

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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See related commentary on page 201

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-naïve 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 $\geq 50\%$ 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 tissue 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-naïve 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 3 trial of

AA-P treatment prior to chemotherapy for mCRPC patients,⁵ through the Yale University Open Data Access Project. The clinical cutoff 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 (CT) or magnetic resonance imaging (MRI) at baseline, every eight 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: 1) we developed a multivariable prognostic model for radiographic progression using Cox proportional hazards (PH) modelling and calculated a risk score; and 2) 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 two new lesions and required confirmation on a subsequent scan within six weeks. For lesions detected <12 weeks after randomization, confirmation required the presence of two additional lesions, and for those detected ≥12 weeks after randomization, confirmation required the continued presence of two 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 (BMI), Eastern Cooperative Oncology Group (ECOG) performance status, extent of baseline disease (bone, soft, or both), Gleason score, prior radiation therapy or prostatectomy, presence of pain (Brief Pain Inventory-Short-form [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 six 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 two variables to predict radiographic progression and divided the subjects into risk strata based on these variables. We estimated the probability of RPFS at six 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 Supplementary Table 1. On average at baseline, men were 70.5 years of age (standard deviation [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 eight weeks after starting treatment was -66.3% (IQR -88.0, -19.6) and 60% of subjects had a decline in PSA greater than 50%.

Fig. 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] 494–588). 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 Supplementary Table 1. The multivariable model, including baseline variables, only had a C-statistic of 0.67 (Supplementary Table 2). The final multivariable model included extent of disease at baseline, ECOG status, pain score, PSA, LDH, ALP, albumin,

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; HR: hazard ratio; LDH: lactate dehydrogenase; PSA: prostate-specific antigen; SD: standard deviation.

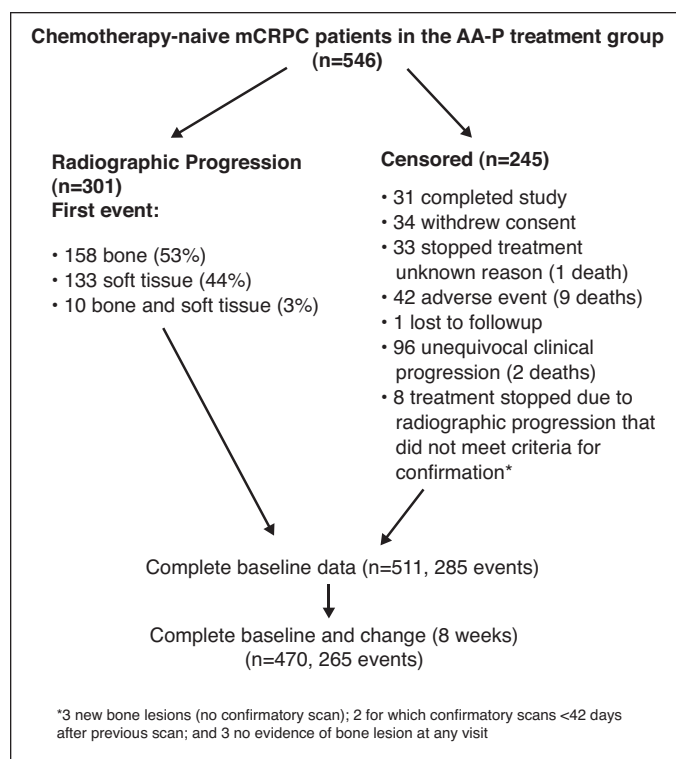


Fig. 1. Disposition of patients and dataset for analysis. AA-P: abiraterone acetate plus prednisone.

and change in PSA and ALP at eight weeks (C-statistic=0.71) (Table 1).

Due to missing data, we did not include change in pain at eight 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.

Fig. 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 six 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, 77) (Table 2). The probability of RPFS ranged from 45–80% at 12 months.

Best subset regression identified two two-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

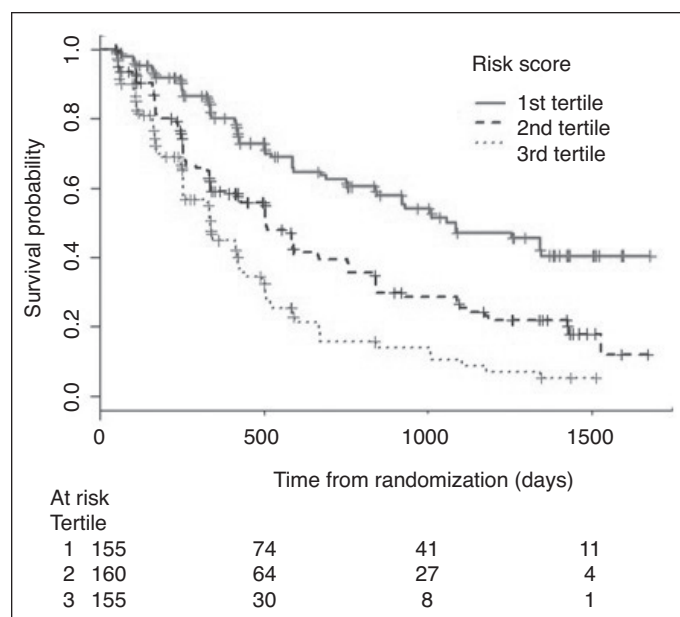


Fig. 2. Kaplan-Meier curves showing radiographic progression-free survival by tertiles of risk score. The risk score was calculated for each subject by multiplying their covariate values by the appropriate regression coefficient from the final multivariable model (Table 2). Subjects were divided into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

were found when change in ALP was used instead of PSA (Supplementary Table 3). Fig. 3 shows the Kaplan-Meier plots for subjects stratified into six groups based on these two variables. The survival curve for the lowest risk stratum (stratum 1; bone-only disease at baseline and $\geq 50\%$ 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 six 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 41–67) at six months and 34% (95% CI 22, 47) at 12 months.

We applied the multivariable model developed for overall radiographic progression to bone progression only (Supplementary Table 4). The best two-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 three strata ($p > 0.16$). In the lowest risk stratum (35% of subjects), the probability of RPFS at six 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 73–88% at six months and from 52–75% 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 two-variable model (0.64) was almost identical to that with the risk score based on nine 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 al¹⁷ 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 base-

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.

line variables only. However, because independent review was not done for the entire duration of the study, we were able to use a later clinical cutoff 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 al¹⁷ included baseline variables only (lymph node disease, number of bone metastases, PSA, LDH, and hemoglobin), whereas we included change in laboratory measure-

ments as indicators of early treatment response. Changes in PSA and ALP at eight weeks were strongly associated with overall and bone-specific progression. The PCWG3 criteria⁶ 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-P¹⁹ 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 survival²⁴⁻²⁶ and with bone progression specifically^{27,28} in mCRPC patients, independent 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 six 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.

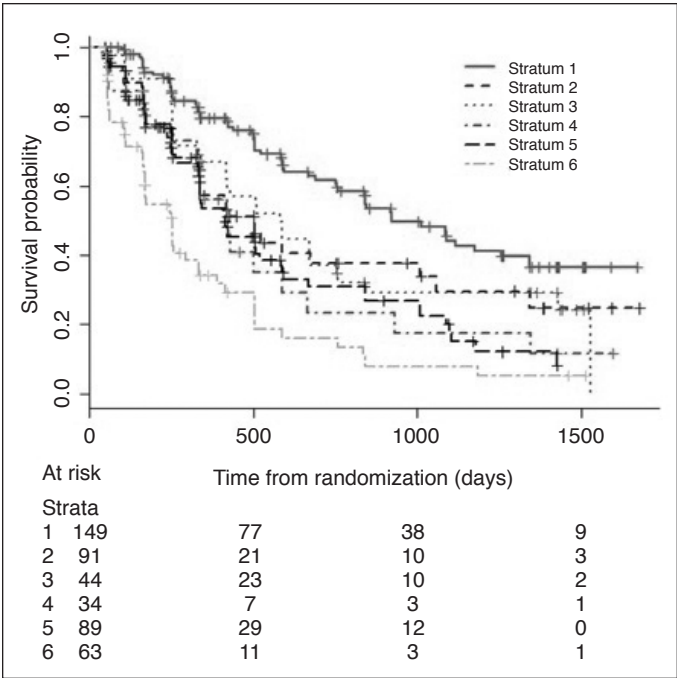


Fig. 3. Kaplan-Meier curves showing radiographic progression-free survival for patients stratified by extent of baseline disease and the percent change in prostate-specific antigen (PSA) at 8 weeks. Stratum 1=bone only disease at baseline and ≥50% decline in PSA; stratum 2=bone only disease at baseline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

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)

^aEvents of soft tissue progression censored. ^bMedian ALP=93.0 IU/L. ALP: alkaline phosphatase; CI: confidence interval; ND: not determined; RPFS: radiographic progression-free survival.

Conclusion

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 one in five patients in this group experienced progression by one 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 six months (55%) and may benefit from earlier and/or more frequent imaging. Compared to an imaging schedule of every three months for all patients, if we imaged at one 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.

Competing interests: Dr. Finelli has been an advisory board member for Abbvie, Astellas, Bayer, Janssen, Ipsen, Sanofi, and TerSera; and has participated in clinical trials supported by Astellas, Bayer, and Janssen. The remaining authors report no competing personal or financial interests related to this work.

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This paper has been peer-reviewed.

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Supplementary Table 1. Distribution of characteristics 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	277 (51)			
Soft only	92 (17)	1.0		0.605
Bone and soft	175 (32)	1.46 (1.07, 2.01)	0.02	
Missing	2	2.33 (1.81, 3.00)	<0.0001	
Gleason score				
<6	65 (12)	1.0	0.07	0.553
7	160 (29)	0.86 (0.58, 1.26)		
8	93 (17)	0.91 (0.59, 1.40)		
≥9	170 (31)	1.08 (0.73, 1.58)		
Missing	58 (11)	0.57 (0.34, 0.96)		
Prior radiation therapy				
No	263 (48)	1.0	0.21	0.515
Yes	283 (52)	0.87 (0.69, 1.09)		
Prior prostatectomy				
No	370 (68)	1.0	0.44	0.512
Yes	176 (32)	0.91 (0.72, 1.15)		
ECOG, n (%)				
0	413 (76)	1.0	0.06	0.522
1	133 (24)	0.75 (0.56, 1.01)		
Pain (BPI Item 3), n (%)				
0	271 (50)	1.0		
1-2	168 (31)	1.44 (1.12, 1.87)	0.005	
≥3	93 (17)	1.58 (1.14, 2.18)	0.006	
Missing	14 (3)	1.89 (0.70, 5.11)	0.21	0.549
PSA (ng/ml)				
Median (IQR)	42.0 (100)			
Log PSA	3.76 (1.53)	1.22 (1.13, 1.31)	<0.0001	0.593
Lactate dehydrogenase (U/L)				
Normal	487 (89)	1.0		
High (≥ 250 IU/L)	56 (10)	1.99 (1.38, 2.87)	0.0002	0.540
Missing	3 (1)			

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

Supplementary Table 1 (cont'd). 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
Alkaline phosphatase (IU/L)				
Median (IQR)	93.0 (66)			
Log ALP	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	203 (40)	1.0	<0.0001	0.593
≥50% decrease	304 (60)	0.54 (0.42, 0.69)		
Mean (SD)	-44.1 (61.4)		0.0001	0.628
Median (IQR)	-66.3 (68.4)	1.01 (1.00, 1.01)		
Percent change in ALP at 8 weeks (n,%), n=537				
<20 % increase	404 (75)	1.0		
≥20% increase	133 (25)	2.10 (1.62, 2.72)	<0.0001	0.581
Mean (SD)	11.5 (51.7)	1.01 (1.00, 1.01)	<0.0001	0.593
Median (IQR)	1.5 (8)			
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; 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		
Normal	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.