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Elevated Alkaline Phosphatase Velocity Strongly Predicts Overall Survival and the Risk of Bone Metastases in Castrate Resistant Prostate Cancer

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Abstract

OBJECTIVES—In patients with a rising prostate-specific antigen level (PSA) during treatment with androgen deprivation therapy (ADT), identification of men who will progress to bone metastasis and death remains problematic. Accurate risk stratification models are needed to better predict risk for bone metastasis and death among patients with castrate resistant prostate cancer (CRPC). This study evaluates whether alkaline phosphatase kinetics predict bone metastasis and death in patients with CRPC.

METHODS AND MATERIALS—A retrospective cohort study of 9547 patients who underwent treatment for prostate cancer (PCa) was conducted using the Center for Prostate Disease Research (CPDR) multi-center national database. From the entire cohort, 347 were found to have CRPC and, of those, 165 had two or more alkaline phosphatase measurements during follow up. To determine an Alkaline Phosphatase Velocity (APV) the slope of the linear regression line of all AP values was plotted over time. Rapid APV was defined as the uppermost quartile of APV values which was found to be 6.3 IU/L/yr. CRPC was defined as two consecutive rising PSA values after achieving a PSA nadir <4ng/mL and documented testosterone values less than 50ng/dL. The primary study outcomes included Bone Metastasis Free Survival (BMFS) and Overall Survival (OS).

RESULTS—Rapid APV and PSADT less than 10 months were strong predictors of both BMFS and OS in multivariable analysis. Faster PSADT was a stronger predictor for BMFS (OR 12.1 $p < 0.0001$ vs 2.7 $p = 0.011$) whereas rapid APV was a stronger predictor of poorer OS (OR 5.11 $p = 0.0001$ vs. 3.98 $p = 0.0034$). In those with both a rapid APV and faster PSADT, the odds of developing bone metastasis and death exceeded 50%.

CONCLUSION—APV is an independent predictor of OS and BMFS in patients with CRPC. APV, in conjunction with PSA-based clinical parameters, may be used to better identify CRPC patients who are at highest risk of metastasis and death. These findings need validation in prospective studies.

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Keywords

prostate cancer; bone metastasis; bone-metastasis free survival; overall survival; alkaline phosphatase; prostate specific antigen (PSA); PSA doubling time (PSADT); alkaline phosphatase velocity (APV)

INTRODUCTION

Alkaline phosphatase (AP) has long been known as a nonspecific bone turnover marker that has been used to evaluate efficacy of treatment as well as to predict overall survival in men with castration resistant prostate cancer (CRPC).¹⁻⁴ Currently, PSA-based methods are employed to stratify men by risk of going on to develop bone metastases^{5,6} despite evidence that this may not enrich clinical trials sufficiently.⁷ Given the conflicting data currently available and the resulting lack of accurate predictive models, this study analyzed the Center for Prostate Disease Research multi-center national database in an attempt to identify whether Alkaline Phosphatase Velocity (APV) identifies patients at highest risk for bone metastases. Alkaline phosphatase has long been known as a bone turnover marker with very stable intra-individual measurement kinetics, thus it was hypothesized that APV might improve current PSA-based risk stratification.^{8,9}

Men who progress to CRPC and then to bone metastases are much more likely to die of their disease than patients with any other stage of prostate cancer. In addition, the morbidity and cost of caring for these patients increase dramatically as they enter this late stage of their disease. As such, it is a clinical imperative to improve identification of patients most likely to progress to this terminal stage of the disease.

MATERIALS AND METHODS

Study Population

The study population was comprised of men enrolled in the institutional review board-approved Center for Prostate Disease Research (CPDR) multicenter national database as previously described.¹⁰ The study population included patients with biopsy-confirmed PCA detected between January 1, 1989 and December 31, 2010 who had androgen deprivation therapy (ADT) as primary treatment or secondary to either radical prostatectomy (RP) or external beam radiation therapy. Indication for ADT was not recorded, though patients were excluded if detectable metastases were observed either prior to or at the time of ADT initiation or within the first 12 months following ADT initiation to reduce the likelihood of occult metastases. In this retrospective cohort, as in most settings apart from randomized clinical trials, the rationale and timing for bone imaging is variable. This study population was restricted to castrate resistant prostate cancer subjects who achieved a PSA nadir of ≤ 4 ng/mL, had rising PSA despite ADT, and a testosterone value < 50 ng/dL ($n=347$). Hussain *et al.* demonstrated that men who have a PSA nadir > 4 ng/mL have a very short median survival of 13 months, therefore we excluded these individuals so that the effect of APV would be evaluated in men who better reflect the majority of men with CRPC.¹¹ Rising PSA was defined two consecutive increases above nadir for radiation or primary ADT subjects

and two consecutive rises above undetectable for subjects who underwent prostatectomy. Patients taking medications such as bisphosphonates that could affect AP levels or kinetics were excluded. Finally, only those with no radiographic evidence of metastasis at baseline and two or more AP measurements at least 3 months apart following initiation of ADT were considered (n=165).

Demographic and Clinical Characteristics

The following demographic and clinical data for each subject were obtained: age at PCa diagnosis, race/ethnicity, PSA at diagnosis (ng/mL), clinical T stage (T1–T2b, T2c), biopsy Gleason sum (2–7, 8–10) and PSA doubling time (PSADT). The PSADT was calculated as previously described by Pound et al.¹² PSADT was computed using all available PSA values at least 3 months apart after CRPC. If the slope of the linear regression line was 0 (i.e., elevated but constant PSA levels), the PSADT was arbitrarily set to 120 months. Too few subjects were observed per PSADT strata of Freedland et al.; therefore, the cut points of Pound et al. were used to dichotomize PSADT as <10 versus ≥10 months.^{12,13}

Finally, a kinetics measure of alkaline phosphatase velocity (APV) was calculated by using the slope of the linear regression line of the AP values plotted against time in years. This was computed using all AP values drawn at least 3 months apart obtained after CRPC developed but before radiographic scan-detected bone metastases. APV was dichotomized at the upper quartile of all observed AP values in this study sample (<6.3 vs. ≥6.3 U/L/year) in order to compare those with the fastest rate of change to all other patients. The APV measure could not be treated continuously due to non-normality and skew in its distribution.

An indicator variable was used to examine treatment as primary ADT versus ADT secondary to RP, or ADT secondary to EBRT. Time variables of interest included time elapsed between: (1) date of PCa diagnosis and ADT treatment, (2) date of ADT initiation and PSA nadir and (3) date of ADT initiation and time at which rising PSA status was documented.

Study Endpoints

The study endpoints included bone metastasis free survival (BMFS) and overall survival (OS). Presence of bony metastases was ascertained by review of each patient's complete radiographic scan history, captured as part of ongoing data collection activities for the CPDR multicenter national database. Duration of BMFS was calculated as the number of years elapsed from time point of documented rising PSA status until end of study period. Subjects who had no evidence of bone metastases were censored at end of study period. Overall survival was used because overall survival data are recorded and available in CPDR and because determining prostate cancer specific mortality is challenging under the best of circumstances.¹⁴

Statistical Analysis

Student *t* tests or Wilcoxon-Mann-Whitney tests were used to compare distributions in continuous patient characteristics, including age and time variables, across APV groups.

Mantel Haenzsel chi-square tests were used to examine whether there were significant differences in the distributions of categorical variables across APV groups.

Kaplan Meier crude estimation time-to-event curves were used to model BMFS across strata of APV split at upper quartile (<6.3 U/L/year versus ≥ 6.3 U/L/year). The log rank test and its associated p-value were used to assess the effects of APV on bone metastasis-free survival. Multivariable Cox proportional hazards analyses were used to model BMFS controlling for demographic, clinical, treatment, and time covariates. To improve model parsimony, a stepwise approach was used to select and retain variables, using the forward selection criterion of $p = 0.20$, and backward selection criterion of $p = 0.15$.

All statistical tests are 2-sided (summary alpha error = 0.05), and the decision rule was based on a p-value < 0.05 . All statistical analyses were performed using SAS version 9.3 and R.

RESULTS

Demographics

Among the 347 subjects in the database with rising PSA following ADT, 165 (47.6%) patients in the cohort had two or more AP values, permitting an APV calculation. Demographic and clinical characteristics were compared for those patients included in the analysis versus those excluded due to inadequate AP data in Table 1. Patients with AP data had a higher median diagnostic PSA (16.5 vs. 10.1 ng/mL, $p < 0.0001$), a shorter median time from ADT to CRPC (16.9 vs. 21.7, $p = 0.0503$), and a higher proportion who developed bone metastases at any point during follow up (21.8% vs. 8.8%; $p = 0.0007$). Post-ADT PSA nadir values were noted to be significantly lower in the AP group without data versus those with AP data ($p < 0.0001$) though values were small in both groups. A higher proportion of those with AP data had T2c disease ($p = 0.0260$) and faster PSADT ($p = 0.0130$).

Univariable comparisons of clinical and pathological characteristics of the study sample were also performed across APV strata. Higher median post-ADT PSA nadir was observed in the rapid versus slow APV group (0.16 versus 0.09 ng/mL, respectively; $p = 0.0233$). Also, PSADT was significantly different across APV strata ($p < 0.0001$); among those with faster PSADT, APV was less likely to be slow than rapid (34% vs. 76%). The median number of AP lab values available for each patient was 4.0 and did not differ across slow versus rapid APV groups ($p = 0.33$).

Table 2A summarizes the univariable comparisons of clinical and pathological characteristics of the study sample across metastasis status. Longer median follow-up time after ADT was observed among those who did not experience metastasis ($p = 0.0335$). Median PSA nadir values following ADT were significantly higher among those who developed metastasis ($p = 0.0017$) though values were small in each group. As expected, those with faster PSADT and rapid APV were significantly more likely to eventually be detected with metastasis ($p < 0.0001$ and $p = 0.0004$, respectively). In Figure 1, the unadjusted Kaplan-Meier estimation curve illustrates that rapid APV predicts shorter BMFS ($p < 0.0001$). Few metastatic events were observed after 10 years follow-up time.

When PSADT and APV were examined jointly, it was noted that 54.8% of patients with both rapid APV (≥ 6.3 U/L/yr) and shorter PSADT (< 10 months) developed bone metastases whereas only 33.3% developed bone metastases when PSADT was short but APV was less than 6.3U/L/yr. (*data not shown*).

Table 2B summarizes the univariable comparisons of clinical and pathological characteristics of the study sample across survival status. A shorter median time of follow up from CRPC was observed among those who died ($p=0.0034$). Median PSA nadir values following ADT were statistically significantly higher among those who died ($p=0.0180$) though values were very small in each group. The number of bone scans was also statistically different with an average of 3 among those who died compared to 2 for those who did not ($p=0.0012$). A greater proportion of men who died had higher clinical T stage (T2 or greater) compared to those who were alive at last follow up ($p=0.0111$). As expected, those with faster PSADT and rapid APV demonstrated poorer overall survival ($p<0.0001$ and $p=0.0001$, respectively). In Figure 2, the unadjusted Kaplan-Meier estimation curve illustrates that rapid APV predicts significantly shorter OS ($p<0.0001$).

In Table 3A, a step-wise multivariable Cox proportional hazards model demonstrated that both faster PSADT and rapid APV were significant independent predictors of poorer BMFS; subjects with rapid APV were 2.7 times as likely to develop a bone metastasis over time compared to subjects with a slower APV (HOR = 2.70; 95% CI = 1.25, 5.80; $p = 0.011$) and those with faster versus slower PSADT had a 12-fold increased odds of developing a bone metastasis (HOR=12.1, 95% CI = 3.59, 40.54; $p<0.0001$).

To assess for a detection bias given that bone scans were done at the discretion of the treating physician, the number of bone scans per APV strata was evaluated. Among patients with rapid APV, the median number of bone scans was 3.0 with a range of 1–7; whereas, among men with a slower APV, the median was 2.0 with a range of 1–9 ($p=0.101$) (*data not shown*).

In Table 3B, a step-wise multivariable Cox proportional hazards model demonstrated that both faster PSADT and rapid APV were significant independent predictors of poorer OS. A four-fold increase in death was observed for faster PSADT (HOR=3.98, 95% CI = 1.58, 10.01; $p=0.0034$) whereas a more than five-fold increase in death was observed among patients with a rapid APV (HOR=5.11, 95% CI =2.24, 11.67; $p = 0.0001$).

In patients with rapid APV and faster PSADT, the odds of all-cause death approached 60% whereas only 23.8% of patients with a faster PSADT but slower APV experienced this outcome. (*data not shown*).

COMMENT

Biomarkers of bone turnover have been used in clinical practice for decades, but their predictive utility has not been definitively proven. Historically, single cut-points for bone biomarkers have been used to identify risk of prostate cancer development as well as disease progression and death.^{15–17} Despite the numerous evaluations of newer bone turnover markers, none has proven valuable in predicting which men are at highest risk for

developing bone metastases.^{2,16,18–20} These data indicate that a rapid APV is associated with an increased risk of bone metastasis and overall survival independent of other more commonly used parameters such as PSA, PSA nadir and PSADT. Our data indicate that the addition of APV to PSADT-based stratification methods may significantly enhance clinical ability to identify men at the greatest risk for developing bone metastases.

Historically, the previous applications of AP in the literature relied on values above the normal reference range; in contrast, our data suggests that the predictive value of APV for both bone metastasis and overall survival is predominantly within the normal range. In clinical practice, small changes in AP values within the normal range are generally not considered to be significant, and only when the values rise above the normal reference range are additional investigations undertaken. The findings presented here suggest that subtle but consistent changes of AP within the normal reference range may be of greater clinical value than previously thought.

The limitations of these data, in addition to the usual limitations of retrospective analyses, include the lack of availability of prostate cancer-specific mortality (PCSM) although accurate determination of PCSM has been shown to be problematic even in the most controlled settings.¹⁴ The relative scarcity of AP data resulted in an exclusion cohort that was slightly larger as the inclusion group. Furthermore, there may be evidence of an ascertainment bias since the group with adequate AP data also had statistically significant differences in PSA at diagnosis, time from ADT to CRPC and post-ADT PSA nadir. The PSA nadir differences may be statistically significant, but with values of 0.1 for both groups, it is most certainly not clinically relevant. And it stands to reason that the group with longer median follow up is more likely to have more laboratory values suggesting that most of these differences are not the result of ascertainment bias. Among the men who developed CRPC, the men in the AP-adequate cohort appeared to be at higher risk for developing bone metastases compared to the group for which AP data is lacking. It is very likely that these differences do not undermine the utility of APV as a metric for predicting BMFS. Conversely, data clearly show that in this high-risk cohort, APV is a strong independent predictor of BMFS and OS particularly when applied in conjunction with previously established PSADT parameters. Previous clinical trials have attempted to enrich their study population for men at high risk for developing bone metastases using only PSA-based parameters, but this approach was inadequate because the study was closed early due to inadequate number of events.⁷ It is precisely this type of high risk population in which APV might be useful to better identify men at highest risk for developing bone metastases.

Another limitation of this study is the chosen endpoint of BMFS. PCSM was not available within the database, and other studies have used similar surrogates in evaluating prostate cancer and bone metastases.^{5,21} However, BMFS is dependent upon timing of bone scans which was done at the discretion of the treating physician and therefore uncontrolled. However, no significant difference in scan frequency per APV strata was found. Furthermore, both the mean and median values for AP were within the normal reference range for AP in both APV strata suggesting that bone scans were not ordered based upon AP values or kinetics. Finally, the OS analysis of APV also demonstrates strongly significant

predictive value suggesting that the impact of different bone scan frequency is unlikely to be a major confounder.

As more expensive therapies for metastatic prostate cancer are being brought to market, it is increasingly important to be able to accurately identify appropriate patients in order to avoid overtreatment and unnecessary expense. Clinical application of APV in conjunction with PSADT could enable physicians to reserve more effective, toxic and expensive therapies for those who need them most.

CONCLUSIONS

Alkaline Phosphatase Velocity (APV) appears to be a strong independent predictor of bone metastases and overall survival in men with rising PSA on ADT in this retrospective cohort study. These data suggest the hypothesis that subtle changes within the normal range of alkaline phosphatase may be clinically relevant. Further study is needed to prospectively and externally validate these hypothesis-generating findings.

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REFERENCES

1. Sonpavde G, Pond GR, Berry WR, et al. Serum alkaline phosphatase changes predict survival independent of PSA changes in men with castration-resistant prostate cancer and bone metastasis receiving chemotherapy. *Urol Oncol*. 2010; 30:607–613. [PubMed: 20888271]
2. Cook RJ, Coleman R, Brown J, et al. Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. *Clin Cancer Res*. 2006; 12:3361–3367. [PubMed: 16740758]
3. Jung K, Miller K, Wirth M, Albrecht M, Lein M. Bone turnover markers as predictors of mortality risk in prostate cancer patients with bone metastases following treatment with zoledronic acid. *Eur Urol*. 2011; 59:604–612. [PubMed: 21190792]
4. Lein M, Wirth M, Miller K, et al. Serial markers of bone turnover in men with metastatic prostate cancer treated with zoledronic Acid for detection of bone metastases progression. *Eur Urol*. 2007; 52:1381–1387. [PubMed: 17321667]
5. Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet*. 2012; 379:39–46. [PubMed: 22093187]

6. Smith MR, Saad F, Oudard S, et al. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. *J Clin Oncol.* 2013; 31:3800–3806. [PubMed: 24043751]
7. Smith MR, Kabbavar F, Saad F, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J Clin Oncol.* 2005; 23:2918–2925. [PubMed: 15860850]
8. Harris EK, Brown SS. Temporal changes in the concentrations of serum constituents in healthy men. Distributions of within-person variances and their relevance to the interpretation of differences between successive measurements. *Annals of clinical biochemistry.* 1979; 16:169–176. [PubMed: 533223]
9. Van Steirteghem AC, Robertson EA, Young DS. Variance components of serum constituents in healthy individuals. *Clinical chemistry.* 1978; 24:212–222. [PubMed: 627051]
10. Brassell SA, Dobi A, Petrovics G, Srivastava S, McLeod D. The Center for Prostate Disease Research (CPDR): a multidisciplinary approach to translational research. *Urol Oncol.* 2009; 27:562–569. [PubMed: 19720304]
11. Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). *J Clin Oncol.* 2006; 24:3984–3990. [PubMed: 16921051]
12. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA.* 1999; 281:1591–1597. [PubMed: 10235151]
13. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA.* 2005; 294:433–439. [PubMed: 16046649]
14. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med.* 2012; 367:203–213. [PubMed: 22808955]
15. Ozu C, Nakashima J, Horiguchi Y, Oya M, Ohigashi T, Murai M. Prediction of bone metastases by combination of tartrate-resistant acid phosphatase, alkaline phosphatase and prostate specific antigen in patients with prostate cancer. *Int J Urol.* 2008; 15:419–422. [PubMed: 18452459]
16. Brown JE, Cook RJ, Major P, et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. *J Natl Cancer Inst.* 2005; 97:59–69. [PubMed: 15632381]
17. Robinson D, Sandblom G, Johansson R, et al. Prediction of survival of metastatic prostate cancer based on early serial measurements of prostate specific antigen and alkaline phosphatase. *J Urol.* 2008; 179:117–122. discussion 22–3. [PubMed: 17997442]
18. Garnero P, Buchs N, Zekri J, Rizzoli R, Coleman RE, Delmas PD. Markers of bone turnover for the management of patients with bone metastases from prostate cancer. *Br J Cancer.* 2000; 82:858–864. [PubMed: 10732759]
19. Jung K, Lein M, Stephan C, et al. Comparison of 10 serum bone turnover markers in prostate carcinoma patients with bone metastatic spread: diagnostic and prognostic implications. *Int J Cancer.* 2004; 111:783–791. [PubMed: 15252851]
20. Smith MR, Cook R, Lee KA, Nelson JB. Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. *Cancer.* 2011; 117:2077–2085. [PubMed: 21523719]
21. Mason MD, Sydes MR, Glaholm J, et al. Oral sodium clodronate for nonmetastatic prostate cancer—results of a randomized double-blind placebo-controlled trial: Medical Research Council PR04 (ISRCTN61384873). *J Natl Cancer Inst.* 2007; 99:765–776. [PubMed: 17505072]

Figure 1.

Kaplan-Meier Bone Metastasis-Free Survival Curves among CRPC Patients Stratified by APV (N=165)

Figure 2.
Kaplan-Meier Overall Survival Curves among CRPC Patients Stratified by APV (N=165)

Table 1

Comparison of CRPC Prostate Cancer Patients in the CPDR Multicenter National Database stratified by availability of Alkaline Phosphatase Data

Variable		Patients without AP data	Patients with AP data	p-value
Number of bone scans after CRPC		182	165	
Age at diagnosis (yr)	Mean(SD)	68.3(9.0)	67.2(8.1)	0.2441
PSA at diagnosis (ng/mL)	Median(range)	10.1(1,121.9)	16.5(3.1,414.2)	<0.0001
Time from diagnosis to primary Tx (months)	Median(range)	2.7(0,114.2)	2.8(0,66.5)	0.5283
Time from ADT to PSA nadir (months)	Median(range)	7.5(0.5,24)	8.6(0,23.8)	0.3099
Time from ADT to CRPC (months)	Median(range)	21.7(3.1,125.6)	16.9(3,132.6)	0.0503
Follow-up time after ADT (months)	Median(range)	50.4(3.7,156.3)	71.6(13.9,198.1)	<0.0001
Post-ADT PSA nadir (ng/mL)	Median(range)	0.1(0,4.0)	0.1(0,3.5)	<0.0001
Pre-CRPC Alkaline Phosphatase	Median(range)	80(0.1,270)	84(0.8,257)	0.1459
Post-CRPC Alkaline Phosphatase	Median(range)	79.5(20, 2080)	79(36.7, 206)	0.5089
Race/Ethnicity	CA & other	132(72.5)	117(70.9)	0.6835
	AA	47(25.8)	46(27.9)	
Biopsy Gleason sum	7	109(59.9)	96(58.2)	0.7259
	8	50(27.5)	48(29.1)	
Clinical T stage	T1–T2b	128(70.3)	104(63.0)	0.0260
	T2c	40(22.0)	56(33.9)	
ADT type	Primary ADT	41(22.5)	47(28.5)	0.2937
	RP/2° ADT	58(31.9)	42(25.5)	
	EBRT/2° ADT	83(45.6)	76(46.1)	
PSADT (Pound et al.)	10 mos	125(68.7)	92(55.8)	0.0130
	<10 mos	57(31.3)	73(44.2)	
Bone metastasis	no	166(91.2)	129(78.2)	0.0007
	yes	16(8.8)	36(21.8)	

Table 2

A) Clinical and Pathological Characteristics of Castrate Resistant Prostate Cancer Patients Stratified by Metastasis Status. **B)** Clinical and Pathological Characteristics of Castrate Resistant Prostate Cancer Patients stratified by Overall Survival Status

A)				
Variable	statistics	No metastasis	Metastasis	p-value
N(%)		129 (78.2)	36 (21.8)	
Age at diagnosis (year)	Mean(SD)	67.5(7.6)	66.4(9.6)	0.4969
PSA at diagnosis (ng/mL)	Median(range)	16.7(3.1,414.2)	16.3(4.2,380.4)	0.7479
Time from diagnosis to primary Tx (months)	Median(range)	2.8(0,66.5)	3.2(0.3,63)	0.4701
Time from ADT to PSA nadir (months)	Median(range)	8.7(0,23.7)	6.9(0.2,23.8)	0.4872
Time from ADT to CRPC (months)	Median(range)	17.4(3.2,132.6)	13.6(3,73.9)	0.1056
Follow-up time after ADT (months)	Median(range)	76.2(13.9,165.6)	54.2(14.2,198.1)	0.0335
Post-ADT PSA nadir (ng/mL)	Median(range)	0.1(0,3.1)	0.1(0,3.5)	0.0017
Pre- CRPC Alkaline Phosphatase	Median(range)	81(0.8,257)	94(57,131)	0.0952
Post- CRPC Alkaline Phosphatase	Median(range)	78(41,206)	81.5(36.7,166)	0.4761
Race/Ethnicity	CA & other	91(77.8)	26(22.2)	0.9466
	AA	36(78.3)	10(21.7)	
Biopsy Gleason sum	7	78(81.3)	18(18.7)	0.384
	8	36(75.0)	12(25.0)	
Clinical T stage	T1–T2b	85(81.7)	19(18.3)	0.1327
	T2c	40(71.4)	16(28.6)	
ADT type	Primary ADT	37(78.6)	10(36.4)	0.9362
	RP/2° ADT	32(76.2)	10(23.8)	
	EBRT/2° ADT	60(79.0)	16(21.0)	
PSADT (Pound <i>et al.</i>)	10 months	87(94.6)	5(5.4)	<.0001
	<10 months	42(57.5)	31(42.5)	
APV (upper quartile split)	<6.3 U/L/yr	105(84.7)	19(15.3)	0.0004
	6.3 U/L/yr	24(58.5)	17(41.4)	

B)				
Variable	statistics	Alive	Dead	p-value
N(%)		129 (78.2)	36 (21.8)	
Age at diagnosis (year)	Mean(SD)	66.6(7.8)	69.5(8.7)	0.0582
PSA at diagnosis (ng/mL)	Median(range)	16.9(3.1,414.2)	16.1(4.8,380.4)	0.9037
Time from diagnosis to primary Tx (months)	Median(range)	2.8(0,66.5)	2.9(0.2,63)	0.7200
Time from ADT to PSA nadir (months)	Median(range)	8.5(0,23.7)	8.7(0.9,23.8)	0.8686
Time from ADT to CRPC (months)	Median(range)	19.2(3,132.6)	15.9(3,61.4)	0.1430
Time from ADT to metastasis (months)	Median(range)	23.8(3.8,136.5)	22.1(4.5,62.5)	0.0379
Post-CRPC PSA nadir (ng/mL)	Median(range)	0.1(0,3.1)	0.1(0,3.5)	0.0180
Testosterone	Median(range)	19.1(0.1,50)	19.1(0,45)	0.8888

B)

Variable	statistics	Alive	Dead	p-value
Pre- CRPC Alkaline Phosphatase	Median(range)	84(0.8,186)	83.5(44,257)	0.7294
Post- CRPC Alkaline Phosphatase	Median(range)	80(41,206)	75(36.7,166)	0.1585
Number of bone scans after CRPC	Median(range)	2(1,9)	3(1,7)	0.0012
Follow up after CRPC (months)	Median(range)	73.7(18.9,198.1)	52.4(13.9,127.9)	0.0034
Number of post-CRPC Alkaline Phosphatase values	Median(range)	4(2,21)	4(2,16)	0.6726
Race/Ethnicity	CA & other	88(75.2)	29(24.8)	0.185
	AA	39(84.8)	7(15.2)	
Biopsy Gleason Sum	6 or less	73(76.0)	23(24.0)	0.674
	7 or more	38(79.2)	10(20.8)	
Clinical T stage	T1–T2b	87(83.7)	17(16.4)	0.0111
	T2c or above	37(66.1)	19(33.9)	
ADT type (combined)	Primary ADT	33(70.2)	14(29.8)	0.1178
	Secondary ADT	96(81.4)	22(18.6)	
PSADT (Pound <i>et al.</i>)	>=10 mos	84(91.3)	8(8.6)	<.0001
	<10 mos	45(61.6)	28(38.4)	
APV (upper quartile split)	<6.3 U/L/yr	106(85.5)	18(14.5)	0.0001
	>=6.3 U/L/yr	23(56.1)	18(43.9)	

Table 3

A) Step-wise Multivariable Cox Proportional Hazards Model of Time to Bone Metastases among CRPC Patients. **B)** Step-wise Multivariable Cox Proportional Hazards Model of Overall Survival

A)		
Parameter	OR (95% CI)	P value
Post-ADT PSA nadir (ng/mL)	1.42 (0.93, 2.18)	0.106
PSADT (Pound et al.) <10 vs. 10 months	12.1 (3.59, 40.54)	<0.0001
APV (upper quartile split) 6.3 U/L/yr vs. <6.3 U/L/yr	2.70(1.25, 5.80)	0.011
B)		
Parameter	OR (95% CI)	P value
Post-CRPC PSA nadir (ng/mL) in months	1.72 (1.14, 2.57)	0.0092
PSADT (Pound et al.) <10 vs. 10 months	3.98 (1.58, 10.01)	0.0034
APV (upper quartile split) 6.3 U/L/yr vs. <6.3 U/L/yr	5.11 (2.24, 11.67)	0.0001