A Contemporary Prognostic Nomogram for Men with Hormone-Refractory Metastatic Prostate Cancer: A TAX327 Study Analysis

Andrew J. Armstrong,1 Elizabeth S. Garrett-Mayer,2 Yi-Chun Ou Yang,2 Ronald de Wit,3 Ian F. Tannock,4 and Mario Eisenberger2

Abstract

Purpose: To develop a prognostic model and nomogram using baseline clinical variables to predict death among men with metastatic hormone-refractory prostate cancer (HRPC).

Experimental Design: TAX327 was a clinical trial that randomized 1,006 men with metastatic HRPC to receive every three week or weekly docetaxel or mitoxantrone, each with prednisone. We developed a multivariate Cox model and nomogram to predict survival at 1, 2, and 5 years.

Results: Ten independent prognostic factors other than treatment group were identified in multivariate analysis: (a) presence of liver metastases [hazard ratio (HR), 1.66; P = 0.019], (b) number of metastatic sites (HR, 1.63 if ≥2 sites; P = 0.001), (c) clinically significant pain (HR, 1.48; P < 0.0001), (d) Karnofsky performance status (HR, 1.39 if ≤70; P = 0.016), (e) type of progression (HR, 1.37 for measurable disease progression and 1.29 for bone scan progression; P = 0.005 and 0.01, respectively), (f) pretreatment prostate-specific antigen (PSA) doubling time (HR, 1.19 if <55 days; P = 0.066), (g) PSA (HR, 1.17 per log rise; P < 0.0001), (h) tumor grade (HR, 1.18 for high grade; P = 0.089), (i) alkaline phosphatase (HR, 1.27 per log rise; P < 0.0001), and (j) hemoglobin (HR, 1.11 per unit decline; P = 0.004). A nomogram was developed based on this multivariate model and validated internally using bootstrap methods, with a concordance index of 0.69.

Conclusions: This multivariate model identified several new independent prognostic factors in men with metastatic HRPC, including PSA doubling time, and led to the successful development of a clinically applicable nomogram. External prospective validation may support the wider use of this prognostic baseline model for men with HRPC treated with chemotherapy.

Despite the recent demonstration of palliative and survival benefits with docetaxel-based regimens, men with metastatic hormone-refractory prostate cancer (HRPC) have a poor prognosis, with a median survival of 16 to 20 months (1, 2). The biology of prostate cancer is heterogeneous, with expected survival depending on performance status, presence of visceral metastases, baseline prostate-specific antigen (PSA), advanced primary Gleason sum, baseline hemoglobin, lactate dehydrogenase, albumin, and alkaline phosphatase (3, 4). Nomograms have been developed as stratification tools for phase III clinical trials evaluating cytoxic chemotherapy based on data from multiple studies that assessed prognostic factors (3–5).

Baseline PSA kinetics [PSA doubling time (PSADT) or PSA velocity] have not been shown conclusively to be an independent prognostic factor in HRPC, with most analyses based on retrospective reviews of relatively small numbers of patients (6–9). These analyses were limited by the number of controllable covariates, the duration of follow-up, potential confounders, and measurement bias. Furthermore, past prognostic analyses are limited by the inclusion of various types of nontoxic therapy and did not include patients treated with docetaxel-based therapy (3, 4).

In 2004, docetaxel was approved for the treatment of men with metastatic HRPC based on large multicenter randomized clinical trials (1, 2). The TAX327 study randomized 1,006 patients to receive one of two schedules of docetaxel or mitoxantrone, each given with low-dose prednisone, and showed an extension of overall survival, improvement in quality of life, pain control, PSA decline, and objective tumor response (2). A second phase III study using estramustine phosphate in combination with docetaxel confirmed the survival advantage of docetaxel-based chemotherapy (1).
The aim of the current analysis is to develop a multivariate prognostic model, based on the TAX327 trial, to investigate the independent prognostic significance of novel prognostic variables, such as pretreatment PSA kinetics, the presence of pain, number of metastatic sites, and the type of disease progression at baseline, in addition to traditional prognostic markers.

**Materials and Methods**

TAX327 was a randomized, nonblinded, multinational phase III study involving 1,006 men with progressive metastatic HRPC. Full details of the eligibility and baseline characteristics are provided in the original report (2). Briefly, men were eligible if they had documented metastatic prostatic adenocarcinoma in the face of castrate levels of serum testosterone (<50 ng/mL) and had evidence of progression as defined by clinically or radiographically measurable disease or by PSA criteria. Baseline information collected on each individual included serum PSA, age, performance status, pain and analgesic score, hemoglobin, alkaline phosphatase, prior Gleason sum or tumor grade, presence of visceral metastases, location and number of metastases, prior therapies, and how progression was defined, in addition to other clinical variables. An approved and signed Institutional Review Board informed consent form was obtained for all participants at each participating institution.

In a subset of 686 men, three or more consecutive baseline PSA measurements each separated by at least 1 week were available for our prognostic evaluation of PSA kinetics. PSA velocity was calculated assuming first-order kinetics as the rise in serum PSA (ng/mL) over time based on individual linear regression before study initiation. PSADT was calculated from these data. PSADT was entered into the model using both continuous and log-transformed variables as well as categorical variables separated by median values.

The main end point of this analysis was duration of survival as defined by the time from randomization to death, with the survival data updated as of November 2006. Patients who were alive as of the cutoff date were administratively censored, whereas patients lost to follow-up were censored. The Kaplan-Meier product limit estimator was used to estimate the survival distribution (10). Univariate and multivariate Cox proportional hazards modeling was done using Stata 8.2 software (StataCorp LP). Cox proportional hazards assumptions were tested using Schoenfeld residual analysis for univariate and multivariate analysis using as a level of significance of 0.01. Comparisons of baseline characteristics were done using 95% confidence intervals (95% CI), t tests, and exploratory statistical analysis. Covariates of interest for univariate analysis included age, performance status, pain at baseline, baseline levels of hemoglobin, alkaline phosphatase and PSA, presence of visceral and/or liver metastases, pretreatment PSADT, type of progression (measurable, nonmeasurable, bone scan, and PSA-only progression), number of metastatic sites, Gleason score, presence of multiple bony metastases, and prior estramustine or second-line hormonal therapy. Variables (other than PSADT) were prospectively collected on case report forms. Tests for interaction were done for baseline PSA and PSADT. Collinearity and normality of variables were evaluated before inclusion. All variables with skewed distributions (PSA and alkaline phosphatase) were log transformed before incorporation. Internal validation of the model was done using the concordance index and internal bootstrap resampling methods, respectively.

In this data set, high-grade tumors were defined by a primary Gleason sum of ≥8 or a WHO grade of 3 to 4 for those tumors who did not have Gleason sums. This combined variable was included due to the omission of Gleason scoring in 288 subjects (28.6%) and the similarities in morphology in Gleason 8 to 10 compared with WHO 3 to 4.5 The similarities in the point estimates for overall survival on univariate analysis for each of these categories compared with the joint category further validate this assumption. Multiple sites of involvement on bone scan were defined as the presence of more than two regions of nuclear tracer uptake, such as spine and ribs or long bones and pelvis. Performance status was graded using the Karnofsky scale. Pain intensity at baseline was evaluated by the present pain intensity score from the McGill-Melzack questionnaire, and an analgesic score was calculated as the mean daily intake of analgesics, with a score of 4 assigned to a standard dose of narcotic (e.g., 10 mg morphine) and a score of 1 for a standard dose of non-narcotic (e.g., acetamysalicylic acid or 325 mg acetaminophen; ref. 11). A present pain intensity of ≥2 and/or an analgesic score of ≥10 were defined in the original protocol as indicative of the presence of significant pain (2, 11).

The assumptions of the Cox model for our analysis was tested in two ways using binary versions of PSADT alone and also using PSADT and median baseline PSA. In both cases, there was not strong evidence of violation of the proportional hazards assumption based on graphical displays or by using P values (P = 0.07 and 0.04, respectively), and thus, this model design was appropriate for the current analysis.

A stepwise procedure including a bootstrap was used for determining the final model for the nomogram. All variables that were significant in univariate analyses based on an α level of 0.10 were included in a Cox multiple regression model. The covariate with the largest P value was removed, and the model was refit iteratively until all covariates in the model had P values <0.10. This model was considered the final model for the data set. To prevent against overfitting, this procedure was repeated 500 times using bootstrapped data sets. Covariates that were included in more than half of the final models in the 500 bootstrapped samples were used to define the final set of covariates. The final set of covariates was included in a Cox regression using the original data set. This final Cox proportional hazards regression model was used to create a nomogram for prediction of median and 1-, 2-, and 5-year overall survival, and our approach for development of the nomogram and validation was similar to that described by Kattan et al. (12). The R Design library was used to produce the nomogram and to estimate the c-indices for validation (13, 14). The concordance index is the probability that given two randomly drawn patients that the patient who dies first has the higher predicted mortality based on the model. A higher concordance index on a 0 to 1 scale indicates a higher predictive ability.

**Results**

Of 1,006 men with HRPC accrued between March 2000 and June 2002, 686 men had three or more baseline PSA measurements separated each by more than 1 week for calculation of pretreatment PSA kinetics. At the time of this analysis on November 6, 2006, there were 800 mortality events of 1,006 subjects and 18,886 person-months of follow-up, with the longest time to event being 70.8 months. Men in the PSA kinetic subset of the overall database had slightly different baseline characteristics than those patients not included in this subset of 686 men. For example, pain, poor performance status, and visceral metastases were more common in those subjects excluded from this analysis, whereas the proportion of men with PSA-only progression at entry were more likely to be in the PSA kinetic subgroup (Supplementary Table S1). However, the median survival of men in this subgroup did not differ from those that were excluded due to lack of sufficient PSA data, which indicates that these two groups have similar clinical outcomes. PSADTs did not differ according to treatment group at baseline (Supplementary Fig. S1). In addition, the covariates of interest were well distributed across treatment groups within the PSA kinetic subset, and the median survival for each treatment arm reflects that seen in...
the overall updated survival analysis (Supplementary Table S2; ref. 15).

The median baseline PSADT in this cohort of men was 55.8 days (mean, 79 days; range, 5-1245 days; SD, 92 days). As a secondary analysis, men with a more rapid PSADT (<55 days) were more likely to have pain at baseline, progression on bone scan, multiple hotspots on the baseline bone scan, a lower baseline hemoglobin, and higher baseline alkaline phosphatase compared with those men with a slower PSADT (≥55 days; Table 1).

In univariate Cox proportional hazards analysis (Table 2), all traditional prognostic markers showed a significant association with overall survival, confirming prior reports and adding validity to the Halabi nomogram (3). These variables included performance status, baseline hemoglobin and alkaline phosphatase, tumor grade (Gleason sum or by WHO criteria), presence of visceral metastases, and baseline serum PSA. Neither lactate dehydrogenase nor albumin was uniformly measured in the TAX327 database due to the high variability of normal values used in this multinational study and, thus, could not be included in this analysis. The variables with the greatest risk of death included liver metastases [hazard ratio (HR), 2.28], more than two sites involved (HR, 1.99), poor performance status (HR, 1.90), and presence of pain at baseline (HR, 1.72).

In univariate analysis, a shorter pretreatment PSADT (<55 versus ≥55 days) was associated with a 46% increase in the risk of death (HR, 1.46; 95% CI, 1.24-1.73; P < 0.001). Other variables with prognostic significance included extent of involvement on bone scan (more than two regions involved) and type of progression at baseline. Progression by measurable disease or by bone scan was associated with a 50% increase in the risk of death (HR, 1.26 and 1.36, respectively; P = 0.003 and P < 0.001, respectively), whereas a PSA-only progression at baseline was associated with a 25% decrease in the risk of death (HR, 0.75; 95% CI, 0.61-0.92; P = 0.003). Non-Caucasian race was not significantly associated with better survival but this was based on only 70 non-Caucasian subjects (HR, 0.80; P = 0.13).

In multivariate Cox proportional hazards analysis, 635 men were available for analysis after exclusion of missing data from Table 1.

### Table 1. Baseline characteristic of patients according to more rapid (<55 d) or slower (≥55 d) PSA Doubling Time (PSADT) at baseline

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>PSADT &lt;55 d, n = 343 (95% CI)</th>
<th>PSADT ≥55 d, n = 343 (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>68 (66-69)</td>
<td>69 (68-71)</td>
<td>0.047</td>
</tr>
<tr>
<td>Performance status (% ≥80)</td>
<td>87 (83-91)</td>
<td>90 (87-94)</td>
<td>0.22</td>
</tr>
<tr>
<td>Pain at baseline (% yes)</td>
<td>48 (43-53)</td>
<td>38 (33-43)</td>
<td>0.004</td>
</tr>
<tr>
<td>Visceral metastases (% yes)</td>
<td>20 (16-25)</td>
<td>21 (17-26)</td>
<td>0.78</td>
</tr>
<tr>
<td>Liver metastases (% yes)</td>
<td>5 (3-8)</td>
<td>6 (3-8)</td>
<td>0.87</td>
</tr>
<tr>
<td>Type of progression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>19 (15-23)</td>
<td>23 (18-27)</td>
<td>0.26</td>
</tr>
<tr>
<td>Measurable disease</td>
<td>22 (18-27)</td>
<td>25 (21-30)</td>
<td>0.32</td>
</tr>
<tr>
<td>Bone scan</td>
<td>71 (67-76)</td>
<td>60 (55-65)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean hemoglobin (g/dL)</td>
<td>12.6 (12.4-12.7)</td>
<td>12.1 (12.7-13.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean PSA (ng/dL)</td>
<td>650 (330-970)</td>
<td>350 (230-470)</td>
<td>0.09</td>
</tr>
<tr>
<td>Median PSA</td>
<td>180 (160-220)</td>
<td>90 (70-110)</td>
<td></td>
</tr>
<tr>
<td>Mean alkaline phosphatase (IU/L)</td>
<td>490 (420-560)</td>
<td>360 (290-430)</td>
<td>0.01</td>
</tr>
<tr>
<td>High-grade tumor (% high grade)</td>
<td>40 (35-46)</td>
<td>36 (30-41)</td>
<td>0.22</td>
</tr>
<tr>
<td>Multiple hotspots on bone scan (% yes)</td>
<td>87 (83-90)</td>
<td>78 (73-82)</td>
<td>0.001</td>
</tr>
<tr>
<td>No. sites of metastases (% &gt;2)</td>
<td>13 (9-16)</td>
<td>11 (8-15)</td>
<td>0.50</td>
</tr>
<tr>
<td>Treatment group (% q3w docetaxel)</td>
<td>34 (29-39)</td>
<td>36 (31-42)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

In an analysis of PSADT as a predictor of mortality in HRPC, Kaplan-Meier survival curves were constructed according to PSADT, categorized by month groupings: <1 month, 1 to 2 months, 2 to 3 months, 3 to 6 months, and >6 months, representing 109, 264, 151, 118, and 44 subjects, respectively. Using a PSADT <1 month as a reference, we found a decreasing risk of death as PSADT lengthened, with a relative hazard of 0.79, 0.69, 0.53, and 0.37 for those with a PSADT of 1 to 2 months, 2 to 3 months, 3 to 6 months, and >6 months (P < 0.001 for trend; Fig. 1). Although the categorical separation of PSADT at the median (55 days) provided a significant prognostic separation, the monthly categorical separation
providing a more refined stratification for the prognostic nomogram. In bivariate analysis, baseline PSA and PSADT contained independent prognostic information, and a simple two-variable model with these terms had a moderate concordance index of 0.60. Survival curves based on PSA and PSADT categories are shown in Fig. 2. The test for interaction between baseline PSADT and PSA was nonsignificant (P = 0.18).

The internal validity of the multivariate model was evaluated by the nonparametric bootstrap resampling method. The concordance index of the final multivariate model was 0.69 and the index-corrected c-index was 0.68, indicating a moderately high level of predictive discrimination. A nomogram was developed using this multivariate model that may be used to predict overall survival at 1, 2, and 5 years and is

<table>
<thead>
<tr>
<th>Table 2. Univariate Cox proportional hazards analysis</th>
</tr>
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<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>Liver metastases (yes/no)</td>
</tr>
<tr>
<td>No. sites involved (&gt;2 vs ≤2)</td>
</tr>
<tr>
<td>Performance status at baseline (≤70 vs ≥80)</td>
</tr>
<tr>
<td>Pain at baseline</td>
</tr>
<tr>
<td>Multiple hotspots on bone scan (yes/no)</td>
</tr>
<tr>
<td>Visceral metastases (yes/no)</td>
</tr>
<tr>
<td>Baseline PSA ≥114 ng/mL (vs &lt;114 ng/mL)</td>
</tr>
<tr>
<td>Per log unit rise in ng/mL</td>
</tr>
<tr>
<td>PSADT (&lt;55 vs ≥55 d)</td>
</tr>
<tr>
<td>Baseline alkaline phosphatase (per log unit rise in IU/L)</td>
</tr>
<tr>
<td>Type of progression</td>
</tr>
<tr>
<td>Measurable disease (vs nonmeasurable disease)</td>
</tr>
<tr>
<td>Bone scan progression (vs no bone scan progression)</td>
</tr>
<tr>
<td>Rising PSA only (vs other progression definition)</td>
</tr>
<tr>
<td>Prior estramustine (yes/no)</td>
</tr>
<tr>
<td>High-grade tumor</td>
</tr>
<tr>
<td>Gleason &gt;7 or grade 3-4 WHO</td>
</tr>
<tr>
<td>Prior radiotherapy (yes/no)</td>
</tr>
<tr>
<td>Age (≥65 vs &lt;65 y)</td>
</tr>
<tr>
<td>Race (non-Caucasian vs Caucasian)</td>
</tr>
<tr>
<td>Baseline hemoglobin (per unit decline, g/dL)</td>
</tr>
<tr>
<td>Treatment group</td>
</tr>
<tr>
<td>q3w docetaxel</td>
</tr>
<tr>
<td>Mitoxantrone (vs q3w docetaxel)</td>
</tr>
<tr>
<td>Prior antiandrogen (yes/no)</td>
</tr>
</tbody>
</table>

**NOTE:** Number of evaluable subjects reported separately. HRs for each covariate in full data set (n = 1,006 with 800 events reported) did not significantly differ from PSA kinetic subset (n = 686; data not shown) and full data set is reported here for greater precision of these estimates.

<table>
<thead>
<tr>
<th>Table 3. Multivariate Cox proportional hazards analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>Chemotherapy type (vs q3w docetaxel)</td>
</tr>
<tr>
<td>Weekly docetaxel</td>
</tr>
<tr>
<td>Mitoxantrone</td>
</tr>
<tr>
<td>Liver metastases</td>
</tr>
<tr>
<td>No. metastatic sites (&gt;2 vs ≤2)</td>
</tr>
<tr>
<td>Pain at baseline</td>
</tr>
<tr>
<td>Performance status (&lt;70 vs ≥80)</td>
</tr>
<tr>
<td>Progression type</td>
</tr>
<tr>
<td>Measurable disease</td>
</tr>
<tr>
<td>Bone scan progression</td>
</tr>
<tr>
<td>Baseline PSADT (&lt;55 vs ≥55 d)</td>
</tr>
<tr>
<td>Baseline log PSA [for every unit rise in log(PSA) in ng/dL]</td>
</tr>
<tr>
<td>Tumor grade (Gleason ≥8 or WHO 3-4 vs Gleason ≤7 or WHO 2-3)</td>
</tr>
<tr>
<td>Alkaline phosphatase, log scale (per log unit rise, IU/L)</td>
</tr>
<tr>
<td>Hemoglobin (per unit decline, g/dL)</td>
</tr>
</tbody>
</table>

**NOTE:** n = 635 with 518 failures, excluding missing values for pain, performance status, and tumor grade at baseline. Concordance index = 0.69.
shown in Fig. 3 with instructions. Note that PSADT is represented using an ordinal scale in months rather than a separation at the median.

**Discussion**

The importance of a prognostic model rests on its ability to capture clinically relevant and measurable variables for routine use by clinicians to inform patients, improve palliation and treatment decisions, and create homogeneous prognostic strata for randomized comparative trials of therapeutic agents. The prognostic nomogram developed by Halabi et al. (3) collects readily available clinical information, such as primary tumor Gleason sum, performance status, PSA, lactate dehydrogenase, alkaline phosphatase, hemoglobin, and presence of visceral metastases: it divides patients into quartiles of risk with good discriminatory ability for median overall survival in men with HRPC. However, this nomogram and several prognostic models before it were based on data from many smaller and older trials where the majority of patients were not treated with currently used chemotherapeutic regimens, such as docetaxel or mitoxantrone with prednisone (3, 4, 16, 17). Although PSA kinetics are thought to carry prognostic information in HRPC, only recently have they been investigated together with traditional prognostic factors in a systematic way (6–9, 17–19). Given the large and multinational scope of the current study, and the availability of multiple clinical variables including pretreatment PSA kinetics in a large subset of subjects, we were able to develop a comprehensive baseline prognostic model for men with HRPC.
We found baseline PSADT to be independently associated with overall survival, regardless of baseline PSA. We also found that patients with relatively fast PSA kinetics (PSADT < 55 days) were more likely to have pain at baseline, higher serum PSA and alkaline phosphatase, lower hemoglobin concentration, more hotspots on the baseline bone scan, and be of younger age. Despite these confounding associations, PSADT retained independent prognostic significance in our multivariate model, and a nomogram was developed that incorporates PSA kinetics along with other significant prognostic variables.

Our study was based on a large phase III trial of men with progressive metastatic HRPC, but PSA kinetics were not calculated nor stratified for nor considered in the primary analysis. Our analysis is thus retrospective and based on a subset of these individuals who had sufficient baseline data to allow an estimation of PSADT and included only men with three or more PSA values separated by more than 1 week. Given the short PSADTs in this cohort of patients with a median of 55 days, this separation of measurements in time seems reasonable. We found that this subgroup of patients with sufficient data on PSA kinetics had a similar median survival to those excluded from the nomogram development and thus should not limit the generalizability of this analysis. These modest differences should not influence the generalization or significance of our findings, and external validation of this model using prospective data sets that capture PSA kinetics is planned.

PSADT has emerged as an easily obtainable and clinically relevant prognostic marker in several stages of prostate cancer, including pre-prostatectomy, pre-radiation therapy, rising PSA after local therapy, nonmetastatic HRPC, and, most recently, metastatic HRPC (6–9, 20–24). After primary therapy, observations across different studies suggest that the PSADT may shorten as the disease progresses, although longitudinal studies are needed to address PSA acceleration within the same groups of patients. Despite this shortening in median doubling time in metastatic HRPC, heterogeneity still exists in overall survival, as indicated by our multivariate model and nomogram.

In addition to PSA and PSADT, we identified several important prognostic markers from our data set, including number of metastatic sites (three or more), type of chemotherapy, presence of pain, presence of liver metastases, and type of progression at baseline (measurable disease or bone scan compared with PSA only). Baseline pain and pain response have been evaluated as prognostic markers in...
numerous data sets and should be considered a validated prognostic factors based on this and prior analyses (16, 25–28). Liver metastases were found to carry greater influence than overall visceral metastases: they may be more common with neuroendocrine differentiation, which may itself have prognostic import (16, 28–30). An additional novel independent factor in this analysis was the mode of disease progression at baseline, wherein men who had progression by bone scan or measurable soft tissue disease had a 1.28- and 1.40-fold increased risk of death, respectively, compared with those men without these modes of progression, such as PSA-only or nonmeasurable disease progression (P = 0.014 and 0.002, respectively).

The nomogram and multivariate model was found to have a bootstrap concordance index of 0.69, indicating that, for 31% of patient pairs, the patient predicted to have a better prognosis died first. This predictive ability compares favorably with the concordance indices (0.67-0.68) seen with prior nomograms that have not been validated in the current era of docetaxel-based chemotherapy (3, 4, 31). Prior nomograms have not included patient symptoms, such as pain, nor have they examined the independent role of disease burden or PSA kinetics. The lack of complete predictive ability illustrates that, despite the inclusion of 10 independently significant variables, additional factors may contribute to overall survival. Other potential factors that were not examined in this model include lactate dehydrogenase, albumin, serum biomarkers for vascular endothelial growth factor and other cytokines, circulating tumor cells, type of treatment beyond progression, and other unmeasured prognostic factors (3, 4, 32–37). The addition of these biomarkers in future studies may increase the predictive ability of this nomogram, whereas the addition of PSA kinetics, pain, mode of progression, and number of sites of metastases may add predictive ability to other nomograms that did not contain these variables.

In conclusion, we have developed a baseline prognostic model and nomogram for men with HRPC using the largest clinical trial data set available for this disease. This model shows internal validity to a similar degree compared with historic models in the pre-docetaxel era and includes simple and easily obtainable clinical variables that may be useful for clinical prognostication or stratification of subjects in clinical trials in this population. In addition, we have shown that PSA DT, baseline pain, mode of progression, and the number of metastatic disease sites are independently associated with risk of death in men with HRPC, despite accounting for traditional risk factors. Prospective external validation of this model is planned and will be essential for more widespread clinical application.

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