoperative PSA ≥ 0.10 ng/mL and receiving salvage treatment (eg, radiotherapy, hormonal manipulation, or chemotherapy). Before March 1996, the PSA cutoff for BCR was ≥ 0.4 ng/mL, rather than ≥ 0.1 ng/mL, in accordance with the PSA assays used in our institution.⁹ Of the 2,938 eligible patients, 384 developed BCR. Metastases occurred in 63 patients. At last follow-up, 75 patients had died, 11 of them from prostate cancer. The median follow-up times for patients free of recurrence and those free of metastasis or prostate cancer-specific death were 2.1 and 2.9 years, respectively, from radical prostatectomy. This apparently short follow-up is related to the large number of patients treated in recent years; 512 patients were known to be free of recurrence and 761 patients were known to be free of metastasis or prostate cancer-specific death at 5 years after surgery.

PSA Dynamics Definitions

We used 20 definitions of PSA dynamics, including 11 PSADT¹⁰⁻²¹ and seven PSAV^{1,2,16,18,22-24} definitions used as predictive tools in published literature and the two dynamics tools from the Memorial Sloan-Kettering Cancer Center Web site.^{25,26} The definitions are detailed in the Appendix Table A1 (online only). We included definitions used at all stages of disease from diagnosis to hormone-refractory disease, regardless of the primary treatment modality. We recorded, where specified, time intervals between PSA values, time intervals between first and last PSA value, and minimum number of PSA values used to calculate PSA dynamic. Mathematical manipulation of the PSA value, such as log values, logistic regression, and linear regression, was also recorded.

Our application of the definition was exactly as published, except for published definitions where the first PSA was after treatment, for which we replaced first post-treatment PSA with last PSA before intervention and worked backwards. For example, Freedland et al¹² used the first PSA at post-prostatectomy BCR and used all PSA values at least 3 months apart over the next 2 years. We used the last PSA before intervention and all PSA values at least 3 months apart in the 2 years before this PSA. For the definitions by Lee et al¹⁴ (The University of Texas M. D. Anderson Cancer Center [M. D. Anderson] 1 and 2), we used two methods because the published definition uses the first two values after BCR. For the first definition, we used the first two available values regardless of how long before treatment they occurred, and for the second definition, we used the last two values before treatment.

We truncated PSADT values greater than 240 months at 240 months, except for the Freedland et al¹² definition, which was truncated at 100 months as specified in the definition. Calculated negative values remained negative but were truncated at -240 months.

For the D'Amico et al¹ A and D'Amico et al² B PSAV definitions, we analyzed the PSAV not only as continuous variables, but also catego-

rized as more than 2.0 ng/mL/yr, in accord with the analyses in the original publications. Therefore, we tested a total of 22 definitions of PSA dynamics.

Statistical Methods

Univariate Cox proportional hazards regression was used to calculate the association between PSA dynamics and either time to BCR or time to metastasis after radical prostatectomy. To measure predictive accuracy, we used the concordance index (c-index), which can be used to quantify discrimination for survival time data and has a similar interpretation as the area under the receiver operating curve. The c-index uses values from 0.5 to 1, with 0.5 indicating lack of discrimination (no better than a coin flip) and 1.0 indicating perfect accuracy. To determine the enhancement in predictive accuracy associated with each PSA dynamic beyond that of PSA alone, we evaluated the c-index of PSA alone, PSA plus each PSA dynamic, and PSA dynamic plus a published multivariable predictive model (Kattan preoperative nomogram),⁶ which includes PSA, clinical stage, and biopsy Gleason grade. We corrected for over-fit and obtained CIs for c-indices using bootstrap methods. Because the definitions required particular numbers of PSA measurements taken at particular intervals, most definitions were not calculable for all patients in our study cohort. Therefore, to allow for comparison between PSA alone and PSA plus each PSA dynamic, we estimated c-indices in the subset of patients for whom the respective dynamic was calculable. Hence, these estimates for different definitions are not directly comparable. All statistical analyses were conducted using Stata 9.2 (StataCorp, College Station, TX). The study was conducted under the Health Insurance Portability and Accountability Act guidelines and received institutional review board approval.

RESULTS

Patient characteristics are listed in Table 1, and PSA dynamics results are listed in Table 2. Seventy-three percent of patients (2,131 of 2,938 patients) had more than two pretreatment PSA values, with 21% ($n = 626$) having more than five PSA values, that could be used in dynamic calculations. Depending on the definition, the percentage of patients for whom a dynamic could be calculated varied from 30% to

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	No. of Patients (N = 2,938)	%
Age at surgery, years		
Median	60	
Interquartile range	55-65	
Total PSA, ng/mL		
Median	5.62	
Interquartile range	4.14-8.10	
Clinical stage $\geq$ T2 ($n = 2,854$)	1,127	39
Biopsy Gleason grade ($n = 2,537$)		
≤ 6	1,519	52
7	832	28
≥ 8	186	6
Pathology Gleason grade ($n = 2,759$)		
≤ 6	1,118	38
7	1,436	49
≥ 8	205	7
Extracapsular extension ($n = 2,884$)	797	28
Seminal vesicle invasion ($n = 2,907$)	178	6
Positive surgical margins ($n = 2,913$)	517	18
Lymph node dissection performed	2,594	88
Lymph node involvement	119	4

Abbreviation: PSA, prostate-specific antigen.

Table 2. Summary of PSA Doubling Time and Velocity Definitions

Definition	Patients With Calculable Dynamic		Doubling Time (months)		Velocity (ng/mL/yr)	
	No.	%	Median	Interquartile Range	Median	Interquartile Range
Doubling time						
MSKCC ²⁵	2,938	100	23	5-52		
M. D. Anderson 1 ¹⁴	2,929	100	6	-2-14		
Shulman et al ¹⁷	2,923	99	7	2-13		
M. D. Anderson 2 ¹⁴	2,904	99	3	-6-10		
Ward et al ²⁰	2,558	87	10	-9-25		
Freedland et al ¹²	2,338	80	17	0-35		
Trapasso et al ²¹	2,131	73	30	10-59		
Egawa et al ¹¹	2,000	68	34	16-65		
Hanks et al ¹³	1,605	55	38	18-68		
Stephenson et al ¹⁹	1,499	51	9	-10-22		
Smith et al ¹⁸	1,261	43	43	25-76		
D'Amico et al ¹⁰	967	33	39	25-62		
Velocity						
MSKCC ²⁶	2,938	100			0.18	0.03-0.41
Thompson et al ²⁴	2,899	99			0.21	0.00-0.47
D'Amico et al ¹ A	2,630	90			1.01	-1.74-4.15
Sengupta et al ¹⁶	2,338	80			0.23	0.00-0.48
Rozhansky et al ²²	2,128	72			0.68	-3.21-5.60
Thiel et al ²³	1,457	50			0.69	0.34-1.38
Smith et al ¹⁸	1,261	43			0.16	0.08-0.27
D'Amico et al ² B	876	30			1.15	-0.36-3.13

Abbreviations: PSA, prostate-specific antigen; MSKCC, Memorial Sloan-Kettering Cancer Center; M. D. Anderson, The University of Texas M. D. Anderson Cancer Center.

100%. Less than one third of our study cohort had a calculable dynamic for two definitions, D'Amico et al¹⁰ PSADT and D'Amico et al² B PSAV. Four PSADT and three PSAV definitions were calculable for at least 90% of our study cohort.

Results of univariate analyses are listed in Table 3. A single PSA alone was highly associated with both recurrence ($P < .001$) and metastasis ($P = .002$), with c-indices in the entire study cohort of 0.714 and 0.688, respectively. Eleven definitions were significantly associated with BCR or metastasis on univariate analysis, although in one definition, a longer PSADT paradoxically predicted shorter survival (M. D. Anderson 1: hazard ratio for metastasis = 1.25 for each additional month). There were two PSADT and four PSAV definitions associated with both BCR and metastasis.

The predictive accuracies of a single PSA alone, each dynamic definition, and a single PSA plus each dynamic definition are listed in Table 4. For prediction of BCR, the D'Amico et al¹⁰ PSADT and Smith et al¹⁸ PSAV definitions enhanced the predictive accuracy beyond that of PSA alone. In both cases, the increment was small and associated with wide CIs. For prediction of metastasis, Thiel et al,²³ D'Amico et al² B, Sengupta et al,¹⁶ and Smith et al¹⁸ PSAV definitions were implicated to have a higher predictive accuracy. Again, improvements in accuracy were small and associated with wide CIs. Therefore, we interpret our findings as providing insufficient evidence that PSA dynamics can enhance prediction of BCR or metastasis compared with a prediction model based on a single PSA value alone.

We performed various sensitivity analyses. We repeated all analyses excluding the 240 patients who received neoadjuvant hormonal therapy with no important changes in our results. Because our cohort included various age groups, we included age as a covariate

in all analyses with no substantive difference in results when adjusting for age. Although PSA dynamics may not be of value overall, it is plausible that they may be predictive in subgroups, such as men at low risk. We conducted sensitivity analyses in two low-risk groups (low PSA: 655 men with PSA < 4 ng/mL, with 35 BCR and eight metastasis events; and low grade and moderate PSA: 1,362 men with biopsy Gleason score ≤ 6 and PSA < 10 ng/mL, with 47 BCR and seven metastasis events). In the low-PSA subgroup, no dynamic was significantly associated with metastasis, and only one dynamic (Thiel et al²³ PSAV) was significantly associated with BCR. In the low-grade and moderate-PSA subgroup, no dynamic was significantly associated with BCR, whereas only Thiel et al²³ PSAV had a c-index for metastasis more than 0.6. In all instances, however, the estimates are based on few events, and the CIs around the enhancements are wide; nonetheless, we did not see any obvious evidence that PSA dynamics are useful in low-risk patients.

For the outcome of metastasis, we compared the accuracy of the c-index of the Kattan preoperative nomogram⁶ to that of the standard nomogram plus each dynamic definition that potentially increased the predictive accuracy of a single PSA alone in Table 4 (Sengupta et al¹⁶ PSAV, Thiel et al²³ PSAV, Smith et al¹⁸ PSAV, and D'Amico et al² B PSAV). None of these definitions importantly enhanced the predictive accuracy of the Kattan preoperative nomogram. For example, D'Amico et al² B PSAV, which enhanced the predictive accuracy of PSA alone by 0.03, enhanced the predictive accuracy of the standard preoperative nomogram by only 0.012.

In our analyses, we tested 22 hypotheses for each end point. Given this multiple testing, we evaluated whether the positive results we observed were compatible with chance. We created random new

Table 3. Associations Between Different Definitions of PSA Dynamics and Outcomes After Radical Prostatectomy in Univariate Cox Proportional Hazards Regression

Definition	No. of Patients	Outcome: Biochemical Recurrence				Outcome: Metastasis			
		No. of Events	Hazard Ratio	95% CI	P	No. of Events	Hazard Ratio	95% CI	P
PSA	2,938	384	1.25	1.21 to 1.29	< .001	63	1.16	1.06 to 1.27	.002
Doubling time									
MSKCC ²⁵	2,938	384	0.91	0.83 to 1.01	.07	63	0.81	0.63 to 1.04	.09
M. D. Anderson ^{1 14}	2,929	382	1.01	0.91 to 1.11	.9	62	1.25	1.02 to 1.52	.03*
Shulman et al ¹⁷	2,923	382	1.01	0.91 to 1.11	.9	62	1.09	0.87 to 1.37	.5
M. D. Anderson ^{2 14}	2,904	381	0.96	0.87 to 1.06	.4	63	1.20	0.95 to 1.51	.12
Ward et al ²⁰	2,558	293	0.97	0.86 to 1.09	.6	48	0.88	0.65 to 1.21	.4
Freedland et al ¹²	2,338	253	0.83	0.72 to 0.95	.007*	43	0.92	0.68 to 1.25	.6
Trapasso et al ²¹	2,131	259	0.88	0.78 to 0.99	.03*	42	0.75	0.57 to 0.98	.03*
Egawa et al ¹¹	2,000	226	0.92	0.81 to 1.05	.2	35	0.78	0.57 to 1.07	.12
Hanks et al ¹³	1,605	164	0.90	0.78 to 1.04	.15	23	0.76	0.55 to 1.06	.11
Stephenson et al ¹⁹	1,499	184	1.13	0.98 to 1.31	.08	32	0.96	0.68 to 1.36	.8
Smith et al ¹⁸	1,261	126	0.87	0.74 to 1.02	.08	17	0.72	0.50 to 1.03	.08
D'Amico et al ¹⁰	967	113	0.56	0.42 to 0.75	< .001*	15	0.33	0.11 to 0.97	.04*
Velocity									
MSKCC ²⁶	2,938	384	0.97	0.90 to 1.05	.4	63	0.99	0.86 to 1.13	.8
Thompson et al ²⁴	2,899	377	0.98	0.90 to 1.06	.5	62	0.99	0.85 to 1.15	.9
D'Amico et al ^{1 A}	2,630	345	1.03	0.93 to 1.14	.6	56	1.10	0.86 to 1.43	.4
> 2.0 ng/mL/yr	1,045/2,630†	345	1.71	1.38 to 2.11	< .001*	56	1.42	0.84 to 2.40	.19
Sengupta et al ¹⁶	2,338	253	1.27	1.15 to 1.41	< .001*	43	1.15	0.86 to 1.53	.3
Rozhansky et al ²²	2,128	295	1.10	1.02 to 1.18	.013*	48	1.01	0.89 to 1.15	.9
Thiel et al ²³	1,457	160	1.36	1.28 to 1.44	< .001*	23	1.53	1.34 to 1.76	< .001*
Smith et al ¹⁸	1,261	126	1.26	1.15 to 1.37	< .001*	17	1.28	1.09 to 1.50	.003*
D'Amico et al ^{2 B}	876	90	1.16	1.08 to 1.25	< .001*	16	1.28	1.14 to 1.44	< .001*
> 2.0 ng/mL/yr	323/876†	90	2.16	1.42 to 3.27	< .001*	16	3.24	1.12 to 9.35	.03*

NOTE. Hazard ratios are shown for a standard deviation increase in the PSA dynamic.

Abbreviations: PSA, prostate-specific antigen; MSKCC, Memorial Sloan-Kettering Cancer Center; M. D. Anderson, The University of Texas M. D. Anderson Cancer Center.

*Significant association.

†No. above the cutoff/total No.

variables by adding noise to PSA in our data, fixing the correlation close to that typically observed between PSA and PSA dynamics. After a simulation experiment, we calculated that, for 22 different variables, as in our data set, the expected number of random variables expected to enhance predictive accuracy for BCR and metastasis would be approximately one and approximately three, respectively. It is apparent that our finding of two and four enhanced predictions could have occurred purely by chance.

DISCUSSION

PSA dynamics measured before radical prostatectomy have been shown to be associated with disease recurrence or clinical progression, and it has been suggested that they aid prediction of outcome after radical prostatectomy.^{1,11,27} We propose that, for a PSA dynamic to be of value for clinical decision making or patient counseling, it must improve predictive accuracy beyond that of a single pretreatment PSA alone. Otherwise, there is no reason for a clinician to access the patient's prior PSA values and calculate a PSA dynamic; the clinician can simply use the most recent PSA value for decision making. In our current study, although half of the pretreatment PSA dynamics definitions showed a univariate association with outcome after radical prostatectomy, only a minority increased predictive accuracy beyond

that of a single pretreatment PSA. These improvements were small with wide CIs. We believe these improvements could have been produced by chance, given the large number of definitions tested. Moreover, of four velocity definitions that seemed to add to the predictive value of a single PSA, none substantially improved the accuracy of a model that controlled preoperative stage and grade, as well as PSA, using the Kattan preoperative nomogram.

In previous studies, several of the definitions were reported to be associated with outcome after radical prostatectomy. Only some of those associations were replicated in our study. Similar to D'Amico et al, we found PSAV more than 2 ng/mL/yr to be associated with BCR (D'Amico et al^{1 A} and D'Amico et al^{2 B}) and metastases (D'Amico et al^{2 B}). Our findings also confirmed that the Sengupta et al¹⁶ and Thiel et al²³ PSAV definitions are associated with BCR or metastases ($P < .001$). For the PSADT definitions of Egawa et al,¹¹ Hanks et al,¹³ and Stephenson et al,¹⁹ however, we were unable to confirm associations with outcome, despite our study having greater statistical power than the original studies. We have also published a systematic review²⁸ showing that absolutely no prior studies have reported whether prediction of outcome after surgery was enhanced when PSA dynamics were added to a model incorporating PSA alone.

Both PSADT and PSAV are influenced by the method of calculation,^{3,29} and we noted important variation between definitions. For

Table 4. Predictive Accuracy for Each Definition of PSA Dynamics Alone, Single PSA Alone, and PSA Dynamics Plus Single PSA Combined

		Outcome: Biochemical Recurrence (concordance index)			Outcome: Metastasis (concordance index)		
Definition	No. of Patients	Dynamic Alone	PSA Alone*	PSA Plus PSA Dynamic	Dynamic Alone	PSA Alone*	PSA Plus PSA Dynamic
Doubling time							
MSKCC ²⁵	2,938	0.552	0.714	0.699	0.534	0.688	0.649
M. D. Anderson 1 ¹⁴	2,929	0.484	0.714	0.707	0.550	0.686	0.684
Shulman et al ¹⁷	2,923	0.448	0.714	0.714	0.474	0.682	0.659
M. D. Anderson 2 ¹⁴	2,904	0.496	0.712	0.704	0.557	0.688	0.688
Ward et al ²⁰	2,558	0.506	0.723	0.714	0.507	0.650	0.622
Freedland et al ¹²	2,338	0.532	0.731	0.699	0.495	0.720	0.661
Trapasso et al ²¹	2,131	0.579	0.714	0.704	0.569	0.675	0.653
Egawa et al ¹¹	2,000	0.587	0.718	0.702	0.591	0.756	0.693
Hanks et al ¹³	1,605	0.601	0.715	0.697	0.600	0.647	0.639
Stephenson et al ¹⁹	1,499	0.543	0.722	0.715	0.513	0.657	0.641
Smith et al ¹⁸	1,261	0.623	0.714	0.695	0.668	0.714	0.710
D'Amico et al ¹⁰	967	0.671	0.712	0.733 (0.683 to 0.785)†	0.639	0.684	0.677
Velocity							
MSKCC ²⁶	2,938	0.404	0.714	0.707	0.403	0.688	0.680
Thompson et al ²⁴	2,899	0.414	0.715	0.704	0.411	0.684	0.680
D'Amico et al ¹ A	2,630	0.587	0.713	0.710	0.609	0.656	0.648
> 2.0 ng/mL/yr	1,045/2,630‡	0.574	0.713	0.681	0.596	0.656	0.642
Sengupta et al ¹⁶	2,338	0.615	0.731	0.725	0.667	0.720	0.724 (0.584 to 0.896)†
Rozhansky et al ²²	2,128	0.570	0.701	0.700	0.574	0.644	0.639
Thiel et al ²³	1,457	0.719 (0.672 to 0.764)†	0.714	0.706	0.744 (0.522 to 0.945)†	0.713	0.731 (0.555 to 0.957)†
Smith et al ¹⁸	1,261	0.663	0.714	0.725 (0.675 to 0.769)†	0.767 (0.584 to 0.897)†	0.714	0.717 (0.468 to 0.952)†
D'Amico et al ² B	876	0.624	0.725	0.709	0.791 (0.655 to 0.905)†	0.724	0.754 (0.601 to 0.910)†
> 2.0 ng/mL/yr	323/876‡	0.608	0.725	0.702	0.657	0.724	0.704

NOTE. Predictive accuracy is represented by the concordance indices, which are comparable only within rows, but not between rows, because the patients included vary for each definition.

Abbreviations: PSA, prostate-specific antigen; MSKCC, Memorial Sloan-Kettering Cancer Center; M. D. Anderson, The University of Texas M. D. Anderson Cancer Center.

*Calculated in the subgroup of patients for whom the respective PSA dynamic was calculable.

†Dynamics definitions that yielded an apparent improvement in accuracy over a single PSA; 95% CIs are shown in parentheses.

‡No. above the cutoff/total No.

example, the median PSADT was 23 months for Memorial Sloan-Kettering Cancer Center PSADT and 6 months for M. D. Anderson 1 PSADT. This difference is striking because both were calculated for essentially the same patient group. Another example of how the method of calculation resulted in differences in predictive accuracy comes from two similar definitions—D'Amico et al¹ A PSAV, which was not associated with BCR or metastasis, and D'Amico et al² B PSAV, which was associated with both outcomes. D'Amico et al A calculates PSAV from all PSA values within 1 year before diagnosis, whereas D'Amico et al B requires intervals of 6 months between values over the same time period. D'Amico et al B PSAV could be calculated for only 30% ($n = 876$) of the patients for whom D'Amico et al A was calculable. The fact that two fairly similar definitions differed in whether they were associated with the outcomes illustrates the fragility and variability of PSA dynamics and how criteria for selecting PSA values critically influence the results.

We note that the more restrictive definitions were more likely to enhance predictive ability above PSA alone. For example, none of the PSAV definitions that were applicable to at least 50% of patients enhanced prediction of metastasis, whereas all PSAV definitions applicable to less than 50% of patients did so. We believe this is because of greater statistical variability associated with smaller sample sizes, suggesting that apparent enhancements of predictive accuracy were likely a result of chance.

We found that certain definitions are strongly associated with outcome (Table 2) yet do not appreciably improve the predictive ability beyond that of a single PSA. This is because PSA and PSA dynamics are highly correlated,³⁰ and PSA is itself a highly predictive variable (c -index = 0.714 for BCR). If two variables are highly correlated, using both provides little additional information over using only one.

Thompson et al²⁴ used log values to calculate PSAV for the 55- to 91-year-old men biopsied in the control arm of the Prostate Cancer Prevention Trial. They concluded that PSAV alone was significantly associated with an increased risk of prostate cancer but did not add any independent predictive value when added to a prostate cancer risk model containing PSA alone. Furthermore, data from the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer also suggested that PSAV measured close to the time of diagnosis did not improve the diagnostic accuracy of PSA.³¹ Although these studies measure the ability of PSA and PSAV to predict diagnosis rather than recurrence, the statistical point is similar.

It has been proposed that the c -index may be an inappropriate measure of predictive performance and that what matters more is reclassification of patients between risk categories. It can be shown that, when examining the value of an additional predictor, reclassification is highly correlated with changes in the c -index. As an illustration, we evaluated Freedland et al¹² PSADT, which did not increase the c -index. We fit two Cox regression models, one with PSA alone and

the other with PSA and Freedland et al PSADT, and calculated the predicted 5-year probability of recurrence from each model. Considering patients with a predicted probability of more than 20% as being at high risk, the model including Freedland et al PSADT reclassified only 4% of patients (88 of 2,338 patients); critically, there was no significant difference in recurrence rates between the 30 patients reclassified as low risk and the 58 patients reclassified as high risk ($P = .17$). In other words, use of the PSA dynamic would result in the reclassification of a small number of patients.

Our study is subject to certain limitations. First, the follow-up after radical prostatectomy was short (median, 2.1 years in recurrence-free patients) as a result of a large number of patients being treated recently. However, because of our large sample size, we were able to analyze reasonable numbers of events, particularly for BCR ($n = 384$), and we believe our analysis would have revealed any definition that contributed strong predictive power above that of a single PSA. Furthermore, our end point of metastasis ($n = 63$) has a greater number of events than previous studies that demonstrated association between PSAV and death.¹ Second, because this is a retrospective study, all PSA values used in the calculations were obtained from clinical charts, and hence, the PSA values could have come from different assays. This would add error in the calculated dynamics; nonetheless, our findings reflect normal clinical practice.

In summary, many PSA dynamic definitions, when applied to a pretreatment setting, are not calculable for a considerable proportion of patients in routine clinical practice. Although PSAV and PSADT by several definitions are univariately associated with both BCR and metastasis after radical prostatectomy, the accuracy of most published PSAV and PSADT definitions for predicting outcome is less than that of PSA alone. Furthermore, we were unable to obtain evidence that PSA dynamic definitions yielded important improvements in the predictive accuracy of a model incorporating a single pretreatment PSA. In conclusion, although some PSA dynamic definitions do associate with outcome, we see no justification for including PSA dynamics in

statistical models to improve outcome prediction in patients treated with radical prostatectomy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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