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Evaluation of Prediagnostic Prostate-Specific Antigen Dynamics as Predictors of Death from Prostate Cancer in Patients Treated Conservatively

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Abstract

Prostate-specific antigen (PSA) dynamics have been proposed to predict outcome in men with prostate cancer. We assessed the value of PSA velocity (PSAV) and doubling time (PSADT) for predicting prostate-cancer-specific mortality (PCSM) in men with clinically localized prostate cancer undergoing conservative management or early hormonal therapy. From 1990 to 1996, 2333 patients were identified, of whom 594 had two or more PSA values before diagnosis. We examined 12 definitions for PSADT and 10 for PSAV. Because each definition required PSA measurements at particular intervals, the number of patients eligible for each definition varied from 40 to 594 and number of events from 10 to 119. Four PSAV definitions, but no PSADT, were significantly associated with PCSM after adjustment for PSA in multivariable Cox proportional hazards regression. All 4 could be calculated only for a proportion of events, and the enhancements in predictive accuracy associated with PSAV had very wide confidence intervals. There was no clear benefit of PSAV in men with low PSA and Gleason grade 6 or less. Although evidence that certain PSAV definitions help predict PCSM in the cohort exist, the value of

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incorporating PSAV in predictive models to assist in determining eligibility for conservative management is, at best, uncertain.

Keywords

prostate-specific antigen; prostate-specific antigen velocity; prostate-specific antigen doubling time; watchful waiting; prediction

INTRODUCTION

Widespread screening with prostate-specific antigen (PSA) in the US has led to increased diagnosis of small, low-stage cancers, some of which would become lethal if left untreated, but many are unlikely to affect quality or length of life. Concerns about potential overtreatment of insignificant cancers are underscored by recent findings from one of the randomized trials of prostate cancer screening.¹ Results showed that PSA-based screening reduced prostate-cancer-specific mortality (PCSM), but that screening of 1410 men, and treating of 48 men, would be required to prevent one prostate cancer death.¹ Better biomarkers are required to differentiate potentially lethal from more indolent cancers that would be suitable for conservative management.

PSA dynamics (both velocity and doubling time) have been advocated as a means of improving diagnosis and assessment of prostate cancer. PSA velocity (PSAV) has been statistically associated with biopsy outcomes.^{2–3} Pretreatment PSAV has also been associated with recurrence and death after both surgical and radiation therapy.^{4–5} PSA doubling time (PSADT) after biochemical recurrence has been demonstrated to predict time to metastasis and death from prostate cancer, thereby acting as a surrogate endpoint for cancer-specific mortality.^{6–7} Hence, PSA dynamics may be suitable to help predict outcome for men treated conservatively. This could include all stages of disease, from active surveillance of localized cancer to watchful waiting for locally advanced or recurrent cancer.

In contrast to reports advocating use of PSA dynamics, we recently found that although pretreatment PSA dynamics were sometimes associated with outcome after radical prostatectomy, there was no improvement in predictive accuracy beyond that of pretreatment PSA alone.⁸ Although many authors have investigated whether outcome is statistically associated with PSAV or PSADT, scant attention has been paid to whether dynamics improve our ability to predict over and above either a single PSA measurement or a multivariable model including stage, grade, and PSA.^{9–10}

In this study, we examined whether PSA dynamics could distinguish potentially lethal cancers from those that are insignificant. Our study population is a unique cohort in which patients not selected for aggressive curative therapy were managed conservatively by watchful waiting until disease progression occurred, at which point they received therapy. Thus, this cohort is very different from contemporary active surveillance cohorts. It does, however, provide a unique heterogeneous population of men with clinically localized prostate cancer to investigate the role of PSA dynamics in the natural history of prostate cancer. Utilizing this cohort, we assessed the various published definitions of PSAV and PSADT as predictors of death from prostate cancer. To do so, we tested each definition for association with outcome, both alone and after adjustment for the prediagnostic PSA level, and we tested whether any PSA dynamic definition could improve predictive accuracy compared to the prediagnostic PSA level.

MATERIALS AND METHODS

Patients

The study population (Trans-Atlantic Prostate Group [TAPG] cohort) has been described in detail.¹¹ Briefly, potential cases were identified from 6 cancer registries in Great Britain if they were under age 76 years (median 71; IQR 67, 74) at the date of diagnosis and had probable clinically localized prostate cancer diagnosed by transurethral resection of the prostate (TURP) or needle biopsy. Diagnosis between 1990 and 1996 (inclusively) and a baseline PSA were required. Patients treated by radical prostatectomy or radiation therapy within 6 months of diagnosis were excluded. Additional exclusions were those with objective evidence of metastatic disease (by radiology or histology), clinical indications of metastatic disease, or a PSA measurement over 100 ng/mL at or within 6 months of diagnosis. These last two exclusions were a pragmatic method of focusing the study on patients who were very likely to have truly localized disease at presentation. Men who had hormone therapy before diagnostic biopsy were also excluded, because of the influence of hormone treatment on interpreting Gleason grade. We also excluded men who died within 6 months of diagnosis or had less than 6 months of follow-up. In January 2005, the cancer registries were queried to obtain the most up-to-date survival data. Where available, death certificates for deceased patients were reviewed to verify cause of death and outcomes were determined through medical records and cancer registry data. Deaths were divided into two categories, death from prostate cancer and death from other causes, according to standardized World Health Organisation criteria. Patients still alive at last follow-up were censored at that date.

We defined conservative management or watchful waiting as not receiving any therapy (excluding hormone manipulation) within 6 months of diagnosis. Of the 2333 patients eligible, 1663 received watchful waiting treatment. Of these, we identified 594 patients who had two or more PSA values 2 or more months apart before diagnosis; these patients constituted the study group. Of the 594 eligible patients, at last follow-up 119 patients had died from prostate cancer and 165 patients had died from other causes. The median follow-up for survivors was 9 years.

PSA Dynamics Definitions

We utilized 20 definitions (Supplemental Table) used as predictive tools in published literature: 11 PSADT6, 12–22 and 9 PSAV.4–5, 17, 19, 23–25 We also used the 2 dynamics tools from the Memorial Sloan-Kettering Cancer Center (MSKCC) website.²⁶ The definitions are exactly the same as those used in our previous study.⁸ PSA dynamics were calculated using all PSA measurements available before prostate cancer diagnosis.

Statistical Methods

Univariate Cox proportional hazards regression was used to evaluate the association between different definitions of PSA dynamics and PCSM. Multivariable Cox regression was used to determine which definitions of PSA dynamics were significantly associated with PCSM, controlling for a single prediagnostic PSA value. The single PSA value used in the predictive model was the final PSA before diagnosis that was used in the dynamic calculation under consideration.

To measure predictive accuracy, we used the concordance index (c-index), which is a similar concept to the area under the receiver operating characteristic curve that can be used to quantify discrimination for survival time data. To determine the enhancement in predictive accuracy associated with each PSA dynamic beyond that of PSA, we evaluated the c-index of (A) PSA alone, (B) each PSA dynamic alone, and (C) PSA plus each PSA

dynamic. We corrected for overfit and obtained confidence intervals of the difference in predictive accuracy for c-indices using bootstrap methods.²⁷ Each definition required a particular number of PSA measurements taken at particular intervals, hence most definitions were not calculable for all patients in our study cohort. Therefore, to allow for comparison between (A), (B), and (C), we calculated c-indices in the subset of patients for whom the respective dynamic was calculable. Hence, these estimates for different definitions are not directly comparable. We repeated the analyses using a competing risk regression model instead of a Cox regression model, which accounts for the competing risk of dying from causes other than prostate cancer. None of the results from the competing risk model were substantially different from those reported here (data not shown). All statistical analyses were conducted using Stata 10.0 (Stata Corp., College Station, TX) and R (R Foundation for Statistical Computing, www.r-project.org) with the *cmprsk* statistical package.

The study was conducted under the Health Insurance Portability and Accountability Act guidelines and received Institutional Review Board approval.

RESULTS

Patient characteristics are summarized in Table 1 and PSA dynamics results in Table 2. Depending on the definition, the percentage of patients for whom a dynamic could be calculated varied from 7% to 100% (2% to 36% of the whole sample). For 9 definitions, the dynamic was calculable for one third or less of our study cohort (Table 2). Four PSADT and 2 PSAV definitions were calculable for more than 90% of our study cohort.

Results of univariate analyses are shown in Table 3. A single PSA measurement alone was highly associated with PCSM ($p < 0.001$). Several PSAV definitions (4 of 10), but no PSADT definitions, were significantly associated with PCSM (all $p < 0.003$). On multivariable analysis controlling for prediagnostic PSA, 3 of the 4 PSAV definitions that were significant on univariate analysis remained significant predictors of PCSM (all $p < 0.05$, Table 3); additionally, D'Amico A as a continuous variable was a significant predictor of PCSM with adjustment for prediagnostic PSA ($p = 0.01$).

The predictive accuracies of a single PSA alone, each dynamic definition, and a single PSA plus each dynamic are summarized in Table 4. Very small enhancements in predictive accuracy above that of PSA alone were observed for 4 PSADT definitions that were not significantly associated with PCSM (either on univariate or multivariable analysis); these enhancements are likely explained by sampling variability. Two of the 4 PSAV definitions that were significantly associated with PCSM with adjustment for PSA apparently increased predictive accuracy above that of PSA alone. The enhancement in predictive accuracy with 95% confidence interval (CI) for these definitions is given in Table 4. One of these definitions (D'Amico B categorized as >2 ng/mL/yr) included only 15 events, and therefore had very wide confidence intervals. D'Amico A >2 ng/mL/yr increased the c-index from 0.677 to 0.685 (difference of 0.008; 95% CI: $-0.018, 0.036$). All of the 95% confidence intervals include zero, which indicates that none of the definitions significantly enhanced the predictive accuracy of PSA alone.

Our original intention was to include the most promising definitions in a multivariable model including Gleason grade. However, this was possible only for the D'Amico A definition due to the very small number of events for other definitions. After adjusting for both prediagnostic PSA and biopsy Gleason grade, D'Amico A PSAV remained significantly associated with PCSM (entered as continuous: hazard ratio of 0.989 per 1 ng/mL/yr; 95% CI: 0.979, 0.998; $p = 0.019$; entered as binary: hazard ratio of 1.71 for >2 versus ≤ 2 ng/mL/yr; 95% CI: 1.04, 2.79; $p = 0.034$). To characterize these results in a clinical

context, we considered a low-risk group of patients who would reasonably be considered for conservative management (155 patients with biopsy Gleason grade ≤ 6 and PSA ≤ 20 ng/mL). This subgroup had 10 PCSM events, with an 8-year probability of PCSM of 7% (95% CI: 4%, 13%). The critical use of PSAV in this setting would be to determine those patients at low risk of PCSM (who should receive conservative management), and those at high risk (who may benefit from curative therapy). D'Amico A PSAV was calculable for 110 of these patients (71%), but was elevated (>2 ng/mL/yr) in only 9% (10/110), one of whom died of disease. Because only a very small number of patients were reclassified, the likelihood of PCSM in men with PSAV ≤ 2 ng/mL/yr remained high: 8% at 8 years. We believe that any man told he had a 1 in 10 chance of death within 8 years would not be comfortable with conservative management. Our results were not importantly affected by the more restrictive criteria that might be used to select patients suitable for active surveillance rather than watchful waiting (e.g., Gleason grade ≤ 6 and PSA ≤ 10). Of note, D'Amico B PSAV was calculable for only 59 of these patients (61%), and was >2 ng/mL/yr for only 2 (3%); both of these patients were alive at last follow-up (7.1 and 9.9 years after prostate cancer diagnosis).

As a sensitivity analysis, we repeated all analyses, but included in the calculations any PSA values up to 6 months after diagnosis but before hormonal manipulation or TURP. This analysis expanded our cohort to 862 patients, of whom 188 died from prostate cancer. In general, there was no important difference in results. Five PSAV definitions (D'Amico A PSAV as continuous and categorized as >2 ng/mL/yr, D'Amico B PSAV as continuous and categorized as >2 ng/mL/yr, and Smith PSAV), and no PSADT definitions, were significantly associated with PCSM with adjustment for pre-diagnostic PSA. None of the definitions importantly enhanced the predictive accuracy of PSA alone.

Additional sensitivity analyses focused on the 4 velocity definitions that showed promise from our main analyses (D'Amico A PSAV as continuous and categorized as >2 ng/mL/yr, and D'Amico B PSAV as continuous and categorized as >2 ng/mL/yr). We performed analyses for the outcome of metastases or PCSM, and censoring patients who received curative therapy at the time of that treatment. Our key results were essentially unchanged: the 2 D'Amico A velocity definitions were statistically significant on multivariable analysis controlling for PSA ($p < 0.05$ for all analyses); the 2 D'Amico B velocity definitions were statistically significant on univariate ($p < 0.001$ for all analyses) but not on multivariable analysis controlling for PSA ($p > 0.08$ for all analyses). None of the 4 velocity definitions enhanced the predictive accuracy over and above PSA alone.

We compared our results using this TAPG cohort to those previously published using a cohort from MSKCC (Table 5).⁸ The MSKCC cohort used metastasis or biochemical recurrence after radical prostatectomy as the outcome and included 2938 patients. Importantly, D'Amico A PSAV did not even achieve a significant univariate association with metastases in the MSKCC cohort ($p = 0.4$ entered as continuous and $p = 0.19$ entered as binary for >2 ng/mL/yr). D'Amico B PSAV was significantly associated with metastases and biochemical recurrence in the MSKCC cohort; however, this association did not translate into a significant improvement in predictive accuracy for any of the outcomes. The only apparent enhancement observed was for D'Amico B PSAV >2 ng/mL/yr for metastases (c-index for PSA plus dynamic vs with PSA alone: 0.754 vs 0.724), but this was based on only 16 events and this enhancement was not independently replicated in the TAPG cohort.

DISCUSSION

For a PSA dynamic to be of value for clinical decision making or patient counseling in a pretreatment setting, we propose that it must improve predictive accuracy beyond that of a single pretreatment PSA alone. Were this not to be the case, the clinician can just use the

patient's latest PSA value for decision making. Here we report that, among men with clinically localized prostate cancer treated conservatively, a small number (4 of 22) of definitions of prediagnostic PSA dynamics were significantly associated with PCSM on univariate analysis. Three of these 4 definitions, plus 1 other, were statistically significant in a multivariable model controlling for a single prediagnostic PSA value; 2 of these definitions also appeared to improve predictive accuracy. However, the definitions could be applied only to a subset of men; accordingly, our results are based on a small number of events with the improvements in predictive accuracy (assessed by c-index) associated with wide 95% confidence intervals. For example, D'Amico B PSAV >2 ng/mL/yr enhanced the predictive accuracy by 0.003; however, this analysis was based on only 15 events, and we cannot exclude the possibility that this definition leads to only a very small enhancement in predictive accuracy. Any estimates of the risk of PCSM obtained from the current data set with D'Amico B PSAV would be highly variable, and would be extremely difficult to determine how this PSAV definition should be implemented in clinical practice. None of the definitions significantly enhanced the predictive accuracy above that of PSA alone, and none showed an apparent enhancement in both the TAPG and MSKCC cohorts.

Of all 22 definitions used in our study, only the Stephenson PSADT was initially described in a cohort undergoing watchful waiting. In that cohort, a PSADT of less than 120 months correlated with disease progression.²⁰ There was no difference between a PSADT of less than 48 months and PSADT of 48 to 120 months, which seems to be contrary to the concept that a more aggressive disease can be identified by a quicker rise in PSA. When applied to the TAPG cohort, this definition did not associate with outcome on univariate analysis ($p=0.7$). One possible explanation for why we did not validate Stephenson PSADT is because, in the Stephenson study, a rapidly rising PSA might have been used to make treatment decisions such as whom and when to rebiopsy, resulting in verification bias. Other groups who have suggested that PSA dynamics are of benefit in an active surveillance cohort incorporated the dynamic in the treatment algorithm, that is, patients with a rapidly rising PSA were considered to have progressed. Claiming that "PSA velocity predicts progression" therefore becomes little more than the claim that "PSA velocity predicts PSA velocity".

In the present study, PSA dynamics were not utilized in treatment decisions. We can therefore be confident that our results are not subject to selection bias.

This study adds to a growing body of literature showing that PSA dynamics add little or nothing to our ability to predict various outcomes across the spectrum of prostate cancer. Previously we^{8, 28–29} and others^{25, 30–31} have demonstrated that PSA dynamics lead to, at best, only trivial improvements in predictive accuracy beyond that of a single PSA value alone, either before diagnosis or before radical prostatectomy. Furthermore, in a systematic review of the literature,¹⁰ only two papers compared the predictive accuracy of a model containing PSA and PSAV to that of PSA alone: one found no improvement; the other found a very small improvement but was flawed due to verification bias.

In the setting of conservative management, Fall et al³² assessed PSAV and PSADT to predict outcome in the watchful waiting arm of the Scandinavian Prostate Cancer Group No. 4 trial of watchful waiting versus radical prostatectomy. The PSA dynamics were calculated from PSA values in the 2-year period after randomization and assessed in three models as predictors of lethal prostate cancer (metastasis or disease-specific death). They found that both PSA and PSA dynamics were associated with outcome; however, neither PSA alone nor PSA dynamics was an accurate predictor. Although the authors did not examine if the addition of PSA dynamics to PSA alone could improve the ability of PSA to predict outcome, we believe our results, from a cohort of patients treated in a clinical practice

setting, confirm the finding from this randomized trial that PSAV does not contribute meaningful information when trying to predict outcome in patients treated conservatively.

PSA dynamics may be associated with outcome yet may not importantly improve the predictive ability of PSA alone, in part because PSA and PSA dynamics are highly correlated.³³ If two variables are highly correlated, using both provides little additional information over using only one, and PSA is itself a predictive variable (c-index 0.647 for PCSM). We also note that both PSADT and PSAV were strongly influenced by the method of calculation (Table 2), as has been previously noted.^{8, 34–35} In this study, for example, the median PSAV was 0.01 ng/mL/yr by the MSKCC definition and 0.33 ng/mL/yr by D'Amico A. The fact that 2 definitions, calculated for essentially the same patient group, differed so greatly demonstrates the fragility and variability of PSA dynamics and how criteria for selecting PSA values critically influence the results.

Our study is subject to certain limitations. First, our sample size for some definitions was small, but for 12 of the definitions we were able to analyze reasonable numbers (>50) of clinically important events (deaths from prostate cancer), and we believe our analysis would have revealed any definition that contributed strong predictive power above that of a single PSA. Second, all PSA values used in the calculations were obtained from clinical charts. Hence, the PSA values could have come from different assays, which would add to error in the calculated dynamics. That said, this reflects the normal diversity of clinical practice. If it were the case that PSA dynamics aided in the selection of patients for conservative management only if the PSA assays were rigorously controlled, this would have limited practical value.

In our analyses, we tested 22 hypotheses for each endpoint. Given this multiple testing, and considering that the single definition that significantly enhanced predictive accuracy was not previously identified in an independent cohort of patients, it is plausible that this one positive result was simply due to chance. We interpret these results as providing little evidence that any PSA dynamic improves the predictive ability for disease-specific mortality over that of a single PSA value alone. In contrast, the clinical outcome of this cohort of men with untreated prostate cancer has been assessed with respect to tissue-based biomarkers. In particular, expression of heat shock protein 27 (HSP-27) has been identified as a powerful ($p<0.001$) prognostic indicator of poor clinical outcome in individual cases at diagnosis.³⁶ Like PSA, this protein is also under the control of the androgen receptor³⁷ but is more robust. Although powerful, the disadvantage of HSP-27 is that it is currently tissue-based and indicative of active management only when positive at diagnosis.

In conclusion, we see no justification for calculation of PSA dynamics to help predict outcome of patients undergoing conservative management. Instead, we recommend using a single pretreatment or prediagnostic PSA value in an independently validated predictive nomogram. Going forward, we believe that future research should focus on the 4 specific definitions of PSAV that were significantly associated with PCSM. These results must be independently replicated in data sets with large number of events. In particular, researchers should focus on the question of whether PSAV enhances prediction in comparison with standard predictors alone.

Statement of Novelty and Impact

No previous paper has compared the predictive accuracy of PSA dynamics with PSA alone in a cohort of patients with prostate cancer treated conservatively. This paper shows that outcome prediction does not require the calculation of PSA dynamics, rather the most recent PSA can be used for outcome prediction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

CI	confidence interval
HSP	heat shock protein
PCSM	prostate-cancer-specific mortality
PSA	prostate-specific antigen
PSAV	PSA velocity
PSADT	PSA doubling time
TAPG	Trans-Atlantic Prostate Group
TURP	transurethral resection of the prostate

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APPENDIX

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Table 1

Characteristics of 594 patients in this study. Data are median (interquartile range) or frequency (percentage).

Clinical Feature	
Age at surgery (years)	71 (67, 74)
Total PSA (ng/mL)	17 (8.8, 33)
Clinical stage	
≤ T2a	308 (52%)
≥ T2b	70 (12%)
Unknown	216 (36%)
Biopsy Gleason grade	
≤6	200 (34%)
7	149 (25%)
≥8	126 (21%)
Unknown	119 (20%)
Year of diagnosis	
1990	5 (1%)
1991	11 (2%)
1992	39 (7%)
1993	70 (12%)
1994	117 (20%)
1995	172 (29%)
1996	180 (30%)
Early hormones*	214 (36%)
No further treatment	106
Radiotherapy	20
Radiotherapy + hormones	25
Radical prostatectomy	5
Radical prostatectomy + hormones	0
Hormones	58
No early hormones*	380 (64%)
No further treatment	177
Radiotherapy	37
Radiotherapy + hormones	37
Radical prostatectomy	19
Radical prostatectomy + hormones	2
Hormones	108

* Within 6 months of diagnosis

Table 2

Summary of PSA, PSA doubling time (12 definitions), and PSA velocity (10 definitions), calculated at the time of diagnosis.

	Number of patients with calculable value	Median (interquartile range) or Frequency (percentage)
Total PSA, ng/mL	594 (100%)	17 (9, 33)
Doubling Time, months		
MSKCC26	565 (95%)	6 (−5, 26)
Shulman18	561 (94%)	4 (−3, 13)
MD Anderson 216	553 (93%)	3 (−4, 12)
MD Anderson 116	545 (92%)	2 (−4, 11)
Ward21	350 (59%)	1 (−1, 2)
Freedland14	327 (55%)	13 (0, 30)
Egawa13	210 (35%)	22 (7, 45)
Trapasso22	194 (33%)	1 (0, 3)
Stephenson20	135 (23%)	0 (−1, 2)
Hanks15	112 (19%)	32 (8, 60)
Smith19	59 (10%)	30 (16, 50)
D'Amico12	40 (7%)	3 (1, 5)
Velocity, ng/mL/yr		
MSKCC26	594 (100%)	0.01 (−0.02, 0.05)
Thompson25	589 (99%)	0.01 (−0.02, 0.05)
D'Amico A4	492 (83%)	0.33 (−0.50, 1.45)
D'Amico A >2 ng/mL/yr4	492 (83%)	105 (21%)
Rozhansky23	369 (62%)	0.30 (−0.90, 2.03)
Sengupta17	327 (55%)	0.02 (−0.01, 0.04)
D'Amico B5	90 (15%)	0.35 (0.08, 0.90)
D'Amico B >2 ng/mL/yr5	90 (15%)	8 (9%)
Thiel24	82 (14%)	0.15 (0.02, 0.41)
Smith19	59 (10%)	0.02 (0.01, 0.03)

Table 3

Univariate and multivariable Cox proportional hazards regression to evaluate the association between different definitions of PSA dynamics and prostate-cancer-specific mortality. Hazard ratios are shown for a standard deviation increase in the PSA dynamics. Bold face represents significant associations.

	Number of patients	Number of deaths from prostate cancer	Univariate Analysis			Multivariable P Value *
			Hazard Ratio	95% CI	P Value	
PSA	594	119	1.23	1.15, 1.31	<0.001	--
Doubling Time						
MSKCC26	565	112	0.95	0.80, 1.14	0.6	0.6
Shulman18	561	110	0.97	0.81, 1.17	0.8	0.8
MD Anderson 216	553	111	1.01	0.83, 1.23	0.9	0.9
MD Anderson 116	545	108	0.96	0.80, 1.17	0.7	0.7
Ward21	350	65	1.02	0.83, 1.27	0.8	0.8
Freedland14	327	54	0.83	0.61, 1.12	0.2	0.3
Egawa13	210	34	0.74	0.53, 1.05	0.09	0.055
Trapasso22	194	34	0.88	0.60, 1.30	0.5	0.7
Stephenson20	135	26	0.92	0.57, 1.47	0.7	0.7
Hanks15	112	20	0.81	0.54, 1.22	0.3	0.4
Smith19	59	10	0.72	0.39, 1.34	0.3	0.4
D'Amico12	40	10	0.69	0.27, 1.74	0.4	0.16
Velocity						
MSKCC26	594	119	1.02	0.85, 1.21	0.8	0.5
Thompson25	589	118	1.02	0.85, 1.21	0.8	0.5
D'Amico A4	492	106	0.95	0.77, 1.18	0.7	0.01
D'Amico A >2 ng/mL/yr4	492	106	2.62	1.77, 3.88	<0.001	<0.001
Rozhansky23	369	91	0.95	0.76, 1.19	0.7	0.04
Sengupta17	327	54	1.60	1.18, 2.16	0.002	0.3
D'Amico B5	90	15	3.35	2.10, 5.35	<0.001	0.02
D'Amico B >2 ng/mL/yr5	90	15	17.2	5.80, 51.2	<0.001	0.045
Thiel24	82	12	1.51	0.97, 2.35	0.07	0.3
Smith19	59	10	1.26	0.70, 2.27	0.4	0.7

(* Adjusted for PSA)

Table 4

Individual assessment of the enhancement in predictive accuracy associated with each definition of PSA dynamics for prediction of prostate-cancer-specific mortality, after adjustment for the pretreatment PSA level. Concordance indices are comparable only across each row and not comparable row by row as the patients included varied for each definition.

Concordance Index					
	Number of patients	Dynamic Alone	PSA Alone	PSA plus PSA Dynamic	Enhancement* (95% CI)
Doubling Time					
MSKCC26	565	0.525	0.688	0.680	
Shulman18	561	0.523	0.689	0.681	
MD Anderson 216	553	0.511	0.691	0.680	
MD Anderson 116	545	0.509	0.688	0.682	
Ward21	350	0.547	0.692	0.685	
Freedland14	327	0.524	0.707	0.667	
Egawa13	210	0.611	0.727	0.738	
Trapasso22	194	0.576	0.658	0.661	
Stephenson20	135	0.507	0.656	0.649	
Hanks15	112	0.601	0.704	0.712	
Smith19	59	0.692	0.763	0.798	
D'Amico12	40	0.771	0.810	0.803	
Velocity					
MSKCC26	594	0.582	0.692	0.673	
Thompson25	589	0.585	0.693	0.673	
D'Amico A4	492	0.601	0.677	0.626	−0.051 (−0.070, 0.003)
D'Amico A >2 ng/mL/yr4	492	0.600	0.677	0.685	0.008 (−0.018, 0.036)
Rozhansky23	369	0.599	0.671	0.619	
Sengupta17	327	0.617	0.707	0.671	
D'Amico B5	90	0.730	0.773	0.746	−0.027 (−0.059, 0.050)
D'Amico B >2 ng/mL/yr5	90	0.695	0.773	0.776	0.003 (−0.008, 0.033)
Thiel24	82	0.642	0.695	0.667	
Smith19	59	0.662	0.763	0.728	

* Enhancement in predictive accuracy (PSA plus PSA Dynamic versus PSA alone) given for PSA dynamics with adjustment for PSA.

PSA dynamics significantly associated with prostate-cancer-specific mortality with adjustment for PSA: comparison of results against previously published analyses with an MSKCC cohort.⁸

Table 5

	TAPG cohort: disease-specific mortality for untreated patients			MSKCC cohort: metastases after radical prostatectomy		
	Number (%) with calculable dynamic	Number of events	Enhancement PSA + PSA dynamics vs PSA	Number (%) with calculable dynamic	Number of events	Enhancement PSA + PSA dynamics vs PSA
Velocity						
D'Amico A4	492 (83)	106	-0.051	2630 (90)	56	None
D'Amico A >2 ng/mL/yr4	492 (83)	106	0.008	2630 (90)	56	None
D'Amico B5	90 (15)	15	-0.027	876 (30)	16	0.030
D'Amico B >2 ng/mL/yr5	90 (15)	15	0.003	876 (30)	16	None