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Change in PSA velocity is a predictor of overall survival in men with biochemically-recurrent prostate cancer treated with non-hormonal agents: Combined analysis of four phase-2 trials

Daniel L. Suzman, M.D.[1], **Xian C. Zhou, M.S.**[1], **Marianna L. Zahurak, M.S.**[1], **Jianqing Lin, M.D.**[2], and **Emmanuel S. Antonarakis, M.D.**[1,*]

[1]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Baltimore, Maryland [2]Kimmel Cancer Center at Thomas Jefferson University Hospital; Philadelphia, PA

Abstract

Background—Multiple phase-2 trials in men with biochemically-recurrent prostate cancer (BRPC) have assessed the impact of non-hormonal agents on PSA kinetics. We have previously demonstrated that changes in PSA kinetics correlate with metastasis-free survival; however, it is unknown whether these changes also correlate with overall survival (OS).

Methods—We performed a combined retrospective analysis of 146 men with BRPC treated on phase-2 trials using one of four investigational drugs: lenalidomide (n=60), marimastat (n=39), ATN-224 (n=22), and imatinib (n=25). We examined factors influencing OS, including within-subject changes in PSA kinetics (PSA slope, PSA doubling time, and PSA velocity) before and 6 months after treatment initiation.

Results—After a median follow up of 83.1 months, 49 of 146 men had died. In univariate Cox regression analysis, two factors were associated with OS: baseline PSA velocity and change in PSA velocity on therapy. In a landmark multivariable model, stratified by study (which controlled for age, Gleason score, type of local therapy, and use of ADT prior to metastases), baseline PSA velocity and increase in PSA velocity on therapy remained independent predictors of OS. Median OS for men with an increase in PSA velocity on treatment was 115.4 months and was not reached for men with a decrease in PSA velocity (HR=0.47, 95% CI 0.25 to 0.88; P=0.02).

Conclusions—This hypothesis-generating study suggests that within-subject changes in PSA velocity after initiation of non-hormonal therapy may correlate with OS in men with BRPC. If validated in prospective trials, change in PSA velocity may represent a reasonable intermediate endpoint for screening new agents in these patients.

Keywords

Biochemical-recurrence; Prostate Cancer; PSA Kinetics; PSA Velocity; Surrogate Endpoints

[*]Corresponding author: Emmanuel S. Antonarakis, M.D., The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, CRB-1, Rm 1M45, 1650 Orleans St, Baltimore, MD 21287, eantona1@jhmi.edu, Tel: 443-287-0553, Fax: 410-614-8397.

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Introduction

In men with biochemically-recurrent prostate cancer (BRPC) following definitive local therapy, there is currently no consensus on optimal management.[1,2] Although there are multiple potential treatment options, none has yet demonstrated an overall survival benefit, with a meta-analysis demonstrating decreased prostate cancer-specific survival but no increase in overall survival in men treated with early compared with deferred androgen-deprivation therapy (ADT).[3] Nevertheless, given the large proportion of men in this clinical state, there remains great interest in developing therapeutic strategies for BRPC that may provide a survival benefit.

Hormone-sparing therapies have been developed for BCPC with the intention of avoiding the harms of prolonged ADT. To this end, a large number of biological and immunological agents have been evaluated in phase-2 clinical trials in these patients.[4-10] However, the lack of optimal study endpoints has hampered the development of such agents as the long interval between biochemical recurrence and death (or metastatic progression) leads to difficulty in demonstrating an overall survival benefit. In addition, even metastasis-free survival is not a validated endpoint in this setting.[11]

Because of the inability to follow radiographic or clinical parameters in this setting, the majority of such studies have utilized changes in PSA kinetics (PSA doubling time, PSA slope, and PSA velocity) as their primary endpoint. Change in PSA kinetics (specifically PSA decline ≥30%) has been demonstrated to meet Prentice surrogacy criteria for overall survival in the first-line chemotherapy setting in metastatic castration-resistant prostate cancer.[12,13] However, it is unclear whether changes in PSA kinetics may predict overall survival in the setting of BRPC following treatment with non-hormonal agents and whether these may serve as effective intermediate endpoints.

We have previously conducted four phase-2 trials investigating experimental non-hormonal agents in men with PSA-recurrent prostate cancer after local therapy.[5,6,8] All of these studies examined changes in PSA kinetics before and during study drug initiation as their primary endpoint. In an initial combined analysis of these 4 trials, we demonstrated that changes in PSA kinetics resulting after treatment initiation predicted metastasis-free survival (MFS) interval.[14] The present study is an update of the prior analysis of these four trials (n = 146), aiming to investigate the potential relationship between intra-subject changes in PSA kinetics and overall survival. We hypothesized that improvements in PSA kinetics after initiation of non-hormonal treatments would correlate with prolonged overall survival.

Methods

Study Design

The designs of the four phase-2 studies included in this combined analysis have been described previously.[5,6,8] The first study[5] was a randomized phase I/II trial evaluating 3 doses of an oral matrix metalloproteinase inhibitor, marimastat (5 mg, 20 mg, or 40 mg daily). A total of 39 patients were enrolled, and the primary efficacy endpoint was change in median PSA slope after 6 months of the study drug. The second trial[6] was a single-arm phase II study of the oral tyrosine kinase inhibitor, imatinib (800 mg daily). A total of 25 men participated, and the primary endpoint was PSA response rate defined as a 50% decrease in PSA from baseline. The third study[8] was a randomized phase-2 trial of two doses of an oral copper/zinc-superoxide dismutase inhibitor, ATN-224 (30 mg or 300 mg daily). A total of 47 patients were accrued, and the primary endpoint was change in mean PSA slope and mean PSA doubling time on study. The fourth trial[15] was a randomized phase-1/2 study evaluating the oral immunomodulatory drug, lenalidomide (5 mg or 25 mg daily). A total of 60 men were enrolled, and the primary endpoint was change in median PSA slope after 6 months. None of these trials were designed *a priori* to capture data on overall survival.

All four studies were conducted at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD. Three trials were single-center experiences while the ATN-224 study was also performed at 5 other centers. In all studies, eligible patients were required to have PSA-recurrent prostate cancer after local therapy, non-castrate levels of serum testosterone, non-metastatic disease as determined by CT and/or bone scan, and rising PSA levels. All trials used experimental agents that were not expected to mediate their effects through the endocrine axis. While on study, patients were required to have PSA assessments either every month (marimastat, ATN-224) or every 2 months (imatinib, lenalidomide). Patients were treated with study drug for either 6 months (marimastat, ATN-224, lenalidomide) or 12 months (imatinib). In all trials, patients came off study upon PSA progression, clinical/radiographic progression, unmanageable toxicity, or death (whichever occurred first).

The present study was a *post hoc* analysis of OS using combined data from these four phase-2 studies. We retrospectively examined patient records and/or death certificates for information on date and cause of death. OS was defined as the time interval from study entry until death from any cause. Patients were captured at the time of their death or censored at the time of the last known date on which they were alive. The data cut-off date was set as October 31st, 2013. This study was approved by the Johns Hopkins University IRB.

Statistical Analysis

The primary objective was to determine the independent contribution of changes in PSA kinetics on OS. PSADT was calculated as the slope of the simple linear regression of log(base 2) PSA vs time.[16] PSA velocity was calculated as the slope of the simple linear regression of PSA (natural scale) vs time.[17] PSA slope was calculated as the slope of the simple linear regression of the natural log of PSA vs time.[16] Event-time distributions for OS were estimated using the Kaplan-Meier method[18] and 95% confidence intervals (CIs) were calculated using the Brookmeyer-Crowley method.[19] Landmark stratified Cox proportional hazards regressions were used to assess the effects of PSA kinetics on OS. Models were stratified by study, and the landmark time was set at 6 months, because all PSA values during the first 6 months after study entry were used to calculate on-study PSA kinetics. Such a landmark analysis prevents death events that might occur during the first 6 months on-study to be included in the analysis. Our multivariable models were stratified by study to avoid assuming proportional hazards across the 4 different protocols.

In the univariate analysis, factors that entered the model included age (continuous variable), Gleason score (<7 vs. ≥7), tumor stage (T1/2 vs. T3/4), lymph node involvement (N0 vs. N1), modality of primary therapy (surgery ± radiotherapy vs. radiotherapy alone), ADT use prior to metastasis (yes vs. no), baseline PSA values, baseline PSADT (≥6 vs. <6 months), baseline PSA velocity (dichotomous [below vs. above median] and continuous), baseline PSA slope (dichotomous [below vs. above median] and continuous), change in PSADT before and after study initiation (dichotomous [decrease in PSADT vs. no decrease]), change in PSA velocity (dichotomous [increase in velocity vs. no increase] and continuous), and change in PSA slope (dichotomous [decrease in slope vs. no decrease] and continuous). Negative PSADT values were assigned an arbitrarily large constant value and thus PSADT could not be analyzed as a continuous variable. In multivariable analysis, covariates with *P*-values from the univariate model of ≤0.10 as well as variables felt to be of potential clinical importance (including age, Gleason score, and pre-metastatic use of ADT) were included. Notably, because all three PSA kinetic measures are a function of changes in PSA against time and are all strongly interrelated, three separate multivariable models (each evaluating one kinetic measure at a time) were created.

All *P*-values are two-sided, and the significance level was set at ≤0.05. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC) and R version 3.1.0 (National Cancer Institute, Bethesda, MD).

Results

Patient Characteristics

Table 1 describes the clinical characteristics of men in each of the four trials. Twenty-five of 47 patients in the ATN-224 study (those enrolled at the other sites), did not have available data on survival status and were thus excluded from the analysis. All 39 patients in the marimastat study, all 25 patients in the imatinib study, and all 60 patients in the lenalidomide study had full information available to determine OS. With a median follow-up in the combined evaluable cohort of 83.1 months (95% CI, 78.8 to 114.3), 49 of 146 (33.6%) men had died.

Overall (n=146), median age at study entry was 63 years; 58 men (40%) had primary prostatectomy, 27 (18%) had primary radiotherapy, and 61 (42%) had prostatectomy and salvage radiotherapy; 26 men (18%) had Gleason score ≤6, 74 (51%) had Gleason score 7, and 46 (31%) had Gleason score ≥8; 12 men (8%) had T1 disease, 47 (32%) had T2 disease, and 87 (60%) had T3 disease; 16 men (11%) had node-positive disease at diagnosis; and 36 men (25%) received ADT prior to metastatic progression. Median PSA at baseline was 7.7 ng/mL; median PSA doubling time at baseline was 5.0 months; median PSA slope at baseline was 0.14; and median PSA velocity at baseline was 0.59 ng/mL/month.

Correlation of Changes in PSA Kinetics with OS

In univariate proportional hazards regression analyses (stratified by study), significant associations with OS were observed for: baseline PSA velocity (dichotomized) and change in PSA velocity (dichotomized and continuous). (Table 2).

Figure 1 demonstrates the effect of changes in PSADT (increase in PSADT after study entry vs. no increase), changes in (log) PSA slope (decrease in PSA slope vs. no decrease), and changes in PSA velocity (decrease in PSA velocity vs. no decrease) on OS using Kaplan-Meier analysis, when these factors were considered as dichotomous variables. While there were trends between slowing of PSA kinetics and improved OS, only the change in PSA velocity was significantly prognostic for OS.

In landmark multivariable analyses when these factors were considered as dichotomous variables (Table 3), change in PSA velocity emerged as a significant independent predictor of OS. The HR was 0.52 (95% CI 0.27 to 1.00; P = 0.05), indicating a 48% decrease in risk of death if PSA velocity decreased following treatment. Sensitivity analyses for the chosen cut points are reported in the supplemental appendix (supplemental Tables 1-6). However, baseline PSADT, baseline (log) PSA slope, change in PSADT, and change in (log) PSA slope, which were independent predictors of metastasis-free survival (MFS) in the prior analysis, did not retain statistical significance as predictors of OS, either in the univariate or multivariate analyses (Table 3).

In landmark multivariable analyses when these factors were considered as continuous variables (Table 4), both change in PSA velocity (HR = 1.07; 95% CI 1.03 to 1.11; P < 0.01) and change in (log) PSA slope (HR 9.91, 95% CI 1.54 to 63.93; P = 0.02) were independent predictors of OS.

Discussion

In men with hormone-naïve biochemically-recurrent prostate cancer after local therapy, there is a need for surrogate endpoints of clinical benefit given the long natural history of this disease state.[20,21] Changes in PSA kinetics offer an attractive intermediate endpoint given evidence that changes in kinetics following non-hormonal therapy may predict MFS based on our prior analysis of this dataset.[20,21]

This study represents an update to the prior analysis based on extended follow-up for OS. Here, we demonstrate that men whose PSA velocity decreased after study entry had improved OS, a correlation which remained significant after accounting for relevant clinical factors and pre-treatment PSA velocity. In other settings, PSA velocity >2.0 ng/mL prior to either radical prostatectomy or radiation therapy has been demonstrated to predict inferior overall survival[17,22], while high PSA velocity post-relapse predicts failure of salvage radiotherapy.[23] However, to our knowledge, this study is the first to document a correlation between on-study *changes* in PSA velocity and overall survival in men with BRPC receiving non-hormonal therapies.

Interestingly, although dichotomized changes in PSA slope and PSADT were significant independent predictors of MFS in our prior analysis, these only demonstrated a non-significant trend towards predicting OS in the current analysis. Due to the relatively small number of death events observed to date, minor changes in patient classification between the different PSA kinetic schemes may have resulted in significant effects on the statistical analysis. However, continuous change in PSA slope was significantly associated with OS, suggesting that an optimal cut point may be able to be identified in a larger cohort.

These results corroborate data from prior studies that demonstrated associations between changes in PSA in response to hormonal therapy. In one study, a PSA of ≤4 ng/mL after 7 months of ADT in men with metastatic hormone-sensitive prostate cancer predicted OS, as did PSA progression within that timeframe.[13] In a second study, PSA changes in men undergoing either mitoxantrone or docetaxel chemotherapy met Prentice surrogacy criteria for prediction of OS.[12] Specifically, PSA declines of ≥30% in response to chemotherapy predicted OS, although interestingly a decline of ≥50% failed the 'proportion-of-treatment-effect-explained' (PTE) test. Of note, PSA velocity at either 2 or 3 months post-therapy also satisfied Prentice criteria. Surrogacy of changes in PSA kinetics was subsequently demonstrated in the TAX327 study evaluating first-line docetaxel chemotherapy[24], although a recent analysis of the TROPIC trial of cabazitaxel failed to demonstrate that early changes in PSA fully captured changes in survival, suggesting that PSA is not an appropriate surrogate endpoint in the second-line chemotherapy setting[25]. The present study adds to this body of evidence, and suggests that changes in PSA velocity in men with BRPC receiving non-hormonal therapies may correlate with OS.

This study has several limitations. First, this was a retrospective study and none of the four trials included in the combined analysis were designed to capture data on survival. In addition, because the majority of death events occurred after patients had been taken off-study, a significant proportion of patients were lost to follow-up. Further, as a consequence of a retrospective analysis, it is generally difficult to determine whether the variable of interest (*i.e.* change in PSA kinetics, in this case) actually influences survival or if it simply acts as a marker of a more favorable prognosis. This is also true of the other baseline factors in the multivariable analysis including baseline velocity. Second, we had no control over additional therapies (including hormonal therapy, chemotherapy, or other novel therapies) administered to patients after they came off-study in each of the four trials; such subsequent therapies may have influenced OS.

Finally, the causal relationship between the study drugs and PSA kinetics changes cannot be proven in the absence of placebo-control trials. Changes in PSA kinetics after study entry, for example, may have been caused by more frequent PSA assessments on-study compared to pre-study PSA evaluations (which would not have been regulated). To this end, in a placebo-controlled trial evaluating the effect of celecoxib on PSADT in a similar patient population, 20% of 40 men in the placebo group had a post-treatment PSADT that was ≥200% of baseline.[7] A recent analysis confirms the natural variability of PSA kinetic parameters even in the absence of therapy.[26] Phrased alternatively, there is no direct evidence that on-study PSA kinetics were induced by the study drugs tested. Furthermore, these agents have not individually demonstrated improvements in survival, neither as a primary endpoint nor in pre-defined subset analyses. Ultimately, the findings of this study will require confirmation in prospective trials using more effective agents as well as longer and more regimented follow-up.

In conclusion, this hypothesis-generating analysis suggests that within-subject changes in PSA velocity and PSA slope (but not PSADT) after initiation of non-hormonal experimental therapies may correlate with survival in men with PSA-recurrent prostate cancer. Additionally, an intuitive cutpoint of increase vs decrease in PSA velocity after therapy was found to correlate with OS. If these findings are validated in prospective trials using survival as the primary endpoint, changes in PSA velocity may represent a reasonable intermediate endpoint for screening new non-hormonal agents in this patient population moving forward. This may facilitate more rapid advancement of promising non-hormonal agents into larger randomized trials with a primary survival endpoint. Given the long natural history of PSA-recurrent prostate cancer, a robust intermediate endpoint is critical. Ultimately, corroboration of these findings will require satisfaction of the Prentice criteria in the setting of randomized, placebo-controlled trials demonstrating a survival benefit in men with biochemically-recurrent prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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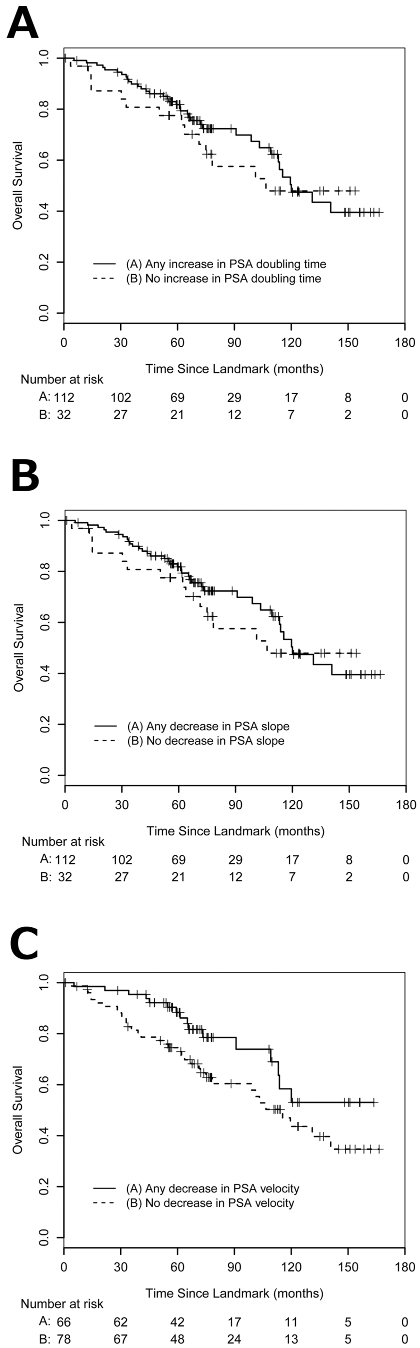

Figure 1.

Overall survival stratified by (A) dichotomous change in PSA doubling time (stratified log-rank test p=0.41), (B) change in (log) PSA slope (stratified log-rank test p=0.41), and (C) change in PSA velocity (stratified log-rank test p=0.02).

Table 1

Patient Baseline Characteristics

Characteristic	**Trial**			
	Marimastat (n = 39)	**Imatinib (n = 25)**	**ATN-224 (n = 22)**	**Lenalidomide (n = 60)**
Minimum PSA requirement for trial entry				
PSA	PSA ≥1.0 ng/mL	PSA ≥1.0 ng/mL	PSA ≥2.0 ng/mL	PSA ≥1.0 ng/mL
PSADT requirement for trial entry				
PSADT	Any PSADT	Any PSADT	PSADT ≤12 months	Any PSADT
Age, y				
Mean (range)	61 (48 to 77)	65 (50 to 77)	62 (53 to 75)	63 (50 to 81)
Median	58	67	63	64
Local therapy				
Prostatectomy only	19 (49%)	5 (20%)	10 (45%)	24 (40%)
Radiotherapy only	4 (10%)	9 (36%)	3 (14%)	11 (18%)
Both	16 (41%)	11 (44%)	9 (41%)	25 (42%)
Gleason score				
≤6	0 (0%)	8 (32%)	5 (23%)	13 (22%)
7	24 (62%)	12 (48%)	7 (32%)	31 (51%)
≥8	15 (38%)	5 (20%)	10 (45%)	16 (27%)
T stage				
T1	0 (0%)	5 (20%)	0 (0%)	7 (12%)
T2	7 (18%)	10 (40%)	12 (55%)	18 (30%)
T3	32 (82%)	10 (40%)	10 (45%)	35 (58%)
N stage				
N0	34 (87%)	25 (100%)	18 (82%)	53 (88%)
N1	5 (13%)	0 (0%)	4 (18%)	7 (12%)
Use of ADT before metastases				
No	27 (69%)	13 (52%)	17 (77%)	53 (88%)
Yes	12 (31%)	12 (48%)	5 (23%)	7 (12%)
Baseline PSA, ng/mL				
Median (Range)	9.6 (1.2 to 59.7)	8 (2.1 to 221)	4.4 (0.7 to 33.5)	7.5 (0.9 to 77.4)
Baseline PSA doubling time, mo				
Median (Range)	4.7 (1.4 to 12.8)	9.2 (1.1 to 30.4)	3.9 (1.2 to 12.2)	4.6 (1 to 58.9)
Baseline PSA slope				
Median (Range)	0.15 (0.05 to 0.49)	0.08 (0.02 to 0.62)	0.18 (0.06 to 0.56)	0.15 (0.01 to 0.71)

Characteristic	Trial			
	Marimastat (n = 39)	**Imatinib (n = 25)**	**ATN-224 (n = 22)**	**Lenalidomide (n = 60)**
Baseline PSA velocity, ng/mL/mo				
Median (Range)	0.4 (0 to 3.9)	0.6 (0.1 to 2.7)	0.7 (0.1 to 16.3)	0.6 (0 to 9.4)
Follow-up Duration, mo				
Median (range)	157.0 (154.2 to 164.4)	126.7 (118.7 to NA)	73.7 (68.9 to 78.8)	83.1 (78.8 to 114.3)
Deaths	18 (46%)	11 (44%)	5 (23%)	15 (25%)

Table 2

Stratified Univariate Cox Regression Analyses for Predicting Overall Srvival in Men with PSA-Recurrent Prostate Cancer Enrolled in All 4 Trials

Variable	Univariate analysis	
	HR (95% CI)	**p-value**
Age, y (continuous)	0.98 (0.94 to 1.02)	0.36
Local therapy		
Surgery (±radiotherapy)	0.65 (0.33, 1.3)	0.23
Radiotherapy only	1 [reference]	
Gleason score		
>7	0.97 (0.41 to 2.27)	0.94
≤7	1 [reference]	
T stage		
T1-2	0.75 (0.4 to 1.4)	0.37
T3	1 [reference]	
N stage		
N0	0.94 (0.36 to 2.42)	0.90
N1	1 [reference]	
Use of ADT prior to metastases		
Yes	0.55 (0.27 to 1.12)	0.10
No	1 [reference]	
Baseline PSA (continuous)	1.00 (0.98 to 1.01)	0.57
Baseline PSA Velocity		
Below median (=0.59 ng/mL/mo)	0.47 (0.26 to 0.84)	0.01
Above median	1 [reference]	
Continuous	0.99 (0.81 to 1.2)	0.90
Δ in PSA velocity		
Decrease	0.47 (0.25 to 0.88)	0.02
No decrease	1 [reference]	
Continuous	1.06 (1.02 to 1.1)	<0.01
Baseline PSADT (mo)		
≥6	0.63 (0.33 to 1.18)	0.147
<6	1 [reference]	
Δ in PSADT		
Increase	0.75 (0.39 to 1.44)	0.39
No increase	1 [reference]	

Variable	**Univariate analysis**	
	HR (95% CI)	**p-value**
Baseline (log) PSA slope		
Below median (=0.14 log[ng/mL]/mo)	0.67 (0.37 to 1.23)	0.20
Above median	1 [reference]	
Continuous	1.54 (0.18 to 12.91)	0.69
Δ in (log) PSA slope		
Decrease	0.75 (0.39 to 1.44)	0.39
No decrease	1 [reference]	
Continuous	5.33 (0.94 to 30.09)	0.06

Table 3

Stratified Landmark Multivariable Cox Regression Analyses for Predicting Overall Survival Considering the Effect of Dichotomous Changes in (A) PSADT, (B) (log) PSA slope, and (C) PSA velocity

Variable	Multivariable analysis					
	(A) PSADT		(B) (log) PSA Slope		(C) PSA Velocity	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, y (continuous)	0.99 (0.94 to 1.03)	0.57	0.98 (0.94 to 1.03)	0.48	0.97 (0.93 to 1.02)	0.25
Gleason score						
<7	1.04 (0.42 to 2.59)	0.93	0.99 (0.4 to 2.46)	0.98	0.99 (0.40 to 2.46)	0.98
≥7	1 [reference]		1 [reference]		1 [reference]	
Local therapy						
Surgery (±radiotherapy)	0.55 (0.25 to 1.20)	0.13	0.58 (0.27 to 1.25)	0.16	0.50 (0.24, 1.07)	0.07
Local therapy	1 [reference]		1 [reference]		1 [reference]	
Use of ADT prior to metastases						
Yes	0.63 (0.3 to 1.32)	0.22	0.60 (0.29 to 1.27)	0.18	0.67 (0.31 to 1.43)	0.30
No	1 [reference]		1 [reference]		1 [reference]	
Baseline PSADT (mo)						
≥6	0.52 (0.27 to 1.07)	0.08				
<6	1 [reference]					
Δ in PSADT						
Increase	0.71 (0.32 to 1.40)	0.33				
No increase	1 [reference]					
Baseline (log) PSA slope						
Below median (=0.14 log[ng/mL]/mo)			0.60 (0.32 to 1.12)	0.11		
Above median			1 [reference]			
Δ in (log) PSA slope						
Decrease			0.79 (0.41 to 1.54)	0.49		
No decrease			1 [reference]			

Variable	Multivariable analysis					
	(A) PSADT		(B) (log) PSA Slope		(C) PSA Velocity	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Baseline PSA Velocity						
Below median (=0.59ng/mL/mo)					0.43 (0.23 to 0.78)	0.01
Above median					1 [reference]	
Δ in PSA velocity						
Decrease					0.52 (0.27 to 1.00)	0.05
No decrease					1 [reference]	

Table 4

Stratified Landmark Multivariable Cox Regression Analyses for Predicting Overall Survival Considering the Effect of Continuous Changes in (A) (log) PSA slope, and (B) PSA velocity

	(A) (log) PSA Slope		(B) PSA Velocity	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, y (continuous)	0.97 (0.93 to 1.02)	0.23	0.97 (0.93 to 1.01)	0.17
Gleason score				
<7	0.98 (0.4 to 2.44)	0.97	0.96 (0.39 to 2.36)	0.93
≥7	1 [reference]		1 [reference]	
Local therapy				
Surgery (±radiotherapy)	0.50 (0.23 to 1.42)	0.08	0.51 (0.24, 1.08)	0.08
Local therapy	1 [reference]		1 [reference]	
Use of ADT prior to metastases				
Yes	0.68 (0.32 to 1.42)	0.30	0.73 (0.35 to 1.52)	0.40
No	1 [reference]		1 [reference]	
Baseline PSADT (mo)				
Δ in PSADT				
Baseline (log) PSA slope	6.77 (0.52 to 88.17)	0.14		
Δ in (log) PSA slope	9.91 (1.54 to 63.93)	0.02		
Baseline PSA Velocity			0.96 (0.76 to 1.22)	0.76
Δ in PSA velocity			1.07 (1.03 to 1.11)	<0.01