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Cut-points for PSA doubling time in men with non-metastatic castration-resistant prostate cancer

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Abstract

Objectives—To examine whether PSADT correlates with metastases, all-cause mortality (ACM), and prostate cancer-specific mortality (PCSM) and identify PSADT cut-points that can be used clinically for risk stratification in men with M0 CRPC.

Materials and Methods—We collected data on 441 men with M0 CRPC in 2000-2015 at five Veterans Affairs hospitals. Cox models were used to test the association between log-transformed PSADT and development of metastasis, ACM, and PCSM. To identify cut-points, we categorized PSADT into groups of every 3 months and then combined groups with similar hazard ratios.

Results—Median follow-up was 28.3 months (IQR: 14.7-49.1). As a continuous variable, PSADT was associated with metastases, ACM, and PCSM (HR 1.40-1.68, all p<0.001). We identified the PSADT cut-points <3, 3-8.9, 9-14.9, ≥15 months. As a categorical variable, PSADT

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Conflicts of Interest: None

was associated with metastases, ACM, and PCSM (all p<0.001). Specifically, PSADT <3 months was associated with about 9 times increased risk of metastases (HR 8.63, 95%CI 5.07-14.7) and PCSM (HR 9.29, 95%CI 5.38-16.0), and 4.7 times increased risk ACM (HR 4.71, 95%CI 2.98-7.43) on multivariable analysis compared to PSADT ≥15 months. Median times to metastasis for patients with PSADT <3, 3-8.9, 9-14.9, and ≥15 months were 9, 19, 40, and 50 months, respectively.

Conclusion—PSADT was a strong predictor of metastases, ACM, and PCSM in patients with M0 CRPC. As with patients at earlier disease stages, <3, 3-8.9, 9-14.9, and ≥15 are reasonable PSADT cut-points for risk stratification in men with M0 CRPC. These cut-points can be used for selecting high-risk men for clinical trials.

Keywords

prostate-specific antigen doubling time; castration-resistant prostate cancer; metastasis; risk stratification

Introduction

Prostate-specific antigen doubling time (PSADT) is an important marker of prostate cancer (PC) aggressiveness. Specifically, shorter PSADT correlates with worse disease outcomes at multiple different stages of prostate cancer.[1-6] While PSADT has been studied at various disease stages, most studies focused on PSADT after recurrence following primary treatment and few considered later stages.

Men with non-metastatic (M0) castration-resistant prostate cancer (CRPC) are at high risk of developing metastases and dying from PC. Risk stratification is needed to determine how closely patients should be followed so they can receive life-prolonging treatments as early as possible as well as to reduce the costs of over-imaging in low-risk men. While PSADT is often used for risk stratification, only a few studies have examined PSA kinetics in men with M0 CRPC. First, a secondary analysis of a clinical trial (n=201) showed faster PSA velocity was associated with increased risk of metastases and all-cause mortality (ACM) in M0 CRPC subjects.[5] Second, another secondary analysis of a 331-person clinical trial with M0 CRPC showed faster PSA velocity was associated with shorter overall survival, but not time to metastases.[7] Third, a post-hoc analysis of a clinical trial examining the efficacy of denosumab in M0 CRPC men at high risk of metastases (PSA ≥8 ng/mL or PSADT ≤10 months) showed that faster PSADT was associated with shorter bone metastasis-free survival and time to bone metastasis.[8] Finally, an observational study of 919 men with M0 CRPC showed that having PSA velocity>1.5ng/ml/year was associated with higher ACM and prostate cancer-specific mortality (PCSM).[9] Of note, though some of these studies examined “PSA velocity”, PSA values were log-transformed, which is mathematically equivalent to analyzing PSADT. However, unlike PSADT, which is commonly used in clinical practice, log-PSA velocity is difficult to interpret clinically. Moreover, with the exception of one paper examining non-log transformed PSA velocity, no study identified optimal cut-points for PSA kinetics. In our previous study of 458 men with CRPC and no known metastases (M0/Mx) at two Veterans Affairs hospitals, we found shorter PSADT was associated with higher risk of metastases.[10] However, the cohort was not restricted to

those with documented M0 CRPC and we did not look at other endpoints such as PCSM and ACM. Thus, in this study we examined whether PSADT correlates with metastases, ACM, and PCSM and identified PSADT cut-points that can be used clinically for risk stratification in men with documented M0 CRPC.

Methods

Study Design

After obtaining Institutional Review Board approval, we collected data on 846 patients diagnosed with CRPC without known metastases (M0/Mx) in the years 2000-2015 from the SEARCH database regardless of primary treatment modality at five Veterans Affairs Medical Centers (Durham, NC; San Francisco, West LA, and San Diego, CA; Augusta, GA). We previously reported methods used to identify these patients.[11, 12] CRPC was defined as a PSA rise of ≥2 and ≥25% from the post-ADT nadir while being castrate.[13] Castration was defined as testosterone <50ng/dL, bilateral orchiectomy, or continuous receipt of luteinizing hormone releasing hormone agonist or antagonist. M0/Mx was defined as the absence of a positive imaging test for distant metastases before CRPC diagnosis. All imaging tests (bone scan, MRI, CT, X-ray) after CRPC diagnosis were assessed by trained personnel to determine development of metastases and metastasis was defined as any lesion >2 centimeters in the smaller diameter. PCSM was defined as having metastases showing progression following hormonal therapy without another obvious cause of death. As we wanted to study PSADT in confirmed M0 CRPC patients, we limited our cohort to those with a negative bone scan after CRPC diagnosis (n=474) and those with calculable PSADT (n=441).

Statistical Analysis

PSADT was calculated by log(2) divided by the slope of the linear regression of log(PSA) over time in months.[14] Subjects with PSADT <0 or >120 were assigned 120 months for ease of analysis. All PSA values two years after CRPC diagnosis but before the development of metastasis were used to calculate PSADT. This calculation required at least two PSA values over at least three months.

Cox proportional hazards models were used to test the association between PSADT and metastasis (primary outcome), ACM (secondary outcome), and PCSM (secondary outcome). In a sensitivity analysis, competing risks regression[15] was used to assess whether the relationship between PSADT and PCSM differed after accounting for non-PC death as the competing risk. Time zero was at the first negative bone scan after CRPC diagnosis. Univariable models and models adjusted for PSA at the time of the negative bone scan were fit, as our previous study in the same cohort showed that PSA and PSADT were the only significant predictors of metastases.[10] PSADT was measured in months and log-transformed in analyses. We also sought to find optimal cut-points for PSADT in M0 CRPC patients. To do this, we categorized PSADT into groups of every 3 months (<3, 3-5.9, 6-8.9, 9-11.9, 12-14.9, 15-17.9, 18-20.9, 21-23.9, 24-119.9, 120) and then combined groups with similar hazard ratios (Supplementary Tables 1 and 2). Harrell's c-index[16] was used to test the accuracy of PSADT as a predictor of each endpoint. Cumulative incidence curves were

used to graphically show the relationship between PSADT and each endpoint. The log-rank test was used to compare survival among the PSADT groups. A sensitivity analysis was performed using PSADT calculated using only PSAs before the negative baseline scan (N=338). Spearman correlation was used to compare PSADT calculated using only PSAs before baseline and PSADT calculated using 2 years of PSAs after negative baseline bone scan.

Statistical analyses were performed in Stata v14.0 (Stata Corp, College Station, TX). $P<0.05$ was the threshold for statistical significance.

Results

Patient Characteristics

Median age was 77 (IQR: 70-83) and median year of negative bone scan was 2006 (IQR: 2004-2010). There were 160 (36%) black patients. Median follow-up from negative bone scan was 28.3 months (IQR: 14.7-49.1) and 44.8 months (IQR: 27.2-69.7) from CRPC diagnosis. Median duration of ADT prior to developing CRPC was 46.3 months (IQR: 24.4-80.5). During follow-up, 223 (51%) developed metastases, 181 (41%) died of PC, and 119 (27%) died of causes other than PC. At the time of initial metastasis diagnosis, 73% had metastasis in the bone only, 17% had soft tissue metastasis only, and 10% had metastasis in the bone and soft tissue.

PSADT and Metastases

On univariable analysis, shorter PSADT was associated with higher risk of metastases (HR=1.68, 95%CI 1.48-1.90, $p<0.001$; Table 2). After segregating patients into groups based on cut-points for PSADT every 3 months and combining groups with similar hazard ratios, we identified the following cut-points: <3, 3-8.9, 9-14.9, ≥15 months. Compared to PSADT≥15 months, the hazard ratios for PSADT 9-14.9, 3-8.9, and <3 months were 1.33 (95%CI 0.87-2.02), 3.30 (95%CI 2.41-4.51), and 10.0 (95%CI 5.93-16.9), respectively ($p<0.001$). After adjusting for PSA, results were largely unchanged. The c-index for the univariable model was 0.676 and 0.704 for the multivariable model.

PSADT and PCSM

Shorter PSADT as both a continuous (HR=1.68, 95%CI 1.46-1.92, $p<0.001$; Table 3) and categorical variable was significantly associated with increased risk of PCSM on univariable analysis ($p<0.001$). Specifically, the hazard ratios for PSADT 9-14.9 months, 3-8.9 months, and <3 months were 1.59 (95%CI 1.03-2.47), 2.90 (95%CI 2.04-4.13), and 12.4 (95%CI 7.25-21.2), respectively, compared to PSADT ≥15 months. Results were similar after adjusting for PSA. The c-indexes of the univariable and multivariable models were 0.679 and 0.729, respectively. With non-PC death as a competing risk, PSADT remained a predictor of PCSM, although results were slightly attenuated (Supplementary Table 3).

PSADT and ACM

Similar to PCSM, on univariable analysis, shorter PSADT both as a continuous (HR=1.40, 95%CI 1.27-1.54, $p<0.001$; Table 4) and categorical variable ($p<0.001$) was associated with

higher risk of ACM. Specifically, the hazard ratios for PSADT 9-14.9 months, 3-8.9 months, and <3 months were 1.42 (95%CI 1.02-1.96), 1.98 (95%CI 1.51-2.61), and 5.83 (95%CI 3.72-9.12), respectively, compared to PSADT ≥15 months. After adjusting for PSA, results were similar. The c-indexes for the univariable and multivariable results were 0.610 and 0.652, respectively.

Figures 1a-c show the Kaplan-Meier curves for metastases, PCSM, and ACM stratified by PSADT group. Men with a PSADT<3 months had a median 9 months to metastases, 16 months to PCSM, and 15 months to ACM. In contrast, men with a PSADT>15 months, had a median time to metastases of 50 months, 67 months to PCSM, and 46 months to ACM.

Sensitivity Analysis

The Spearman correlation between PSADT calculated with 2 years of PSAs after negative baseline bone scan and PSADT calculated using only PSAs before baseline was 0.73. All results were similar when using only PSA values before the baseline negative imaging scan, although c-indices were slightly lower (0.66 vs. 0.70 for metastases).

Discussion

We previously showed in men with M0/Mx CRPC, PSADT is a strong predictor of developing metastases.[10] However, whether PSADT predicts later outcomes (i.e. PCSM and ACM) and the best cut-points to categorize PSADT in this population remain unclear. To address this, we tested the association between PSADT and clinical endpoints after M0 CRPC diagnosis. When treated as a continuous variable, shorter PSADT was associated with increased risk of metastases, PCSM, and ACM, even after adjusting for PSA. We then identified PSADT cut-points of <3, 3-8.9, 9-14.9, ≥15 months, which also significantly predicted all three outcomes with longer PSADT predicting lower risk. PSADT and our defined cut-points can be used for risk stratification in patients with M0 CRPC.

Previous studies have shown associations between PSADT and clinical endpoints among patients with M0 CRPC. We recently analyzed 458 men with M0/Mx CRPC and showed shorter PSADT was associated with higher risk of metastases.[10] However, in our prior study, we did not restrict to those with documented M0 CRPC or look at other outcomes. Two secondary analyses of clinical trials of men with M0 CRPC calculated PSA velocity using log-transformed PSA values, which is mathematically equivalent to analyzing PSADT but difficult to interpret clinically. Similar to our findings, the first study (n=201) found an association between faster PSA velocity and increased risk of metastases and ACM.[5] The other study (n=331) found faster PSA velocity was associated with higher risk of ACM, but not metastases.[7] PSA velocity was only available on a subset of patients, so this lack of association may be attributed to low power. Another post-hoc analysis of a clinical trial (N=1432) examined the efficacy of denosumab in M0 CRPC men at high risk of metastases (PSA ≥8 ng/mL or PSADT ≤10 months). [8] They showed that faster PSADT was associated with shorter bone metastasis-free survival and time to bone metastasis, and denosumab was more effective in men with higher risk of progression, defined by shorter PSADT cut points (≤10, ≤6, ≤4 months). This trial was limited to high risk men (PSADT <10 months) and showed that shorter PSADT was higher risk, but did not investigate

optimal PSADT cut points or examine PCSM. The final study using observational data (n=919) found faster PSA velocity, using non-log transformed PSA values, was associated with higher risk of ACM and PCSM.[9] This study identified an optimal cut-point for PSA velocity in their population of 1.5 ng/ml/year. However, in men with later stage PC, PSADT tends to better capture tumor growth kinetics than PSA velocity given the majority of PSA increases post-definitive therapy show first order kinetics.[17] Though it is clear that PSA kinetics are valuable prognostic factors in men with M0 CRPC, no study has systematically examined PSADT cut-points to aid in clinical risk stratification.

To choose cut-points for PSADT, we divided PSADT into 3-month intervals and tested the association between each PSADT category and metastases and PCSM. As with any linear continuous variable, any cut-point is reasonable if there are sufficient numbers in each group and large enough differences in recurrence risks among groups to have clinical utility. By combining groups with similar hazard ratios, we chose the cut-points <3, 3-8.9, 9-14.9, ≥15 months for PSADT. Our choice was also guided by literature that used these cut-points for risk stratification in the hormone-sensitive stages of PC,[2] which have been externally validated.[18] Intuitively, one might think that PSADT in men who progressed to CRPC would be faster than PSADT at the time of initial recurrence after surgery, thus mandating more cut-points in the shorter end of the PSADT spectrum, such does not appear to be the case. For example, median PSADT in our study was 13.3 months. This is similar to the 9.7 months reported in another study of M0 CRPC patients.[5] Notably, this disease stage is certainly different from metastatic CRPC, in which PSADT tends to be quite short.[6] However, many men with M0 CRPC will not progress or will progress slowly and therefore have slow PSADT. Indeed, almost half of our cohort had PSADT≥15 months and among these men, median time to metastasis was over 4 years, suggesting that observation may be a viable management strategy for these men.

Other prior studies examined PSADT in other PC disease stages. Klotz et al conducted a prospective study of 240 patients undergoing active surveillance and found that PSADT<3 years was associated with higher risk of biochemical failure after definitive treatment.[3] An observational study that included 8,669 men receiving primary localized treatment found that PSADT<3 months following treatment was associated with higher risk of PCSM.[4] Other studies of men with metastatic CRPC found associations between shorter PSADT and increased risk of ACM.[6, 19-21] These studies using single cut-points for PSADT ranging from 45-70 days which were based on median PSADT value in the study[6, 19] or by optimizing the cut-point which was only 10 days different from the median[20]. It is clear that PSADT has practical implications in many PC disease stages. However, it is also clear that there are no standardized cut-points with cut-points ranging from 3 years in patients with localized PC to 45 days for patients with metastatic PC. We hope that by confirming that the PSADT cut-points <3, 3-8.9, 9-14.9, and ≥15 months are valuable in the M0 CRPC population in addition to those recurring after radical prostatectomy[2], researchers and clinicians will be more willing to use these cut-points for risk stratification and allow uniform criteria for clinical trials enrollment. In addition, our data suggest that scanning practices for detection of metastases should be risk-adapted incorporating PSADT, a concept previously proposed by the RADAR group.[22]

A strength of our study is that we used PCSM as a clinical endpoint, while most prior studies examining PSADT did not. Death from PC is the ultimate clinical endpoint that represents the aggressiveness of the disease and how well the disease was managed clinically. In our study, 192 (41%) men died of PC and 132 (27%) died of other causes, meaning only 59% of men with M0 CRPC actually died from PC.[9] In the CaPSURE study of men who all received primary localized therapy and later progressed to M0 CRPC, 40% of the deaths were from PC. This shows that M0 CRPC is not necessarily a fatal disease, with about half of patients dying from other causes. Indeed at earlier stages of the disease, risk of PCSM is even lower, with only 1% of all men treated with localized therapy in the CaPSURE study dying from PC.[23] Given that a large percentage of men – even with M0 CRPC – will die of causes other than PC, it is important that future PC studies include PCSM as an end point.

Our study is not without limitations. As this was an observational study, we were limited to the PSAs available in the Veterans Affairs medical records for calculating PSADT. However, we were still able to calculate PSADT on 93% of patients. Furthermore, there was no consistent timing of scans, PSAs, and visits among patients. Due to inconsistent timing of PSAs, our calculation for PSADT only required two PSA values over at least three months. While this may not always capture an accurate PSA trajectory, we still found that PSADT was a strong predictor of prostate cancer outcome. If PSADT had been calculated using multiple PSA values in an optimized fashion, it is likely it would have been an even stronger predictor of poor outcome. Additionally, our previous study of M0 CRPC patients showed that patients with shorter PSADT had a shorter time to repeat bone scan when the baseline was negative, but these differences were modest when compared to the big difference in risk of metastases.[24] We assumed that patients stayed consistently on ADT after CRPC diagnosis, although there are no data that suggest intermittent ADT impacts PC endpoints. Imaging was at the discretion of the treating physician, so patients could have had metastases without being detected. To calculate PSADT, we used PSAs from after baseline which violates the assumption of Cox models. However, this is common practice in M0 CRPC populations since PSA is undetectable prior to CRPC diagnosis.[5, 7, 9] We assumed that PSA values increased exponentially over time and that using two years' worth of PSAs would smooth over any PSA errors. We only used PSAs that occurred before diagnosis of metastases at which point patients are eligible to receive treatments that affect PSAs. Although we did not study PSADT in patients at the time of initial CRPC diagnosis, but rather at first negative bone scan after CRPC diagnosis, we believe the concept of shorter PSADT correlating with worse prognosis would still hold at the time of initial CRPC diagnosis. Lastly, we did not account for secondary treatments that could affect survival, although most medications were not approved until after most patients had died or been censored as lost to follow-up.

In summary, we found that PSADT was a strong predictor of metastases, ACM, and PCSM in patients with documented M0 CRPC. As with patients at earlier disease stages, <3, 3-8.9, 9-14.9, and ≥15 are reasonable cut-points to use for risk stratification in men with M0 CRPC. These cut-points should be further validated in other M0 CRPC cohorts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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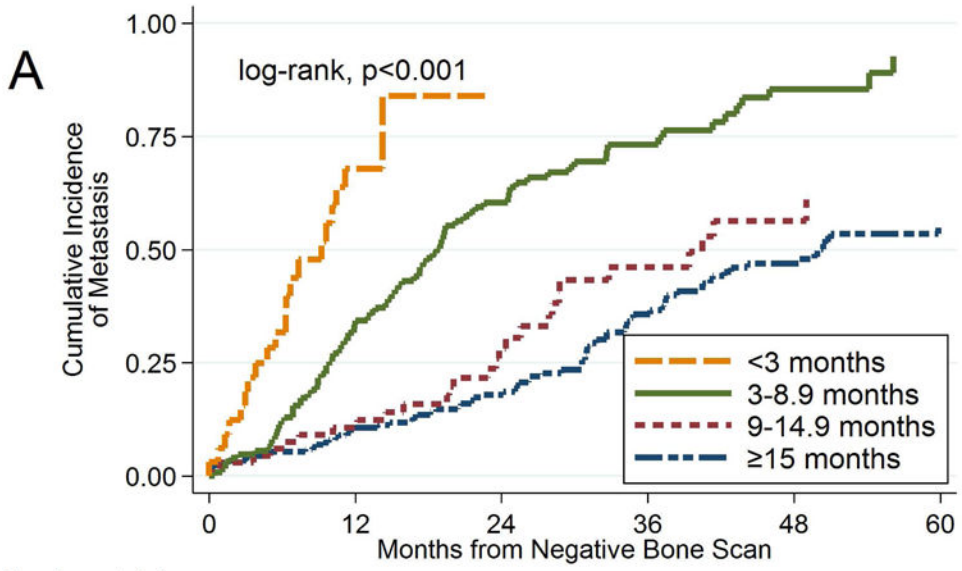
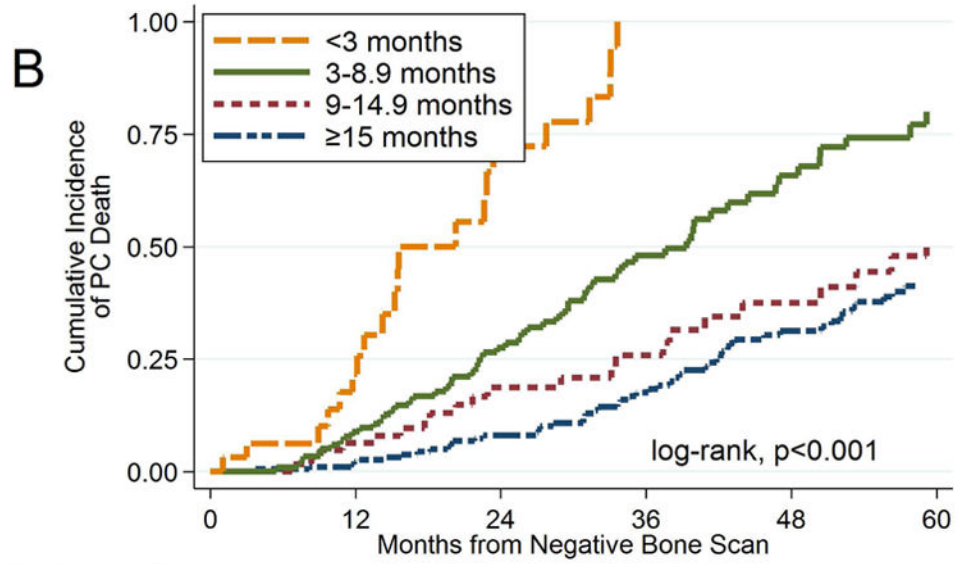


Number at risk						
<3 months	33	7	0	0	0	0
3-8.9 months	128	73	36	17	7	2
9-14.9 months	69	54	32	17	10	8
≥15 months	210	163	122	77	51	33



Number at risk						
<3 months	33	19	5	0	0	0
3-8.9 months	128	98	65	35	17	7
9-14.9 months	69	58	41	28	19	14
≥15 months	210	180	140	102	69	49

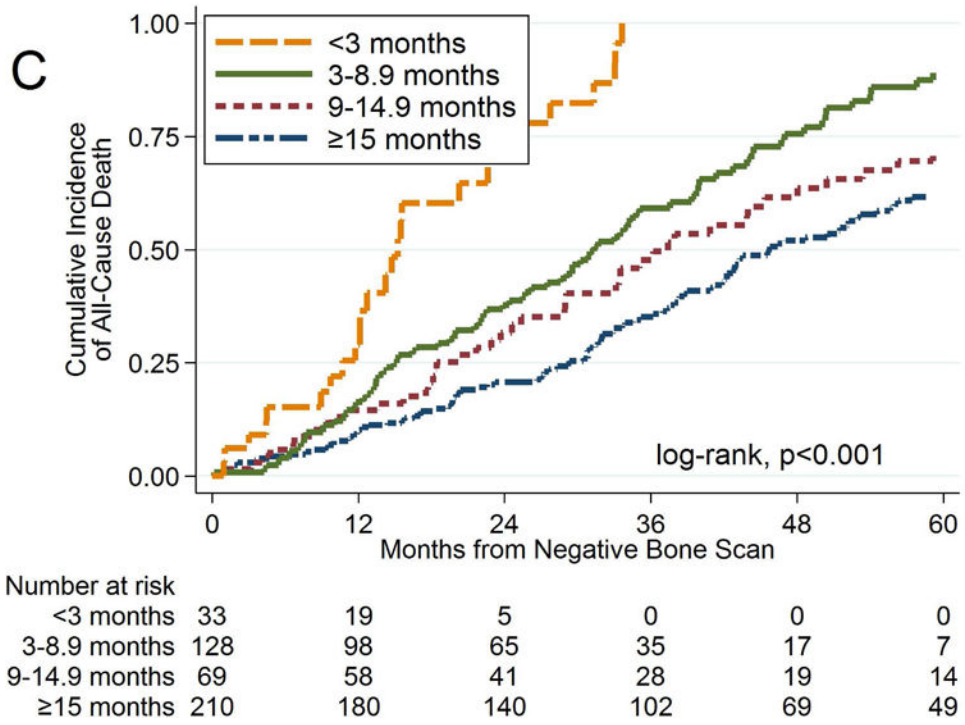


Figure 1.

Cumulative incidence of (A) metastases, (B) prostate cancer-specific mortality, and (C) all-cause deaths among patients with PSADT less than 3 months, PSADT 3-8.9 months, PSADT 9-14.9 months, PSADT greater than or equal to 15 months

Acronyms: PC prostate cancer; PSADT prostate-specific antigen doubling time

Table 1
Patient characteristics at time of negative bone scan

Variables	N (%) or Median (p25-p75)
Number of patients	441
Age (years)	77 (70-83)
Year	2006 (2004-2010)
Race	
Non-black	280 (64%)
Black	160 (36%)
Unknown	1 (<1%)
Treatment center	
Center 1	111 (25%)
Center 2	131 (30%)
Center 3	46 (10%)
Center 4	41 (9%)
Center 5	112 (26%)
Biopsy Gleason score	
2-6	79 (18%)
7	95 (21%)
8-10	114 (26%)
Unknown/No Biopsy	153 (35%)
Primary localized treatment	
None	201 (46%)
Radical Prostatectomy/Radiation	240 (54%)
PSA (ng/mL)	8.0 (4.2-19.4)
PSADT (months)	13.3 (6.4-94.3)
Months from CRPC to negative scan	9.1 (3.9-20.4)
Months from ADT to CRPC	46.3 (24.4-80.5)
Total follow-up (months) *	28.3 (14.7-49.1)

p25: 25th percentile; p75: 75th percentile; PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time; CRPC: castration-resistant prostate cancer

* Reported among patients who did not die

Table 2

PSADT at M0 CRPC as a predictor of metastases

		Univariable			Multivariable*		
	n	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
PSADT****, months (continuous)**	223/441	1.68	1.48-1.90	<0.001	1.59	1.40-1.80	<0.001
PSADT				<0.001			<0.001
≥15 months	87/210	*Ref.*			*Ref.*		
9-14.9 months	29/69	1.33	0.87-2.02		1.31	0.86-2.00	
3-8.9 months	86/129	3.30	2.41-4.51		2.85	2.06-3.94	
<3 months	21/33	10.0	5.93-16.9		8.63	5.07-14.7	

PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time; HR: hazard ratio; CI: confidence interval

*Adjusted for PSA

**PSADT was log-transformed for the continuous analysis

Note: HR>1 for continuous PSADT indicates that a shorter PSADT is associated with increased risk of metastases

c-index=0.676 for univariable model and c-index=0.704 for multivariable model

Table 3

PSADT at M0 CRPC as a predictor of prostate cancer-specific morality

		Univariable			Multivariable*		
	n	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
PSADT****, months (continuous)**	181/441	1.68	1.46-1.92	<0.001	1.56	1.36-1.78	<0.001
PSADT				<0.001			<0.001
≥15 months	68/210	*Ref.*			*Ref.*		
9-14.9 months	29/69	1.59	1.03-2.47		1.56	1.01-2.42	
3-8.9 months	63/129	2.90	2.04-4.13		2.42	1.69-3.47	
<3 months	21/33	12.4	7.25-21.2		9.29	5.38-16.0	

PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time; HR: hazard ratio; CI: confidence interval

*Adjusted for PSA

**PSADT was log-transformed for the continuous analysis

Note: HR>1 for continuous PSADT indicates that a shorter PSADT is associated with increased risk of prostate cancer-specific mortality

c-index=0.679 for univariable model and c-index=0.729 for multivariable model

Table 4

PSADT at M0 CRPC as a predictor of all-cause mortality

		Univariable			Multivariable*		
	n	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
PSADT****, months (continuous)**	300/441	1.40	1.27-1.54	<0.001	1.33	1.20-1.47	<0.001
PSADT				<0.001			<0.001
≥15 months	133/210	*Ref.*			*Ref.*		
9-14.9 months	51/69	1.42	1.02-1.96		1.39	1.00-1.92	
3-8.9 months	90/129	1.98	1.51-2.61		1.72	1.30-2.28	
<3 months	26/33	5.83	3.72-9.12		4.71	2.98-7.43	

PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time; HR: hazard ratio; CI: confidence interval

*Adjusted for PSA

**PSADT was log-transformed for the continuous analysis

Note: HR>1 for continuous PSADT indicates that a shorter PSADT is associated with increased risk of all-cause mortality

c-index=0.610 for univariable model and c-index=0.652 for multivariable model