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Nomogram for Overall Survival of Japanese Patients with Bone Metastatic Prostate Cancer

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Abstract

Objective: We analyzed the relationship between prostate cancer outcome and pretreatment clinical factors, and developed a prognostic nomogram for Overall Survival (OS) of patients with bone metastasis.

Methods: Beginning in 1993 to 2011, 463 consecutive prostate cancer patients with bone metastasis were treated. Data sets from 361 patients were used to develop the nomogram (training data), and data sets of 102 patients were used for validation of the nomogram (validation data). Using the external validation data set, the nomogram was assessed for discriminatory ability, and the predictions were assessed for calibration accuracy by plotting actual survival against predicted risk.

Results: Of 361 training data set, 205 (56.8%) patients died, 169 (46.8%) deaths of which were due to prostate cancer. The Median follow-up of patients were 55.2 months. In multivariate analysis, patient age, serum PSA, clinical T stage, extent of disease on bone scan (EOD), and biopsy Gleason sum were independent prognostic factors. We developed a prognostic model for prostate cancer patients with bone metastasis, consisting of these five factors. This nomogram can be used to estimate 1-, 3-, and 5-year survival probability. External validation of this model using 102 validation data sets showed reasonable accuracy (c-index 0.719), although with slight underestimation.

Conclusion: Our pretreatment prognostic nomogram might be useful for Japanese prostate cancer patients with bone metastasis.

Keywords: Prostate cancer; Nomogram; Prognostic tool; Bone metastasis

Abbreviations: OS: Overall Survival; EOD: Extent of Disease on Bone Scan; CRPC: Castration-Resistant Prostate Cancer; c-index: Concordance Index

Introduction

Prostate cancer is the most common non-cutaneous cancer and the second most frequent cause of death from cancer among men in the United States. In 2010, 10,722 patients (17.4 per 100,000) died of prostate cancer in Japan, being the sixth leading cause of cancer death [1]. The incidence of prostate cancer is lower in Japan than in the United States and western countries; however, the disease has been gradually increasing in Japan in recent years [1]. Huggins and Hodges reported the efficacy of androgen deprivation therapy in advanced prostate cancer in 1941 [2]. Although 80-90% of prostate cancers with metastasis respond to initial androgen ablation therapy, most patients will ultimately develop progressive disease. Although some patients can obtain benefit from second-line hormone therapy, anti-androgen withdrawal therapy, or chemotherapy, the efficacy of these therapies continues for only several months, and most cases finally become Castration-Resistant Prostate Cancer (CRPC) [3,4]. Patients with CRPC show progression of systematic symptoms and local complications. Some reports showed that median survival of advanced prostate cancer was 29 to 34 months from initial treatment, [5] and 5-year survival rate was 20-30% [6]. Because these reports showed a wide range of survival probability, more accurate information on patient-characteristics related to survival is needed.

In the United States and in Europe, some new effective agents for CRPC have been approved such as docetaxel, cabazitaxel, sipuleucel-T, abiraterone, and MDV3100 (enzalutmide) [6-11]. Unfortunately, treatment for CRPC is very limited in Japan even though docetaxel has been approved [12]. It is predicted that survival of CRPC patients may be improved by these drugs. Several groups have reported prognostic models for survival of patients with progressive disease. Almost all reports were of a prognostic nomogram for CRPC patients, and there are few reports about a prognostic nomogram for metastatic prostate cancer patients before treatment. A large study about prostate cancer prognosis for pre-hormonal therapy patients was reported in Japan and US [13], although the endpoint was not survival but recurrence. Our interest is an Overall Survival (OS) prognostic model for hormone-naïve metastatic prostate cancer. Accurate prediction models for prostate cancer survival would be valuable for patient counseling and for considering the early use of cytotoxic therapy. We analyzed the relationship between prostate cancer outcome and pretreatment clinical factors and developed a prognostic nomogram for OS of patients with bone metastasis. Our pretreatment prognostic nomogram might be useful for Japanese prostate cancer patients with bone metastasis.

Methods

Beginning in 1993 to 2011, 463 consecutive prostate cancer patients

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with bone metastasis were treated at Yokohama City University hospital and associated hospitals. All patients were already metastatic at the time of diagnosis and none of the patients treated previously. Data sets from 361 patients were used to develop the nomogram (training data), and data sets of 102 patients were used for validation of the nomogram (validation data). All patients had adenocarcinoma of the prostate confirmed histologically, with bone metastasis (any T, any N, M1b). The 2009 TNM clinical staging system and 2005 International Society of Urologic Pathology Gleason grading system were used. In all patients, clinical stage was evaluated by chest and body Computed Tomography (CT) and bone scan. On the basis of the number or extent of metastases, the scans were divided into five extent of disease on bone scan (EOD) grades as follows (Soloway et al. previously described [14]):0. normal or abnormal due to benign bone disease; 1, number of bony metastases less than six, each of which is less than 50% the size of a vertebral body (one lesion about the size of a vertebral body would be counted as two lesions): 2. number of bone metastases between six and 20, size of lesions as described above; 3, number of metastases more than 20 but less than a "super scan"; and 4, "superscan" or its equivalent, *i.e.,* more than 75% of the ribs, vertebrae and pelvic bones.

Docetaxel therapy was not included as a covariate because of this nomogram is survival predictive tool before treatment.

Each hospital had a same treatment protocol. All patients were treated with androgen deprivation therapy (medical or surgical castration with or without anti-androgen) initially. After failed initial androgen ablation therapy, almost all patients were subsequently treated with substitution of anti-androgen, anti-androgen withdrawal therapy, and/or oral low-dose steroid. Some patients received a bisphosphonate and cytotoxic therapy such as docetaxel or estramustine after development of CRPC. In the terminal state, palliative therapy and pain control with morphine, palliative external beam radiation, and strontium were used as appropriate.

The nomogram was developed using a Cox proportional hazards regression model, with stepwise regression analysis. The predictive variables for the nomogram were patient age at initial treatment, serum Prostate-Specific Antigen (PSA) level before treatment, clinical T stage, and EOD to classify the extent of bone metastasis and biopsy Gleason sum. Relative risks and 95% confidence intervals were derived. The nomogram for OS was developed from the results of a Cox proportional hazards model which could predict 1-, 3-, 5-year OS.

Calibration of the nomogram predictions was evaluated by comparing the predicted probability at 1, 3, 5 years with the Kaplan-Meier survival probability. Using the external validation data set, the nomogram was assessed for discriminatory ability by quantifying the concordance index (c-index), and the predictions were assessed for calibration accuracy by plotting actual survival against predicted risk. The Kaplan-Meier product-limit estimator was used to estimate the survival distribution. Chi-squared test and Mann-Whitney U test was used to assess the difference in baseline factors between the training data set and the validation data set. Log-rank test was used for analysis of difference in survival probability between the training data set and the validation data set. All analyses were conducted by IBM SPSS ver19 and the R stats package. This study was approved by the institutional review board.

Results

Training data

The pretreatment characteristics of 361 patients for the training data set are listed in Table 1. Of these patients, 205 (56.8%) died, 169 (46.8%) deaths of which were due to prostate cancer. Median OS was 55.6 months (95%CI: 45.1-66.1) and cause-specific survival was 68.0 months (95%CI: 53.0-83.0). OS for the training data set patients is shown in Figure 1. In the training data set, 69 (19.1%) patients received docetaxel for treatment of castration-resistant prostate cancer.

Multivariate analysis

In multivariate analysis, patient age at initial treatment, pretreatment serum PSA level, clinical T stage, EOD, and biopsy Gleason sum were independent prognostic factors. Table 2 shows the results of multivariate analysis, which are the basis of construction of the nomogram. These five factors are included in the final nomogram. Figure 2 shows a nomogram that could predict OS of prostate cancer patients with bone metastasis. This nomogram can be used to estimate 1-, 3-, and 5-year survival probability. Each scale position has corresponding prognostic points located on the "Points" scale. To determine the points of each factor, a vertical line is drawn from each factor axis to the "Points" axis. The point values for all five predictors are summed and arrive at the "Total points" value. The vertical line from the "Total points" axis to the "Survival prob." of the "@1 year" or "@3 year" or "@5 year" axis demonstrates the 1-, 3-, or 5-year survival probability of each patient.

Validation data

The pretreatment characteristics of 102 patients for the training data set are listed in Table 1. These data were obtained from five hospitals which perform docetaxel-related clinical trial. Of these patients, 55 (53.9%) died, 44 (43.1%) deaths of which were due to prostate cancer. Median OS was 48.3 months (95%CI: 36.1-60.5) and cause-specific survival was 54.9 months (95%CI: 43.8-65.9). OS for validation data set patients is shown in Figure 1. There was no difference in OS between the training data set and the validation data set (p=0.268). In the validation data set, 36 (35.3%) patients received docetaxel for treatment of CRPC. The docetaxel-use rate was significantly higher in the validation data set than in the training data set (19.1%) (p<0.001).

We evaluated the discriminatory ability of the nomogram by quantifying the concordance index (c-index), and the predictions were assessed for calibration accuracy by plotting actual survival against predicted risk using the external validation data set. C-index of the nomogram was 0.719.

Validation data set data were grouped into quartiles on the basis of the median of the predicted survival duration for calibration of the nomogram. Figure 3 shows the calibration of the nomogram. Predicted survival rate from the nomogram was well correlated with actual

	Training sample	Validation sample	p value
Variables			
No. of patients	361	102	
Age, years (mean. SD)	71.43 (8.68)	70.39 (8.17)	NS
NA. nghnl (median. IQR)	253.8 (728.3-1349.7)	358.0 (652.0-1597.2)	NS
573. T4 (%)	81119.	62.8. 37.2	<0.0001
EOD I. 2. 3. 4 (%)	40.7. 26.6.25.5. 7.2	35.3. 27.5. 28.4. 8.8	NS
Gleason E6, 7, 8-10 (%)	6.4. 18.6, 75.0	3.0, 16.7, 80.3	NS
Use of dooetaxcl (%)	19.	35.	<0.0001
Observation period. years (median, IQR)	3.11(3.11-4.15)	2.58 (2.58-3.51)	0.027

SD: Standard deviation
IQR: Interquartile range
EOD: Extent of disease on bone scan

Table 1: Baseline characteristics of training and validation sample.

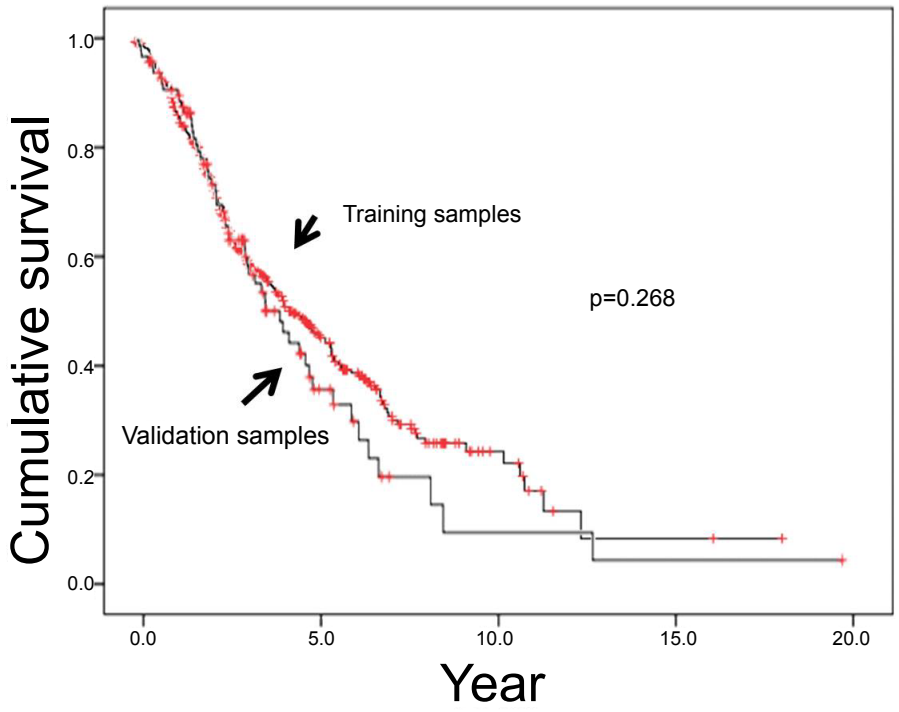

Figure 1: Overall survival in training and validation samples.

Parameter	Probability	Hazard ratio	HR Lower CI	HR Upper CI
Age	0.0002	1.	1.	1.
T stage	0.0002	2.	1.	3.
EOD 2	0.0221	2.	1.	2.
EOD 3	<.0001	2.	2.	4.
EOD 4	<.0001	4.	2.	7.
GS	0.0002	1.	1.	2.
Log PSA	0.0023	0.712	0.572	0.886

EOD: Extent of disease on bone scan
GS: Gleason sum
HR Lower CI: Hazard ratio lower 95% confidential interval
HR Upper CI: Hazard ratio upper 95% confidential interval

Table 2: Multivariate model predicting overall survival.

observation, although our nomogram predicted slightly worse OS than the actual observation. The difference in docetaxel-use rate between the training data and validation data set may have influenced these results.

Discussion

In this study, we developed a nomogram for OS of Japanese patients with bone metastatic prostate cancer. This nomogram is an OS probability prediction tool consisting of five pretreatment factors. These factors, patient age at initial treatment, pretreatment serum PSA level, clinical T stage, EOD, and biopsy Gleason sum, are common clinical factors and may be useful for all patients.

Several groups have reported prognostic models for survival of patients with progressive disease. Almost all reports were of a prognostic nomogram for CRPC patients, and there are few reports about a prognostic nomogram for hormone-naïve progressive prostate cancer before treatment [15-18].

Coopeberg et al. reported a large study on prostate cancer prognosis for hormone-naïve patients in Japan and the US [13]. They assessed 13,740 US men and 19,265 Japanese men with prostate cancer, and developed the Japan Cancer of the Prostate Risk Assessment (J-CAPRA). The CAPRA score from 0 to12 based on Gleason sum, serum PSA level at initial treatment, and clinical stage could predict progression-free survival after primary androgen deprivation therapy. Although the endpoint of J-CAPRA is progression-free survival, our interest is an OS prognostic model for hormone-naïve metastatic prostate cancer. Progression-free survival has been shown to be predictive of OS in men with CRPC [19] although the association between progression-free survival and OS is relatively weak. Some reports indicate improvement in OS without an increase in progression-free survival [9] or improvement in progression-free survival without an increase in survival [20]. Accurate prediction models for prostate cancer survival probability would be valuable for patient counseling and useful for considering the early use of cytotoxic therapy.

We analyzed the relationship between prostate cancer outcome and pretreatment clinical factors, and developed a prognostic nomogram for OS of patients with bone metastasis. Recently, there has been rapid development in treatment for CRPC. In the United States

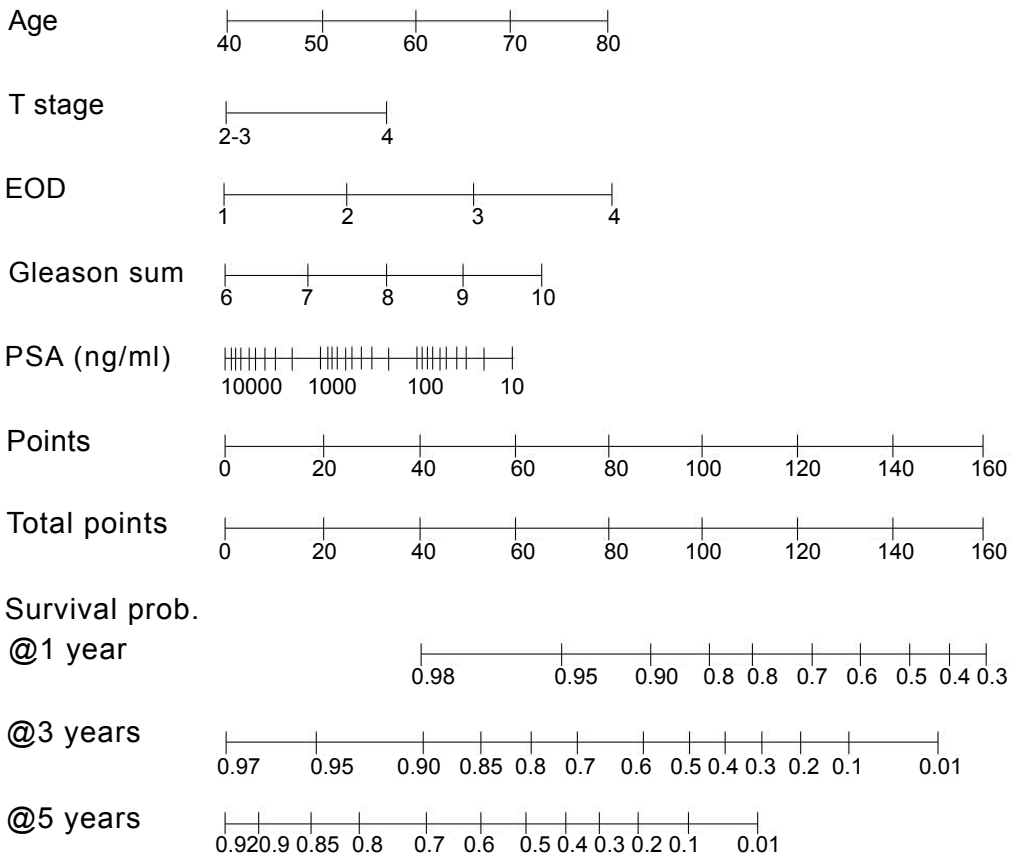

Figure 2: Nomogram that could predict OS of prostate cancer patients with bone metastasis.

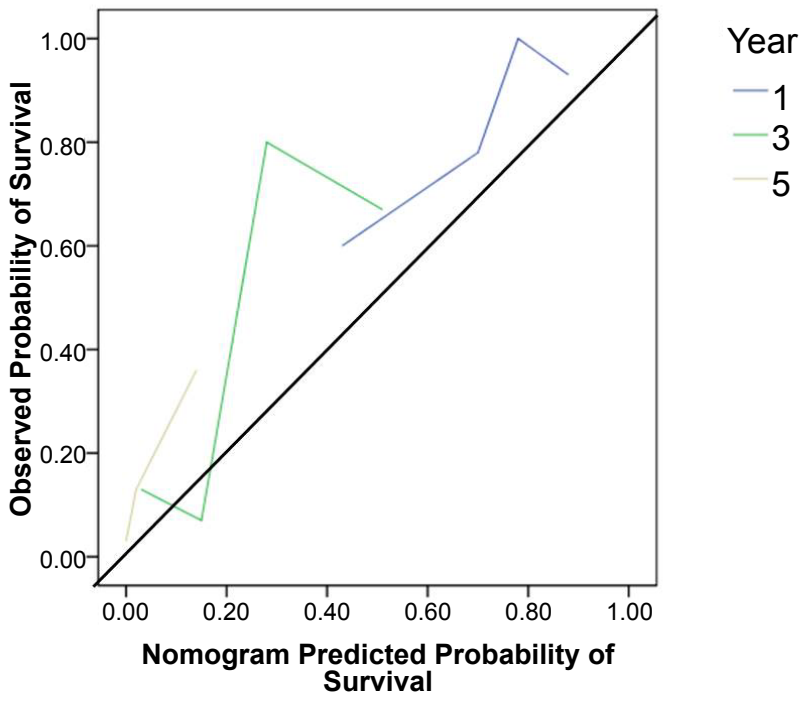

Figure 3: Calibration of the nomogram. Predicted survival rate from the nomogram was well correlated with actual observation, although our nomogram predicted slightly worse OS than the actual observation. The difference in docetaxel-use rate between the training data and validation data set may have influenced these results.

and western countries, some new effective agents for CRPC have been approved such as docetaxel, cabazitaxel, sipuleucel-T, abiraterone, and MDV3100 (enzalutamide) [6,7,9-11,21]. Unfortunately, treatment for CRPC is still very limited in Japan, although docetaxel has been approved [16]. These agents could improve survival of CRPC patients.

External validation of this nomogram was performed using the validation data set of 102 cases. Predicted survival rate calculated by our nomogram was well correlated with practical observation, although our nomogram predicted a slightly worse outcome than the clinical observation. The reason for underestimation may be explained by the fact that in the validation data set, 35.3% of patients received docetaxel, versus 19.1% in the training data set. The docetaxel-use rate was significantly higher in the validation data set than in the training data set ($p<0.001$). Data from six treatment hospitals were used to develop the nomogram (training data), and data sets from the other five hospitals were used for validation of the nomogram (validation data). One of five hospitals which obtained the validation data performed phase 3 study of docetaexel-based combination treatment, so the huge difference concerning docetaxel treatment between training group patients and validation group patients. The difference in docetaxel-use rate between the training data and the validation data set may have influenced the results. As mentioned above, the first limitation of this study is that the predicted survival probability using the nomogram could underestimate the practical actual survival duration under various effective therapies such as docetaxel. Our nomogram was developed from data from the "pre-docetaxel era" or "docetaxel era". For more accurate prediction for prostate cancer patients in the "post-docetaxel era", more recently collected data are needed. Moreover, it would be better that validation samples from a non-Japanese population created has wider applicability.

The second limitation of this study is the fact that patients enrolled in the study had various health status and complications [22,23]. Our nomogram considers neither health status nor patient complications that may influence prostate cancer treatment outcome. Prostate cancer patients are much older than those with other malignancies. Health status and complications should be classified in the rating score and included as predictive factors in the nomogram.

The final limitation of this study is the lack of data about hemoglobin, lactate dehydrogenase, and alkaline phosphatase. These factors were reported as predictive factors for CRPC patients [17,18,24].

In conclusion, we developed a prognostic model for prostate cancer patients with bone metastasis. This model could predict OS from five pretreatment factors which included patient age at initial treatment, pretreatment serum PSA level, clinical T stage, EOD, and biopsy Gleason sum in bone metastatic prostate cancer patients. External validation of this model showed it to be reasonably accurate and similar to practical actual survival probability although with slight underestimation. Our pretreatment prognostic nomogram might be useful for Japanese prostate cancer patients with bone metastasis.

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