Identification of subgroups of metastatic castrate-resistant prostate cancer (mCRPC) patients treated with abiraterone plus prednisone at low vs. high risk of radiographic progression: An analysis of COU-AA-302

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Abstract

Introduction: Radiographic imaging is used to monitor disease progression for men with metastatic castrate-resistant prostate cancer (mCRPC). The optimal frequency of imaging, a costly and limited resource, is not known. Our objective was to identify predictors of radiographic progression to inform the frequency of imaging for men with mCRPC.
Methods: We accessed data for men with chemotherapy-naive mCRPC in the abiraterone acetate plus prednisone (AA-P) group of a randomized trial (COU-AA-302) (n=546). We used Cox proportional hazards modelling to identify predictors of time to progression. We divided patients into groups based on the most important predictors and estimated the probability of radiographic progression-free survival (RPFS) at six and 12 months.
Results: Baseline disease and change in prostate-specific antigen (PSA) at eight weeks were the strongest determinants of RPFS. The probability of RPFS for men with bone only disease and a ≥50% fall in PSA was 93% (95% confidence interval [CI] 87–96) at six months and 80% (95% CI 72–86) at 12 months. In contrast, the probability of RPFS for men with bone and soft metastasis and <50% fall in PSA was 55% (95% CI 41–67) at six months and 34% (95% CI 22–47) at 12 months. These findings should be externally validated.

Conclusions: Patients with chemotherapy-naive mCRPC treated with first-line AA-P can be divided into groups with significantly different risks of radiographic progression based on a few clinically available variables, suggesting that imaging schedules could be individualized.

Introduction

Healthcare spending for cancer imaging has increased faster than that for overall cancer care. [1] This increase includes imaging after diagnosis of advanced cancer. [2,3] More frequent imaging in advanced cancer may detect disease progression earlier and lead to changes in treatment; however, it may also have negative effects such as increased anxiety and more time spent in medical facilities. [4]

Despite early detection and aggressive treatment of early prostate cancer, some men will develop metastatic disease, with about 90% of them developing bone metastases. The recent development of new treatment options (for example, abiraterone acetate and enzalutamide) for men with metastatic castrate-resistant prostate cancer (mCRPC) may increase the importance of monitoring for disease progression; however, the optimal imaging schedule for mCRPC patients is not known.

Given that imaging is an expensive and limited resource, it would be beneficial if the imaging schedule could be risk-adapted for likelihood of disease progression. In this study, we examined factors associated with radiographic progression in mCRPC patients treated with abiraterone acetate plus prednisone (AA-P), and explored the possibility that a few clinically available variables could be used to identify subsets of patients with different risks of developing radiographic progression.

Methods

Data source

We accessed data from participants in the AA-P group (n=546) of COU-AA-302, a randomized Phase III trial of AA-P treatment prior to chemotherapy for mCRPC patients[5], through the Yale University Open Data Access Project**.** The clinical cut-off date was March 31, 2014. Details of the trial eligibility criteria and methods are described elsewhere. [5] Patients with visceral metastases at baseline were excluded. The study protocol included bone scans and computed tomography or magnetic resonance imaging at baseline, every 8 weeks during the first 24 weeks, and every 12 weeks thereafter. Unscheduled scans were performed as determined by treating physicians.

Data analysis

We approached the data analysis in two ways: (i) we developed a multivariable prognostic model for radiographic progression using Cox Proportional Hazards (PH) modelling and calculated a

risk score; and (ii) we identified the two variables most predictive of progression and used them to stratify patients into subsets.

The outcome measure was time from randomization to radiographic progression in bone and/or soft tissue based on the investigator assessment of progression. As previously described [5], bone progression was defined as the appearance of at least 2 new lesions and required confirmation on a subsequent scan with 6 weeks. For lesions detected < 12 weeks after randomization, confirmation required the presence of 2 additional lesions, and for those detected ≥ 12 weeks after randomization, confirmation required the continued presence of 2 lesions. We assigned the time of bone progression as the date of the scan prior to the confirmatory scan. Progression in soft tissue disease was determined by CT or MR imaging based on the modified RECIST.[6] Patients who discontinued treatment or died before experiencing radiographic progression were censored at their last scan.

Baseline variables

We considered the following baseline variables: age, body mass index, ECOG performance status, extent of baseline disease (bone, soft or both), Gleason score, prior radiation therapy or prostatectomy, presence of pain (BPI-SF item 3), and serum levels of prostate specific antigen (PSA), lactate dehydrogenase (LDH), albumin, alkaline phosphatase (ALP) and hemoglobin. We included a missing category for Gleason Score (11% missing) and excluded 35 patients (6%) who were missing data for other baseline variables. PSA and ALP were log transformed as their distributions were highly skewed. All baseline variables were included in a Cox PH model and a manual backward selection process was used to remove covariates that were not statistically significant ($P > 0.05$) and whose exclusion had little effect (change < 0.01) on the concordance statistic (C-statistic) [7] for the model.

Change variables

We calculated the percent change in laboratory variables from baseline to week 8 (the first time PSA was measured). After excluding subjects with missing data for change variables (7% of patients with complete baseline data), the final sample included 470 subjects with 265 events (86% of the total sample of 546). All change variables (continuous) were added to the baseline model and change variables with $p > 0.05$ and little effect on C-statistic were removed. We dichotomized change in PSA and ALP for the final model. For PSA we used 50% decline as the cut-point because it is close to the observed median change in PSA. The cut-point of a 20% increase for ALP was based on the observed shape of the association with progression.

The validity of the PH assumption was checked by plotting the cumulative score residuals against time and by the Kolmogorov-type supremum test.

Risk score

We calculated risk scores for subjects by multiplying their covariate values by the appropriate regression coefficient from the final multivariable model. We estimated the probability of

radiographic progression free survival (RPFS) at 6 and 12 months within each tertile of risk score from the Kaplan-Meier estimates.

Stratified analysis

We used best subset regression to identify the best model (based on model ranking by score and C-statistic) with a maximum of 2 variables to predict radiographic progression and divided the subjects into risk strata based on these variables. We estimated the probability of RPFS at 6 and 12 months within each stratum based on the Kaplan-Meier estimates.

We stratified subjects on the variables most strongly associated with bone progression only because bone progression may be more clinically relevant in terms of symptoms experienced. Furthermore, in this study population progression in soft tissue largely represented growth in lymph node lesions for which the clinical significance may be limited.

Statistical analyses were performed using SAS Drug Development 9.3 and the survival package in R 2.14.0. The study was approved by the University Health Network Research Ethics Board.

Results

The distribution of variables is shown in Supplemental Table 1. On average at baseline, men were 70.5 years of age (SD 8.8) with median PSA of 42.0 ng/ml (interquartile range (IQR) 16.1, 116.0). At baseline, 51% of men had metastatic disease in bone only, 17% in soft tissue only and 32% in both bone and soft tissue. The median percent change in PSA at 8 weeks after starting treatment was -66.3% (IQR -88.0, -19.6) and 60% of subjects had a decline in PSA greater than 50%.

Figure 1 shows the disposition of patients. A total of 301 of the 546 men experienced radiographic progression with a median time to event of 505 days (95% confidence interval (CI) of 494 to 588). Over half (53%) of the first events of progression were in bone, 44% were in soft tissue and 3% were in both bone and soft tissue.

The univariate associations for all covariates with time to radiographic progression are shown in Supplemental Table 1. The multivariable model including baseline variables only had a C-statistic of 0.67 (Supplemental Table 2). The final multivariable model included extent of disease at baseline, ECOG status, pain score, PSA, LDH, ALP and albumin, and change in PSA and ALP at 8 weeks (C-statistic= 0.71) (Table 1).

Due to missing data, we did not include change in pain at 8 weeks in the modelling process. We added it to the final model (446 subjects and 250 events), but it was not significantly associated with radiographic progression (p=0.23).

The association of baseline ALP with progression became stronger over time, while that of change in PSA become weaker (p= 0.03 and p = 0.05, respectively,). Adding interaction terms with time to the multivariable model increased the C-statistic only slightly (from 0.71 to 0.72) and they were not included in the final model.

Figure 2 shows the Kaplan-Meier plots for tertiles of risk score calculated from the multivariable model in Table 1. Compared to the first tertile, the hazard ratios (HR) for the second and third tertiles were 2.01 (95% CI 1.46, 2.77) and 3.43 (95% CI 2.48, 4.74). respectively, and the C-statistic for the model was 0.63. For patients in the first tertile of risk score (33% of patients), the probability of RPFS at 6 months was 92% (95% CI 86, 95), while for those in the highest tertile (33% of patients), the probability of RPFS was 70% (95% CI 61 to 77) (Table 2). The probability of RPFS ranged from 45% to 80% at 12 months.

Best subset regression identified two 2-variable models with a similar C-statistic (0.64). We show results for the model containing extent of baseline disease and percent change in PSA; however, qualitatively similar results were found when change in ALP was used instead of PSA (Supplemental Table 3). Figure 3 shows the Kaplan-Meier plots for subjects stratified into 6 groups based on these 2 variables. The survival curve for the lowest risk stratum (stratum 1; bone only disease at baseline and ≥ 50% decline in PSA) was significantly different from all other strata ($P \leq 0.0007$; log rank test, Tukey adjustment).

The survival curve for the highest risk stratum (Stratum 6: bone and soft tissue disease at baseline and < 50% decline in PSA) was significantly different from all other strata ($P < 0.02$) except for the fifth stratum (p=0.59). The HR comparing the highest to the lowest risk stratum was 4.17 (95% CI 2.85, 6.10).

In the lowest risk stratum (32% of subjects), the probability of RPFS at 6 months was 93% (95% CI 87, 96) and at 12 months was 80% (95% CI 72, 86) (Table 3). In contrast, the probability of RPFS for men in the highest risk stratum was 55% (95% CI 41 to 67) at 6 months and 34% (95% CI 22 to 47) at 12 months.

We applied the multivariable model developed for overall radiographic progression to bone progression only (Supplemental Table 4). The best 2-variable model (C-statistic=0.67) included baseline ALP and change in ALP and we stratified subjects by these variables (Table 4). The survival curve for the lowest risk stratum (baseline ALP below the median and <20% increase in ALP) was significantly different from all other strata ($P \leq 0.0003$, log rank test with Tukey adjustment); however, there were no significant differences between the other 3 strata ($p>0.16$). In the lowest risk stratum (35% of subjects), the probability of RPFS at 6 months was 94% (95% CI 89, 97) and at 12 months was 88% (95% CI 81, 92)**.** In contrast, the probability of RPFS in the other strata ranged from 73 to 88% at 6 months and from 52 to 75% at 12 months.

Discussion

Current guidelines for managing mCRPC do not provide recommendations regarding the frequency of imaging to monitor for radiographic progression. [8,9] At a recent consensus conference, the majority of panelists (54%) voted for regular imaging every 3–6 months for mCRPC patients on first-line therapy, while the remainder voted for imaging based on PSA levels and/or clinical progression. [10] Our analysis shows that mCRPC patients on first line AA-P can be divided into groups with large differences in the probability of radiographic progression

using only two clinically available factors. Importantly, the discriminant ability (C-statistic) for the 2-variable model (0.64) was almost identical to that with the risk score based on 9 covariates (0.63). These results suggest that risk-adapted imaging schedules could be developed for these patients.

As expected, several baseline factors that predict overall survival for mCRPC were also associated with radiographic progression in our multivariable analysis, including extent of disease, [11] LDH, [12-14] PSA, [13,15] ALP, [12-14,16] albumin, [12,14,15] ECOG, [12-15] and pain. [13] To our knowledge there is only one published prognostic model for RPFS in the mCRPC setting. [17] This model was developed in the same population as used here; however, there are differences in the two approaches. For the outcome of radiographic progression, Ryan et al [17] used the results of independent radiographic review, whereas we had access to the investigator assessment only. Although, radiographic progression identified in these two ways showed a high degree of agreement overall (79%) [18], this difference could be responsible for the lower C-statistic we observed for the multivariate model with baseline variables only. However, because independent review was not done for the entire duration of the study, we were able to use a later clinical cut-off date (and larger number of events) by using the investigator assessment. In addition, in day-to-day practice imaging would not undergo central independent review and thus it is more pragmatic to use the investigator assessment.

Another important difference between these analyses is that Ryan et al [17] included baseline variables only (lymph node disease, number of bone metastases, PSA, LDH and hemoglobin), whereas we included change in laboratory measurements as indicators of early treatment response. Changes in PSA and ALP at 8 weeks were strongly associated with overall and bone-specific progression. The PCWG3 criteria [6] suggest that early changes (before 8 or 12 weeks) in PSA should be ignored in determining treatment response because of the potential for flare reactions and later responses. However, PSA flare may be uncommon following AA-P [19] and previous analyses have shown a strong association of early PSA changes with survival and radiographic progression. [16,19-23] PSA declines of 30%, 50%, and 90%, as well as more complex measures of PSA kinetics, are associated with survival and radiographic progression; [20,22] however, it is not clear which measure has the best predictive ability.

In agreement with our results, change in serum ALP, a marker of bone metabolism, has been shown to be associated with survival [24-26] and with bone progression specifically [27,28] in mCRPC patients, independently of changes in PSA. Using baseline level and change in ALP, we identified a group of patients with low risk of bone progression (6% at 6 months) for whom the frequency of bone scans might be reduced.

Strengths of this work include a large sample size, high quality data collected as part of a clinical trial, and a standardized schedule of imaging. Because data on time to disease progression is highly dependent on the imaging schedule, imaging at standard intervals in all patients is necessary for this type of analysis.

The generalizability of our results may be limited as the subjects were highly selected participants in a clinical trial who may be at different risk for progression than patients in the "real" world clinical setting. Our results may not apply to patients who present with visceral metastases at start of treatment or those who are treated with different drugs. In addition, our results apply to current standard imaging technologies and their associated sensitivity and specificity for detecting disease progression. Finally, our models have not been externally validated.

Information about the optimal schedule of imaging to monitor for radiographic progression is needed to inform clinical management of mCRPC. Our analyses suggest that mCRPC patients treated with first-line AA-P can be divided into groups with significantly different risks of experiencing radiographic progression based on a few clinically available variables. For example, patients with bone disease only at the start of treatment who experience an early decline of ≥ 50% in PSA compose a large group (about one-third of patients) with high probability of remaining progression free; only 1 in 5 patients in this group experienced progression by 1 year, and this may not represent clinically significant or symptomatic changes. In the absence of symptoms, imaging may be unnecessary for at least one year in these patients. In contrast, the highest risk group (15% of patients with bone and soft tissue disease and < 50% decline in PSA) had a much lower probability of remaining progression free at 6 months (55%) and may benefit from more earlier and/or more frequent imaging. Compared to an imaging schedule of every 3 months for all patients, if we imaged at 1 year only for the 30% of patients in the low risk stratum, we would expect an overall reduction of about 20% in imaging in the first year post treatment. These findings should be externally validated, and examined in other treatment settings, and may ultimately lead to more efficient imaging schedules and better care for mCRPC patients.

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Figures and Tables

Fig. 1. Disposition of patients and dataset for analysis.

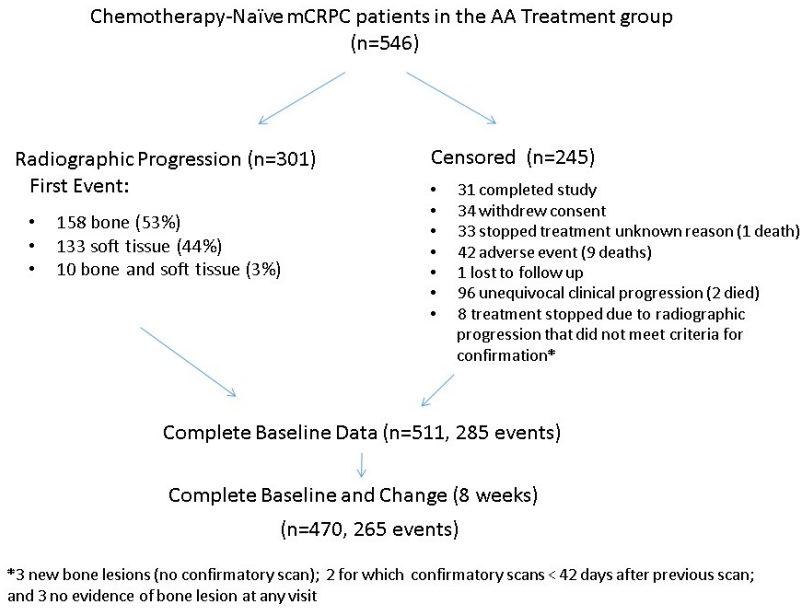
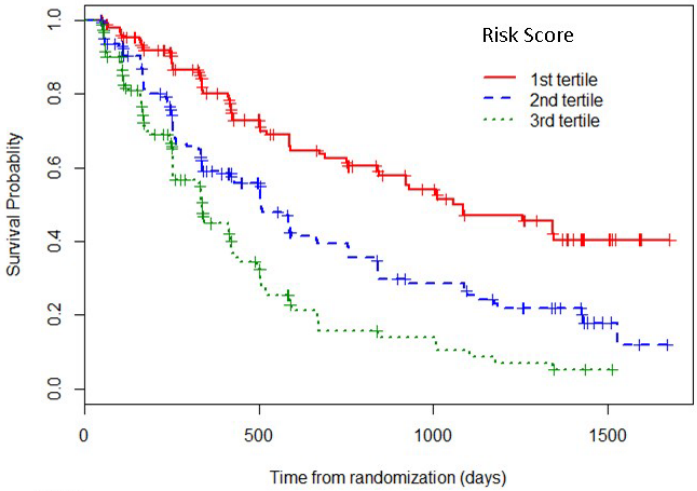


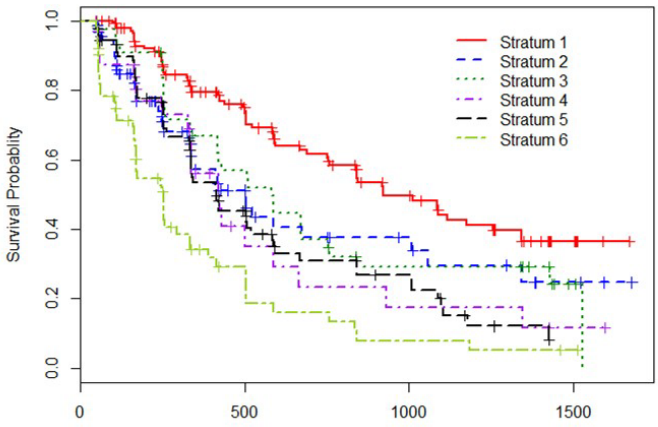
Fig. 2. Kaplan-Meier curves showing radiographic progression-free survival by tertiles of risk score. The risk score was calculated for each subject by multiplying their covariate values by the appropriate regression coefficient from the final multivariable model (Table 2). Subjects were divided into tertiles based on their risk score.



At risk

Tertile				
1	155	74	41	11
2	160	64	27	4
3	155	30	8	1

Fig. 3. Kaplan-Meier curves showing radiographic progression-free survival for patients stratified by extent of baseline disease and the percent change in prostate-specific antigen (PSA) at 8 weeks. Stratum 1=bone only disease at baseline and ≥50% decline in PSA; stratum 2=bone only disease at baseline and <50% decline in PSA; stratum 3=soft only disease at baseline and ≥50% decline in PSA; stratum 4=soft only disease at baseline and <50% decline in PSA; stratum 5=bone and soft disease at baseline and ≥50% decline in PSA; stratum 6=bone and soft disease at baseline and <50% decline in PSA.



At risk

Strata				
1	149	77	38	9
2	91	21	10	3
3	44	23	10	2
4	34	7	3	1
5	89	29	12	0
6	63	11	3	1

Table 1. Multivariable Cox proportional hazards model for time to radiographic progression (n= 470 subjects, 265 events; C-statistic=0.71)			
Variable	**n (%) or mean (SD)**	**HR (95% CI)**	**p**
Extent of disease at baseline			
Bone only	240 (51)	1.0	
Soft only	78 (17)	1.53 (1.08, 2.17)	0.02
Bone and soft	152 (32)	1.99 (1.51, 2.62)	0.0001
ECOG			
0	360 (77)	1.0	
1	110 (23)	0.72 (0.52, 1.00)	0.05
Pain (Item 3)			
0	240 (51)	1.0	
1–2	152 (32)	1.23 (0.93, 1.64)	0.15
≥3	78 (17)	1.70 (1.20, 2.40)	0.003
PSA (log ng/ml)	3.72 (1.52)	1.13 (1.03, 1.23)	0.009
LDH (IU/L)			
"Normal"	417 (89)	1.0	
High (≥250)	53 (11)	1.48 (0.98, 2.23)	0.07
ALP (log IU/L)	4.67 (0.61)	1.33 (1.05, 1.68)	0.02
Albumin (g/L)	40.4 (3.3)	0.97 (0.93, 1.01)	0.12
Change at 8 weeks			
PSA			
<50% drop	282 (60)	1.0	
≥50% drop	188 (40)	0.59 (0.46, 0.76)	<0.0001
ALP			
<20 % increase	355 (76)	1.0	
≥20% increase	115 (24)	1.64 (1.22, 2.20)	0.001

ALP: alkaline phosphatase; ECOG: Eastern Cooperative Oncology Group performance status; HR: hazard ratio; LDH: lactate dehydrogenase; PSA: prostate-specific antigen; SD: standard deviation.

Table 2. Probability of radiographic progression-free survival by tertiles of risk score (n=470 subjects, 265 events)

Score tertile	n (%)	# of events	Median time to event (days) (95% CI)	6-month RPFS probability (95% CI)	1-year RPFS probability (95% CI)
1	155 (33)	61	1057 (839, ND)	92 (86, 95)	80 (72, 86)
2	160 (34)	101	505 (389, 593)	80 (73, 86)	59 (51, 67)
3	155 (33)	103	337 (254, 415)	70 (61, 77)	45 (36, 53)

CI: confidence intervals; ND: not determined; RPFS: radiographic progression-free survival.

Table 3. Probability of radiographic progression-free survival for patients stratified by extent of baseline disease and the percent change in PSA (n=470 subjects, 265 events)

	Covariate Values						
Risk strata	**Extent of baseline disease**	**Fall in PSA at 8 weeks**	**n (%)**	**# events**	**Median time to event (days) (95% CI)**	**6-month RPFS (95% CI)**	**12-month RPFS (95% CI)**
1	Bone only	≥50%	149 (32)	64	921 (754, 1255)	93 (87, 96)	80 (72, 86)
2	Bone only	<50%	91 (19)	42	503 (336, 1008)	77 (66, 85)	57 (44, 68)
3	Soft only	≥50%	44 (9)	31	582 (418, 754)	91 (77, 96)	67 (51, 79)
4	Soft only	<50%	34 (7)	20	424 (328, 588)	77 (57, 88)	56 (35, 73)
5	Bone and soft	≥50%	89 (19)	61	414 (337, 518)	78 (67, 85)	54 (42, 64)
6	Bone and soft	<50%	63 (13)	47	252 (168, 332)	55 (41, 67)	34 (22, 47)

CI: confidence intervals; PSA: prostate-specific antigen; RPFS: radiographic progression-free survival.

Table 4. Probability of radiographic progression-free survival for bone progression[a] (n=470 subjects, 149 events)

	Covariate values						
Risk strata	**Baseline ALP**	**Increase in ALP at 8 weeks**	**n (%)**	**# events**	**Median time to event (days) (95% CI)**	**6-month RPFS (95% CI)**	**12-month RPFS (95% CI)**
1	Below median[b]	<20%	164 (35)	32	ND	94 (89, 97)	88 (81, 92)
2	Below median	≥20 %	45 (10)	18	593 (244, ND)	73 (55, 84)	55 (37, 70)
3	Above median	<20%	191 (41)	71	841 (588, 1174)	88 (82, 92)	75 (68, 81)
4	Above median	≥20 %	70 (15)	28	421 (252, 494)	74 (60, 83)	52 (36, 67)

[a]Events of soft tissue progression censored; [b]median ALP=93.0 IU/L. ALP: alkaline phosphatase; CI: confidence interval; ND: not determined; RPFS: radiographic progression-free survival.

Supplementary Table 1. Distribution of characteristic and their univariate association with time to radiographic progression (n=546)				
Characteristic	**Mean (SD) or number (%)**	**HR (95% CI)**	**p**	**Concordance statistic**
Age (yrs)	70.5 (8.8)	0.99 (0.98, 1.01)	0.38	0.520
BMI (kg/m^2) (n=535)	29.0 (4.8)	0.99 (0.97, 1.02)	0.58	0.499
Extent of disease at baseline, n (%) Bone only Soft only Bone and soft Missing	 277 (51) 92 (17) 175 (32) 2	 1.0 1.46 (1.07, 2.01) 2.33 (1.81, 3.00)	 0.02 <0.0001	0.605
Gleason score <6 7 8 ≥9 Missing	 65 (12) 160 (29) 93 (17) 170 (31) 58 (11)	 1.0 0.86 (0.58, 1.26) 0.91 (0.59, 1.40) 1.08 (0.73, 1.58) 0.57 (0.34, 0.96)	 0.07 	0.553
Prior radiation therapy No Yes	 263 (48) 283 (52)	 1.0 0.87 (0.69, 1.09)	 0.21	0.515
Prior prostatectomy No Yes	 370 (68) 176 (32)	 1.0 0.91 (0.72, 1.15)	 0.44	0.512
ECOG, n (%) 0 1	 413 (76) 133 (24)	 1.0 0.75 (0.56, 1.01)	 0.06	0.522
Pain (BPI Item 3), n (%) 0 1–2 ≥3 Missing	 271 (50) 168 (31) 93 (17) 14 (3)	 1.0 1.44 (1.12, 1.87) 1.58 (1.14, 2.18) 1.89 (0.70, 5.11)	 0.005 0.006 0.21	0.549

PSA (ng/ml) Median (IQR) Log PSA	42.0 (100) 3.76 (1.53)	1.22 (1.13, 1.31)	<0.0001	0.593
Lactate dehydrogenase (U/L) Normal High (≥ 250 IU/L) Missing	487 (89) 56 (10) 3 (1)	1.0 1.99 (1.38, 2.87)	0.0002	0.540
Alkaline phosphatase (IU/L) Median (IQR) Log ALP	93.0 (66) 4.66 (0.61)	1.49 (1.24, 1.78)	<0.0001	0.571
Albumin (g/L) (n=539)	40.4 (3.2)	0.95 (0.92, 0.99)	0.01	0.546
Hemoglobin (g/dl) (n=544)	129.7 (12.2)	0.99 (0.98, 1.00)	0.02	0.557
Percent change in PSA at 8 weeks, n (%), n=507 <50% decrease ≥50% decrease Mean (SD) Median (IQR)	203 (40) 304 (60) -44.1 (61.4) -66.3 (68.4)	1.0 0.54 (0.42, 0.69) 1.01 (1.00, 1.01)	<0.0001 0.0001	0.593 0.628
Percent change in ALP at 8 weeks (n,%), n=537 <20 % increase ≥20% increase Mean (SD) Median (IQR)	404 (75) 133 (25) 11.5 (51.7) 1.5 (8)	1.0 2.10 (1.62, 2.72) 1.01 (1.00, 1.01)	<0.0001 <0.0001	0.581 0.593
Percent change in LDH, n=531	7.7 (26.4)	1.00 (0.99, 1.01)	0.80	0.545
Change in albumin, n=523	-2.4 (7.9)	1.02 (1.00, 1.03)	0.07	0.531
Change in hemoglobin, n=523	2.3 (6.8)	1.04 (1.02, 1.05)	0.0001	0.552

ALP: alkaline phosphatase; BMI: body mass index; BPI: Brief Pain Inventory; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group Performance status; HR: hazard ratio; IQR: interquartile range; LDH: lactate dehydrogenase; PSA: prostate specific antigen; SD: standard deviation.

Supplementary Table 2. Baseline multivariable Cox proportional hazards model (n=511 subjects, 284 events) (C-statistic=0.67).		
Variable	**HR (95% CI)**	**p**
Extent of disease at baseline		
Bone only	1.0	
Soft only	1.55 (1.10, 2.19)	0.01
Bone and soft	2.08 (1.60, 2.71)	<0.0001
ECOG		
0	1.0	0.03
1	0.71 (0.52, 0.97)	
Pain (Item 3)		
0	1.0	
1–2	1.20 (0.92, 1.58)	0.18
≥3	1.70 (1.22, 2.38)	0.002
Laboratory measures		
PSA (log)	1.15 (1.05, 1.25)	0.002
LDH		
Normal	1.0	0.02
High (≥250)	1.64 (1.09, 2.48)	
ALP (log)	1.25 (1.00, 1.56)	0.05
Albumin	0.96 (0.92, 0.99)	0.02

ALP: alkaline phosphatase; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; LDH: lactate dehydrogenase; PSA: prostate-specific antigen.

Supplementary Table 3. Probability of radiographic progression-free survival by risk strata using change in ALP instead of change in PSA (n=470 subjects, 265 events)							
	Covariate Values						
Risk group	**Extent of baseline disease**	**Fall in ALP at C3**	**# total/ events**	**% subjects**	**Median RPFS (days) (95% CI)**	**6-month RPFS (95% CI)**	**12-month RPFS (95% CI)**
1	**Bone only**	**<20%**	**178/74**	**38**	**1057 (839, 1342)**	**91 (85, 94)**	**79 (72, 85)**
2	Bone only	≥20%	62/32	13	336 (247, 494)	75 (60, 85)	43 (27, 57)
3	Soft only	**<20%**	60/39	13	511 (341, 672)	90 (78, 95)	63 (49, 75)
4	Soft only	≥20%	18/12	4	500 (58, 670)	69 (41, 86)	62 (34, 81)
5	Bone and soft	**<20%**	117/83	25	410 (332, 504)	76 (66, 83)	51 (41, 60)
6	**Bone and soft**	≥20%	**35/25**	**7**	**169 (61, 338)**	**44 (27, 61)**	**26 (11, 44)**

ALP: alkaline phosphatase; CI: confidence intervals; PSA: prostate-specific antigen; RPFS: radiographic progression-free survival.

Supplementary Table 4. Multivariable Cox proportional hazards model for bone progression* (149 events, C-statistic=0.73)		
Variable	**HR (95% CI)**	**p**
Extent of disease at baseline		
Bone only	1.0	
Soft only	0.72 (0.42, 1.25)	0.24
Bone and soft	1.29 (0.90, 1.84)	0.16
ECOG		
0	1.0	
1	0.73 (0.48, 1.12)	0.15
Pain (Item 3)		
0	1.0	
1–2	1.38 (0.94, 2.02)	0.10
≥3	2.19 (1.42, 3.39)	0.0004
Laboratory measures		
PSA (log)	1.17 (1.04, 1.32)	0.009
LDH		
Norma	1.0	
High (≥250)	0.91 (0.50, 1.65)	0.75
ALP (log)	1.59 (1.17, 2.14)	0.003
Albumin	1.01 (0.96, 1.06)	0.85
Change in laboratory measures		
PSA		
<50% drop	1.0	
≥50% drop	0.52 (0.37, 0.73)	0.0001
ALP		
<20% increase	1.0	
≥20% increase	2.11 (1.46, 3.07)	<0.0001

*Bone=bone only AND bone and soft (n=10) based on first event. ALP: alkaline phosphatase; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; PSA: prostate-specific antigen.