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Bone-related Parameters are the Main Prognostic Factors for Overall Survival in Men with Bone Metastases from Castration-resistant Prostate Cancer

Karim Fizazi[a,*], *Christophe Massard*[a], *Matthew Smith*[b], *Michael Rader*[c], *Janet Brown*[d], *Piotr Milecki*[e], *Neal Shore*[f], *Stephane Oudard*[g], *Lawrence Karsh*[h], *Michael Carducci*[i], *Ronaldo Damião*[j], *Huei Wang*[k], *Wendy Ying*[k], *Carsten Goessl*[k]

[a] *Institut Gustave Roussy, University of Paris Sud, Villejuif, France;* [b] *Massachusetts General Hospital Cancer Center, Boston, MA, USA;* [c] *Nyack Hospital, Nyack, NY, USA;* [d] *Cancer Research UK Experimental Cancer Medicine Centres, Leeds and Sheffield, UK;* [e] *Department of Radiotherapy, Greater Poland Cancer Center and Department of Electroradiology, Medical University, Poznań, Poland;* [f] *Carolina Urologic Research Center, Myrtle Beach, SC, USA;* [g] *European Georges Pompidou Hospital, Paris, France;* [h] *The Urology Center of Colorado, Denver, CO, USA;* [i] *Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA;* [j] *Universitario Pedro Ernesto, Rio De Janeiro, Brazil;* [k] *Amgen Inc., Thousand Oaks, CA, USA*

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Abstract

Background: Previous studies have reported on prognostic factors for castration-resistant prostate cancer (CRPC); however, most of these studies were conducted before docetaxel chemotherapy was approved for CRPC.
Objective: To evaluate the prognostic value of multiple parameters in men with bone metastases due to CRPC using a contemporary dataset.
Design, setting, and participants: The analysis included 1901 patients with metastatic CRPC enrolled in an international, multicenter, randomized, double-blind phase 3 trial conducted between May 2006 and October 2009.
Outcome measures and statistical analysis: We developed multivariate validated Cox proportional hazards models and nomograms to estimate 12-mo and 24-mo survival probabilities and median survival time.
Results and limitations: The median (95% confidence interval) overall survival was 20 (18, 21) mo. The final model included 12 of the 15 potential prognostic variables evaluated (concordance index 0.72). Seven bone-related variables were associated with longer survival in the final model: alkaline phosphatase $\leq$143 U/l ($p < 0.0001$); bone-specific alkaline phosphatase (BSAP) $<$ 146 U/l ($p < 0.0001$); corrected urinary N-telopeptide (uNTx) $\leq$50 nmol/mmol ($p = 0.0008$); mild or no pain (Brief Pain Inventory—Short Form [BPI-SF] score $\leq$4) ($p < 0.0001$); no previous skeletal-related event (SRE; $p = 0.0002$); longer time from initial diagnosis to first bone metastasis ($p < 0.0001$); and longer time from first bone metastasis to randomization ($p < 0.0001$). Other significant predictors of improved survival included prostate-specific antigen (PSA) level $<$ 10 ng/ml ($p < 0.0001$), hemoglobin $>$128 g/l ($p < 0.0001$), absence of visceral metastases ($p < 0.0001$), Eastern Co-operative Oncology Group (ECOG) score $\leq$1 ($p = 0.017$), and younger age ($p = 0.008$). Nomograms were generated based on the parameters included in the final validated models (with/without uNTx and BSAP). One limitation was that lactate dehydrogenase (LDH) levels, a known prognostic factor, were not available in this study.

* Corresponding author. Department of Cancer Medicine, Institut Gustave Roussy, University of Paris Sud, 39 rue Camille Desmoulins, 94800 Villejuif, France. Tel. +33 1 42114317; Fax: +33 1 42115217.
E-mail address: karim.fizazi@igr.fr (K. Fizazi).

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Conclusions: Bone-related parameters are strong prognostic variables for overall survival in patients with bone metastases from CRPC.
Patient summary: Survival time is variable in patients with bone metastases from prostate cancer. We found that factors related to bone help to predict how long a patient will live.

1. Introduction

Worldwide, prostate cancer is the fifth most common cause of cancer death in men, with an estimated 307 000 deaths in 2012 [1]. Docetaxel plus prednisone has been the standard first-line therapy for symptomatic metastatic castration-resistant prostate cancer (CRPC) [2] since 2004, with a median overall survival of approximately 18 mo [3]. More recently, improved survival has been achieved with hormonal agents (abiraterone, enzalutamide), among other treatments [4–8].

Understanding prognostic factors for survival in metastatic CRPC is important for trial design as well as for informing patients about therapeutic options. Previous studies have identified prognostic variables based on disease characteristics such as prostate-specific antigen (PSA) level [9], PSA doubling time [10], PSA nadir [11], Gleason score [9], presence of visceral metastases [9], performance status [9,12], and pain or analgesic use [12,13]. Hemoglobin [9,12,14] and lactate dehydrogenase (LDH) [9,12] have also been identified as independent prognostic factors. Of particular interest are bone-specific parameters, including history of previous skeletal-related event (SRE) [15,16], pathologic fracture [17], urinary N-telopeptide (uNTx) [14,18–20], alkaline phosphatase [9], and bone-specific alkaline phosphatase (BSAP) levels [14,18,19], which have demonstrated prognostic value. Notably, many of these factors were identified in datasets obtained prior to docetaxel approval, and the analyses were based on small sample sizes.

In this analysis, we examine the impact of baseline variables in a phase 3 trial [21] of bone-targeted agents (denosumab vs zoledronic acid). The objective of this study was to evaluate the risk reduction for time to first SRE between these agents; therefore, the study was not prospectively designed to collect all potential covariates for survival. The objective of this ad hoc analysis was to confirm and extend previously reported prognostic models in a large contemporary dataset.

2. Patients and methods

2.1. Study design and patients

The trial was a randomized, double-blind, phase 3 study comparing denosumab and zoledronic acid in 1901 men (clinicaltrials.gov identifier NCT00321620) [21]. Patients had CRPC (defined as rising PSA levels despite circulating testosterone levels of <0.50 ng/ml), radiological evidence of bone metastasis, but no known brain metastases, and an ECOG score ≤ 2. Baseline demographic and disease characteristics were similar between treatment groups and no differences in overall survival were observed [21]; therefore, the present analyses included all trial participants (Table 1).

2.2. Variables

Fifteen baseline study variables were examined for prognostic value.

2.2.1. Bone-related parameters

1. uNTx corrected for urinary creatinine ($\leq$50 nmol/mmol vs $>$50 nmol/mmol) based on the upper limit of normal (ULN) for healthy adults (50 nmol/mmol); levels $>$50 nmol/mmol were associated with poorer survival [18,19]. uNTx was measured by PPD Industries (Richmond, VA, USA) using an enzyme-linked immunosorbent assay (ELISA; Osteomark, Seattle, WA, USA).
2. BSAP ($<$146 U/l vs $\geq$146 U/l), with the cutoff based on population ULN (146 U/l); levels $\geq$146 U/l were associated with poorer survival [18,19]. BSAP was measured by the University of Liege (Liege, Belgium) using a chemiluminescent assay (Access Ostase reagents on the Access immunoassay system, Beckman Coulter, Brea, CA, USA).
3. Alkaline phosphatase ($\leq$ median vs $>$ median baseline value).
4. Previous SRE (yes vs no), a stratification factor in the study.
5. Worst pain, mild, or none (BPI-SF score $\leq$4), with the cutoff based on literature showing that high pain scores are associated with poorer survival [13].
6. Time from initial diagnosis to first bone metastasis (continuous variable).
7. Time from first bone metastasis to randomization (continuous variable).

2.2.2. Disease-related parameters

1. PSA at study entry ($<$10 vs $\geq$10 ng/ml, cutoff based on the stratification factor).
2. Gleason score as collected from a local pathological report (2–6, 7, 8–10).
3. Current prostate cancer chemotherapy (yes or no), a stratification factor.
4. Visceral metastasis (yes vs no).
5. ECOG performance status ($\leq$1 vs 2).
6. Time from diagnosis of primary cancer to first evidence of metastatic disease (continuous variable).

2.2.3. Demographic and other laboratory parameters

1. Age (continuous variable).
2. Hemoglobin ($\leq$ median vs $>$ median baseline value).

2.3. Statistical methods

As prespecified in the statistical analysis plan, missing baseline values for the following variables were imputed using the mean of the pooled observed data: pain, time from cancer diagnosis to bone metastasis, time from bone metastasis to randomization, Gleason score, and time from cancer diagnosis to first evidence of metastatic disease. Missing baseline

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Table 1 – Demographic and baseline characteristics

Characteristic	All patients (n = 1901)
Median age, yr (range)	71 (38, 93)
ECOG performance status, n (%)	
0	844 (44)
1	924 (49)
2	133 (7)
Median time from diagnosis of prostate cancer to randomization, mo (range)	39.2 (0.5, 484.8)
Previous chemotherapy, n (%)	446 (24)
Current chemotherapy, n (%)	275 (14)
Previous docetaxel use, n (%)	156 (8)
On-study docetaxel use, n (%)	618 (32)
Gleason score, n (%)	
2–6	355 (19)
7	553 (29)
8–10	802 (42)
Missing	191 (10)
Presence of visceral metastases, n (%)	342 (18)
Median PSA, ng/ml (range)	59.5 (0.0, 14076.8)
PSA <10 ng/ml, n (%)	290 (15)
PSA ≥10 ng/ml, n (%)	1611 (85)
Median hemoglobin concentration, g/dl (range)	128 (54, 181)
Previous skeletal-related event, n (%)	494 (26)
Pain (BPI-SF score)	
≤4, n (%)	1169 (61.5)
>4, n (%)	732 (38.5)
Median time from diagnosis of primary cancer to first bone metastasis, mo (range)	24.5 (−16.9[a], 481.8)
Median time from initial diagnosis of bone metastases to randomization, mo (range)	4.6 (0.0, 207.3)
Median alkaline phosphatase, U/l (range)	143.0 (33, 4317)
Median bone-specific alkaline phosphatase, U/l (range)	32.9 (0.0, 1976)
Median urinary N-telopeptide, nmol/mmol (range)	51.9 (4, 3904)

BPI-SF = Brief Pain Inventory—Short Form; ECOG = Eastern Co-operative Oncology Group; PSA = prostate-specific antigen.
[a] In one patient, the diagnosis of bone metastases preceded the diagnosis of the primary tumor; this was the only negative value.

values for uNTx, BSAP, alkaline phosphatase, and hemoglobin were not imputed and were excluded. There were no missing values for previous SRE, PSA, current chemotherapy, ECOG score, visceral metastases, or age. Out of 1901 patients in the study, 1745 (92%) were included in this analysis.

Survival time was defined as the time interval (in months) from randomization to death. If a patient was alive by the primary analysis cutoff date or was lost to follow-up by the analysis cutoff date, then survival time was censored at the last contact date or the analysis cutoff date, whichever was first. Kaplan-Meier estimates were presented graphically for survival distribution by each baseline categorical covariate. A Cox proportional hazards model was used to assess the prognostic significance of baseline covariates in univariate and multivariate analyses. In addition, a Cox proportional hazards model with backward selection based on the full dataset was used to select the potential prognostic factors included in the final model. The baseline covariates with $p < 0.05$ from those selection strategies were included in the final model. Other model selection strategies (such as best subset, forward, and stepwise selections) based on the full dataset were also used to verify the selected prognostic factors in the final model. A concordance index (C-index; range 0–1) [22] was used to assess model predictive discrimination. This index estimates the probability of concordance between predicted and observed responses, with higher index values associated with better discrimination. Internal validation of the final model was done using nonparametric bootstrap resampling with 500 datasets. The same variable selection procedure was repeated for each of the bootstrapped datasets and the selected variables were retained in the final model if the covariates were included in more than half the final models in the 500 bootstrapped samples.

To evaluate the robustness of the process in constructing the prediction model and validating the model based on the full data set, the following steps were implemented [23]:

1. 1000 random learning datasets (based on 70% of the full dataset) and 1000 random validation datasets (based on 30% of the full dataset) were generated with 1000 different random seeds.
2. The prediction model (with variable selection) was constructed based on the learning dataset using a Cox proportional hazards model with backward selection as described above. Then the final prediction model was fitted into the validation dataset.
3. The same model-building and validation process as above was applied to the 1000 learning datasets and 1000 validation datasets.
4. C-index values were generated from each dataset. If the distributions of the two sets of C-index values were similar, the robustness of the model selection and validation process was confirmed and the process was then applied to the full dataset.

The final Cox proportional hazards model after validation was used to create nomograms (with and without uNTx and BSAP). The statistical analyses for model development, as well as model validation and nomogram creation, were done using SAS version 9.2 software and the R 3.0.1 rms package, respectively.

3. Results

3.1. Patients

Baseline demographics and disease characteristics for the overall study population are shown in Table 1. Median (95% confidence interval [CI]) overall survival time was 20 (18, 21) mo.

3.2. Univariate analyses

Point estimates for each variable are shown in Table 2. The bone-specific markers alkaline phosphatase, BSAP, and uNTx were each found to be predictors of survival (all $p < 0.0001$; Fig. 1). Two other bone parameters, pain and history of SRE, were also significant in the univariate analysis (both $p < 0.0001$). PSA <10 ng/ml, absence of visceral metastases, ECOG ≤1, and hemoglobin >128 g/l were each significant prognosticators of longer survival (all $p < 0.0001$; Fig. 2). PSA with a 20-ng/ml cutoff or median cutoff also yielded highly significant results (data not shown); however, we chose the 10-ng/ml cutoff as it matched the stratification factor prespecified in the protocol, which was considered the best clinically meaningful cutoff at the time the trial was designed. Longer time from diagnosis of primary cancer to first evidence of metastatic disease, longer time from diagnosis of primary cancer to first bone metastasis, and longer time from first bone metastasis to randomization were also significant predictors of longer survival in the univariate analysis

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Table 2 – Univariate analyses of potential prognostic baseline variables

Parameter	*n*	Point estimate (95% CI)	*p* value
Corrected uNTx			
≤50 nmol/mmol	868	0.439 (0.383, 0.503)	<0.0001
>50 nmol/mmol	934		
Bone-specific alkaline phosphatase			
<146 μg/l	1578	0.333 (0.284, 0.391)	<0.0001
≥146 μg/l	268		
Alkaline phosphatase			
≤median (143 U/l)	952	0.387 (0.339, 0.442)	<0.0001
>median (143 U/l)	948		
Previous skeletal-related event			
Yes	494	1.399 (1.216, 1.610)	<0.0001
No	1407		
Baseline worst pain			
BPI-SF score ≤4 (mild or no pain)	1169	0.504 (0.443, 0.573)	<0.0001
BPI-SF score >4 (moderate to severe pain)	732		
Time from initial diagnosis to initial bone metastatic disease (mo)[a]	1901	0.997 (0.996, 0.999)	0.0002
Time since first bone metastasis to randomization (mo)[a]	1901	0.993 (0.989, 0.996)	0.0001
PSA level			
<10 ng/ml	287	0.349 (0.277, 0.440)	<0.0001
≥10 ng/ml	1614		
Gleason score			
2–6	355	0.933 (0.781, 1.114)	0.4417
7	744	0.932 (0.808, 1.074)	0.3305
8–10	802		
Current chemotherapy			
Yes	275	1.181 (0.992, 1.407)	0.0614
No	1626		
Visceral metastases			
Yes	342	1.382 (1.181, 1.617)	<0.0001
No	1559		
ECOG status			
≤1	1768	0.447 (0.361, 0.555)	<0.0001
2	133		
Time from primary diagnosis of primary cancer to first evidence of metastatic disease[a]	1901	0.973 (0.958, 0.989)	0.0012
Age at enrollment[b]	1901	1.011 (1.003, 1.019)	0.0078
Hemoglobin			
≤ median (128 g/l)	984	2.026 (1.772, 2.317)	<0.0001
> median (128 g/l)	880		

BPI-SF = Brief Pain Inventory—Short Form; CI = confidence interval; ECOG = Eastern Co-operative Oncology Group; PSA = prostate-specific antigen; uNTx = urinary N-telopeptide.
[a] Reflects the change in the hazard for any increase of 1 mo.
[b] Reflects the change in the hazard for any increase of 1 yr.

($p \leq 0.001$). Younger age was an additional significant predictor of longer survival. Although patients with lower Gleason scores (2–6 and 7) had numerically longer survival than patients with higher Gleason scores (8–10), the difference was not statistically significant ($p = 0.44$ and 0.33, respectively).

3.3. *Multivariate analysis*

The process used to construct and validate the prediction model was found to be robust and was, therefore, applied to the full dataset: mean (standard deviation [SD]) C-index values were 0.7171 (0.007) for the learning datasets and 0.7128 (0.013) for the validation datasets. Among the 15 parameters tested in the multivariate analysis, Gleason score, current chemotherapy, and time from diagnosis of primary cancer to metastases were not significant and were excluded from the final model. Bone-related parameters were all highly significantly correlated to overall survival (all $p < 0.001$). The variables associated with longer survival included uNTx ≤50 nmol/mmol, BSAP <146 U/l, alkaline phosphatase ≤143 U/l, no prior SRE, mild or no pain, longer time from cancer diagnosis to diagnosis of bone metastases, longer time from diagnosis of bone metastases to randomization, PSA <10 ng/ml, absence of visceral metastases, ECOG score ≤1, younger age, and hemoglobin >128 g/l. Results of the 12 significant variables selected for the final model are shown in Table 3. For the continuous variables (age, time from cancer diagnosis to diagnosis of bone metastases, and time from bone metastasis to randomization), the hazard ratios were close to one, yet highly significant, because they reflect the change in the hazard for any increase of one unit. For example, the hazard ratio for age was 1.012, indicating that a 63-yr-old patient had a 1.2% lower risk of death compared to a 64-yr-old patient. For an age difference of 15 yr (eg, age 60 yr vs age 75 yr), the hazard ratio increases to 1.191, indicating that the younger patient has a 19% lower risk of

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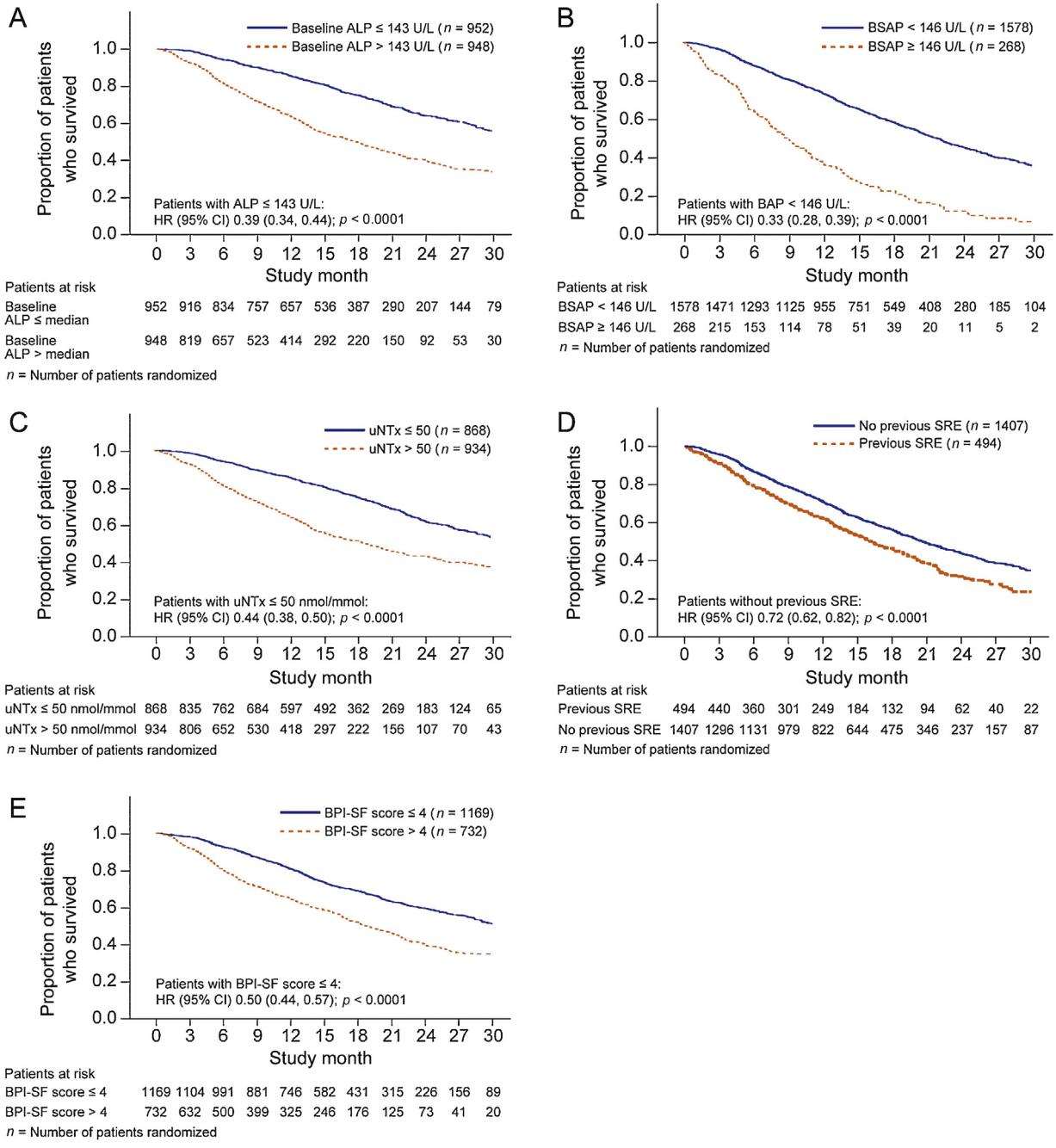

Fig. 1 – Univariate analyses of bone-specific factors. (A) Alkaline phosphatase (ALP ≤ median [143 U/l] vs > median). (B) Bone-specific alkaline phosphatase (BSAP <146 U/l vs ≥146 U/l). (C) Urinary N-telopeptide (uNTx ≤50 nmol/mmol vs >50 nmol/mmol). (D) Previous skeletal related event (SRE; no vs yes). (E) Worst pain absent or mild (Brief Pain Inventory—Short Form [BPI-SF] score ≤4 vs >4).

death. The corrected C-index value of the final model was 0.72, indicating robust discrimination.

As BSAP and uNTx are not commonly measured in clinical practice, we generated an additional model excluding these variables. The same model selection process was implemented (ie, univariable and multivariable analyses with various selection strategies) and all 10 variables were included in the final model. In the 10-variable model, the correlations of each parameter with overall survival were in the same direction and of similar magnitude as in the 12-variable model. The corrected C-index value of the final 10-variable model was approximately 0.71, indicating slightly less discrimination compared with the 12-variable model.

3.4. *Nomograms*

A clinical tool, or nomogram, for the estimation of survival for an individual patient is shown in Supplementary Figure 1 (12-variable nomogram). A second 10-variable nomogram excluding BSAP and uNTx is shown in Figure 3. The precision of the tool is dependent on the full

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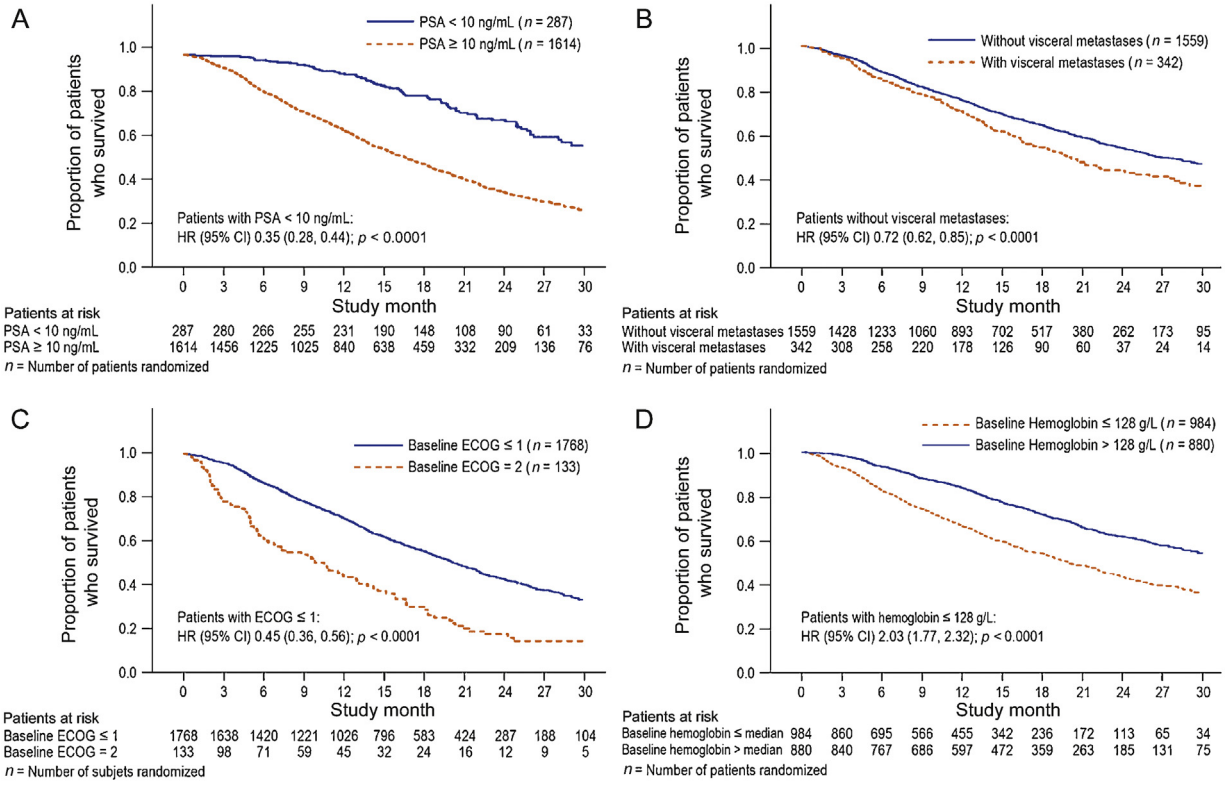

Fig. 2 – Univariate analyses of disease characteristics and laboratory values. (A) Prostate-specific antigen (PSA; <10 ng/ml vs ≥10 ng/ml). (B) Presence of visceral metastases (no vs yes). (C) Eastern Co-operative Oncology Group (ECOG) performance status (≤1 vs 2). (D) Hemoglobin (≤median [128 g/l] vs >median).

Table 3 – Multivariate analysis of baseline prognostic variables for overall survival

Variable	Hazard ratio (95% CI)	*p* value
PSA <10 ng/ml	0.486 (0.381, 0.619)	<0.0001
No previous SRE	0.748 (0.643, 0.871)	0.0002
Pain absent or mild (BPI-SF score ≤4)	0.648 (0.563, 0.745)	<0.0001
ALP ≤ median	0.664 (0.559, 0.789)	<0.0001
BSAP <146 μg/l	0.683 (0.568, 0.822)	<0.0001
Corrected uNTX ≤50 nmol/mmol	0.755 (0.640, 0.889)	<0.0008
Hemoglobin > median	0.614 (0.532, 0.709)	<0.0001
No visceral metastases	0.733 (0.621, 0.864)	0.0002
ECOG score ≤1	0.755 (0.599, 0.950)	0.0167
Age in years	1.012[a] (1.003, 1.021)	0.0081
Time from initial diagnosis to bone metastases diagnosis (mo)	0.997 (0.995, 0.998)	<0.0001
Time from diagnosis of bone metastases to randomization (mo)	0.990[b] (0.986, 0.995)	<0.0001

ALP = alkaline phosphatase; BPI—SF = Brief Pain Inventory—Short Form; BSAP = bone-specific alkaline phosphatase; CI = confidence interval; ECOG = Eastern Co-operative Oncology Group; uNTx = urinary N-telopeptide.
[a] Reflects the change in the hazard for any increase of 1 yr.
[b] Reflects the change in the hazard for any increase of 1 mo.

set of parameters; thus, data from all variables should be included to achieve the most accurate prediction.

4. Discussion

In this analysis from the largest prospective clinical trial of CRPC patients with bone metastases ($n = 1901$), we demonstrate that bone-related parameters are good prognostic variables for overall survival. The analyses reported here both confirm previously identified variables and identify two new prognostic factors. As a whole, this analysis emphasizes the compelling prognostic value of bone-related factors in patients with bone metastases from CRPC. It is well recognized that the population of patients with bone metastases is a mix of patients with de novo metastatic disease and patients progressing from localized disease to metastases; therefore, we believe that the data from this large dataset can generalized to the overall metastatic CRPC population.

We confirmed the role of the following bone-associated variables as highly significant predictors of better overall survival in both univariate and multivariate analyses: lower BSAP levels [14], lower alkaline phosphatase levels [9,24], lower uNTx levels [20], no history of previous SRE [15,16], and mild/no pain [9,13,24]. Lower uNTx was previously reported as a significant predictor of survival in univariate analyses, but not in multivariate analysis, of an older

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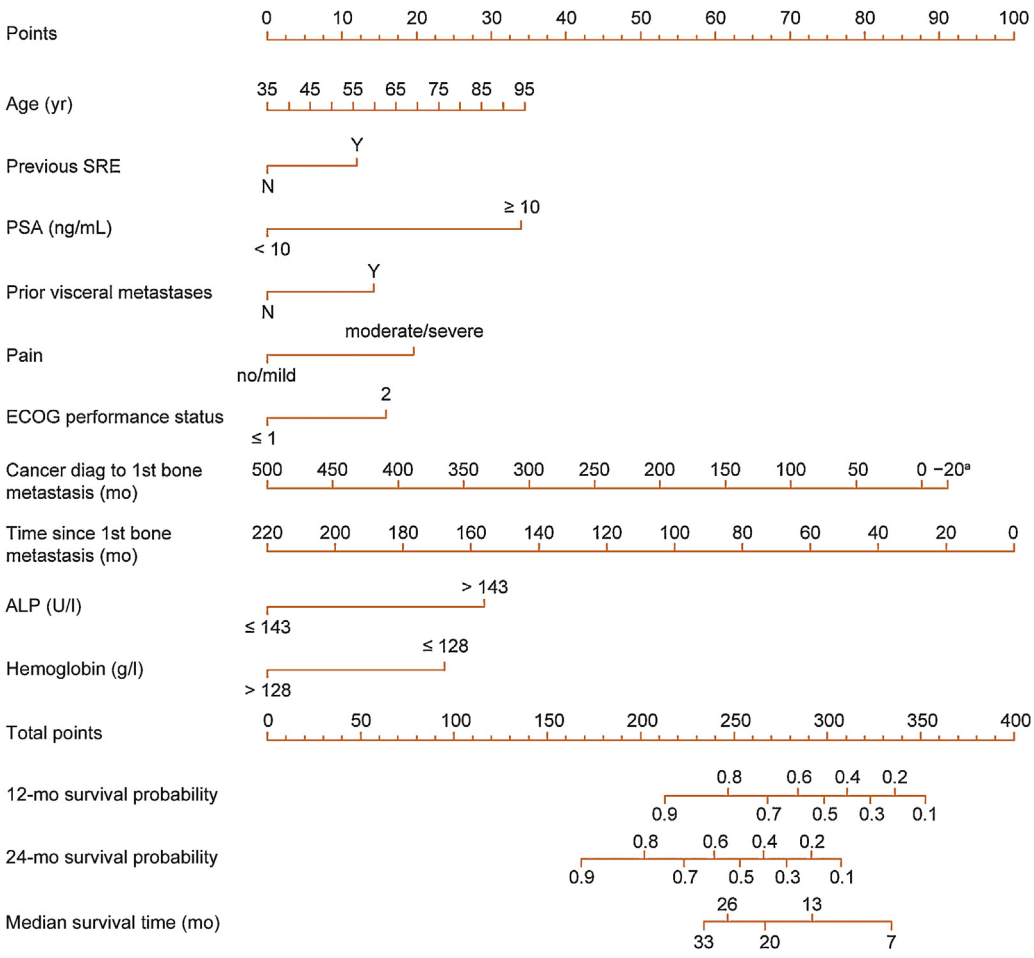

Fig. 3 – Ten variable nomograms for the prediction of 12-mo and 24-mo overall survival probability and median overall survival in months. To use this nomogram, complete the following steps:
1. Identify the scale for the first variable and draw a vertical line at the value until it intersects the "Points" axis; read off the corresponding risk score (points) for that variable.
2. Repeat this process for each variable.
3. Calculate the total risk score, that is, the sum of the points for each variable.
4. Locate the total risk score on the "Total points" axis and draw a vertical line downwards to identify the predicted survival probabilities.
[a]In one patient, the diagnosis of bone metastases occurred months before diagnosis of the primary tumor.

dataset [14]; our findings, by contrast, found the parameter significant in both, as also reported by Rajpar et al [20]. Pain was not specifically collected as a factor related to bone in our study; however, since bone pain is the most common cause of pain in cancer patients [25], we can reasonably assume that most pain was related to bone metastases. We have also identified two new variables with prognostic value: time since first bone metastasis, and time from initial diagnosis to first bone metastasis.

We also confirmed the following disease-specific and laboratory parameters as positive predictors of better overall survival: lower PSA levels [9], absence of visceral metastases [9], better performance status [9,12,14], and higher hemoglobin levels [9,12,14]. In addition, younger age [14] was also confirmed as a significant predictor of favorable outcome (note that the hazard ratio was small because it reflects the change in the hazard for any increase of 1 yr). Similar to Rajpar et al [20], we found that Gleason score had no prognostic value in this dataset, although it was previously found to be important for survival [9,13]. We used traditional cutoffs (2–6, 7, 8–10); other Gleason score cutoffs may have provided different results.

Our results are applicable to future clinical trial design for investigational agents in patients with metastatic CRPC, as they reveal baseline parameters that should be balanced to avoid bias in overall survival calculations. In addition, we incorporated the results of this predictive model into nomograms, which can be used by physicians to assist in estimating prognosis. These are the first nomograms based on a more recent dataset that predicts survival using a predominance of bone-related factors along with more traditional parameters. uNTx and BSAP may not be measured in clinical practice or even in clinical trials; therefore, we developed a second simplified nomogram without these parameters. Our nomograms can be adapted for a clinical setting (in the absence of a randomized clinical trial); for example, survival time can be calculated from a specific index date (such as the present date or specific calendar date, date of prostate cancer diagnosis, or the bone metastases date) depending on the research purposes.

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We note that the baseline covariate of time from diagnosis of bone metastases to randomization may not be meaningful if the index date used is the bone metastases date. Of the previously published nomograms for metastatic CRPC patients, two used data pooled from studies performed in the 1990s and included only one bone-related parameter (alkaline phosphatase) [9,12]. Two additional nomograms were recently published, including one from the TAX327 phase 3 trial based on patients receiving docetaxel and prednisone, and one from the CALGB-90401 trial based on similar standard treatment with/without bevacizumab; however, neither model incorporated bone-related factors except for alkaline phosphatase and pain or pain surrogate [24,26].

4.1. Limitations

Since clinical trial participation is an independent positive predictor of survival [27], our nomograms may overestimate survival in patients not participating in a clinical trial. We acknowledge that the utility of nomograms to predict survival in routine patient management is as yet untested, and the complexity of these prognostic tools may be a barrier to their application. Use of nonlinear terms for covariates could have increased the magnitude of prediction in the model; however, we chose to use a less complicated model more easily used by clinicians. As the dataset contains only patients with an ECOG score of 1 or 2, the model may not be applicable for scores >2. Quantitation of disease burden such as number of bone metastases could not be taken into consideration, because these data were not recorded. LDH, a known prognostic factor [9,12], was not collected in this study. The cutoff points for the variables used in our model were based on the literature; other cutoff points may have yielded different results. In addition, the categorization of continuous variables may have caused information loss and may have introduced error through the assumption that all values of a variable within a category are equivalent. Our dataset is more contemporary than those previously published; however, the relevance of our model for patients receiving the new generation of treatments requires further investigation.

5. Conclusions

In conclusion, bone-related parameters were found to be strong predictors of overall survival in addition to established disease stage factors in multivariate analyses using a large contemporary trial population of metastatic CRPC patients. The main utility of these findings is in the stratification of prospective clinical trials, although survival prediction in routine clinical practice is also feasible.

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Author contributions: Karim Fizazi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Fizazi, Goessl, Massard, Smith, Brown.
Acquisition of data: Fizazi, Goessl, Smith, Shore, Milecki, Karsh, Oudard, Rader, Carducci.
Analysis and interpretation of data: Fizazi, Massard, Goessl, Smith, Ying, Shore, Milecki, Karsh, Oudard, Rader, Brown, Wang, Carducci.
Drafting of the manuscript: Fizazi, Ying, Wang, Goessl.
Critical revision of the manuscript for important intellectual content: Massard, Shore, Smith, Milecki, Karsh, Oudard, Rader, Brown, Carducci.
Statistical analysis: Wang, Ying.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2014.10.001.

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