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ORIGINAL ARTICLE

# Predicting factors for progression to castration resistance prostate cancer after biochemical recurrence in patients with clinically localized prostate cancer who underwent radical prostatectomy

**Takeshi Hashimoto[1] · Jun Nakashima[2,3] · Takeshi Kashima[1] · Yuri Yamaguchi[1] · Naoya Satake[1] · Yoshihiro Nakagami[1] · Kazunori Namiki[1] · Yoshio Ohno[1]**

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## Abstract

**Background** To determine prognostic factors associated with progression to castration-resistant prostate cancer following biochemical recurrence which is lethal prostate cancer and establish a risk stratification model of progression to castration-resistant prostate cancer.

**Methods** We retrospectively reviewed the data of 550 patients who experienced biochemical recurrence after radical prostatectomy. The endpoint of the present study was progression to castration-resistant prostate cancer. The actuarial probabilities of progression to castration-resistant prostate cancer-free survival were determined using Kaplan–Meier analysis. Univariate and multivariate Cox proportional hazards regression analyses were used to identify independent predictors of biochemical recurrence.

**Results** Fifty-two patients experienced progression to castration-resistant prostate cancer during the follow-up period. The progression to castration-resistant prostate cancer-free survival rate after biochemical recurrence at 10 years was 76.8%. In multivariate analysis, pathological Gleason score ≥ 9, lymphovascular invasion, and prostate-specific antigen velocity ≥ 0.4 ng/mL/year were independent predictive factors for progression to castration-resistant prostate cancer. The patients were stratified into three groups using a risk stratification model incorporating these variables. The 10-year progression to castration-resistant prostate cancer-free survival rates were 96.7% in the low-risk group, 84.7% in the intermediate-risk group, and 24.5% in the high-risk group.

**Conclusions** The present results suggest that the pathological Gleason score, lymphovascular invasion, and prostate-specific antigen velocity were independent predictive factors for progression to castration-resistant prostate cancer. The risk stratification model established in the present study could be useful for patient counseling and in identifying patients with a poor prognosis.

**Keywords** Radical prostatectomy · Biochemical recurrence · Castration-resistant prostate cancer · Risk stratification model

✉ Takeshi Hashimoto
ha-tkc@tokyo-med.ac.jp

Jun Nakashima
njun@iuhw.ac.jp

Takeshi Kashima
takeshikashima922@yahoo.co.jp

Yuri Yamaguchi
yuri.ishizawa7@gmail.com

Naoya Satake
satake@tokyo-med.ac.jp

Yoshihiro Nakagami
nakagami@tokyo-med.ac.jp

Kazunori Namiki
k-namiki@tokyo-med.ac.jp

Yoshio Ohno
yoshio-o@tokyo-med.ac.jp

[1] Department of Urology, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan

[2] Department of Urology, Sanno Hospital, Tokyo, Japan

[3] Clinical Medicine Research Center, International University of Health and Welfare, Tokyo, Japan

## Introduction

Most prostate cancer patients identified in the prostate-specific antigen (PSA) era have favorable prognosis, and the disease is generally curable with radical prostatectomy (RP) [1]. However, once the serum PSA level elevates after RP, the patient is understood to have recurrent prostate cancer, even if they have no signs or symptoms of recurrent prostate cancer. Indeed, a previous study indicated that patients with biochemical recurrence (BCR) after RP were at an increased risk of metastasis and, eventually, dying from prostate cancer [2]. If the successive therapy is absent, the median time from BCR to clinical progression is about 5 years, and almost 40% of men will die from prostate cancer [2, 3]. However, with proper treatment, many prostate cancer patients can be treated until death from other causes. In real clinical practice, some prostate cancers after BCR rapidly become aggressive, while in others the natural prostate cancer history might slowly progress. However, there are still few investigations on the natural history of prostate cancer after BCR. It was suggested that many patients will die from prostate cancer within 3 years once prostate cancer develops to castration-resistant prostate cancer (CRPC) [4]. Consequently, progression to CRPC can be a powerful surrogate for the prediction of prognosis, even in patients who undergo RP and develop BCR. However, very few studies have evaluated this lethal prostate cancer after BCR and its risk factors in patients treated by RP. In addition, to our knowledge, no study to date has established a risk stratification model of progression from BCR to CRPC. Therefore, the aim of the present study was to determine predictive factors associated with progression to CRPC following BCR in patients treated by RP and establish a risk stratification model of progression to CRPC.

## Patients and methods

Between 2000 and 2018, 2816 patients with localized prostate cancer underwent RP at our institution. Of those patients, 674 experienced BCR during the follow-up period. The inclusion criteria for the study are shown in Fig. 1. After excluding these patients who were treated with neoadjuvant or adjuvant therapy and who were treated in other institution or were unable to follow-up, we identified and analyzed 550 patients who experienced BCR after RP for localized prostate cancer. The study design was approved by the institutional review board (IRB approval no. T2019-0158). The association between perioperative factors and progression to CRPC after BCR was evaluated. BCR was defined as two continuous PSA values 0.2 ng/mL or more after RP. CRPC was defined according to the European Association of Urology guidelines as either the PSA value rises three times consecutive at least 1 week apart, leading to two 50% increases compared to the nadir, with a PSA 2.0 ng/mL or more, radiological progression on bone scan, or enlargement

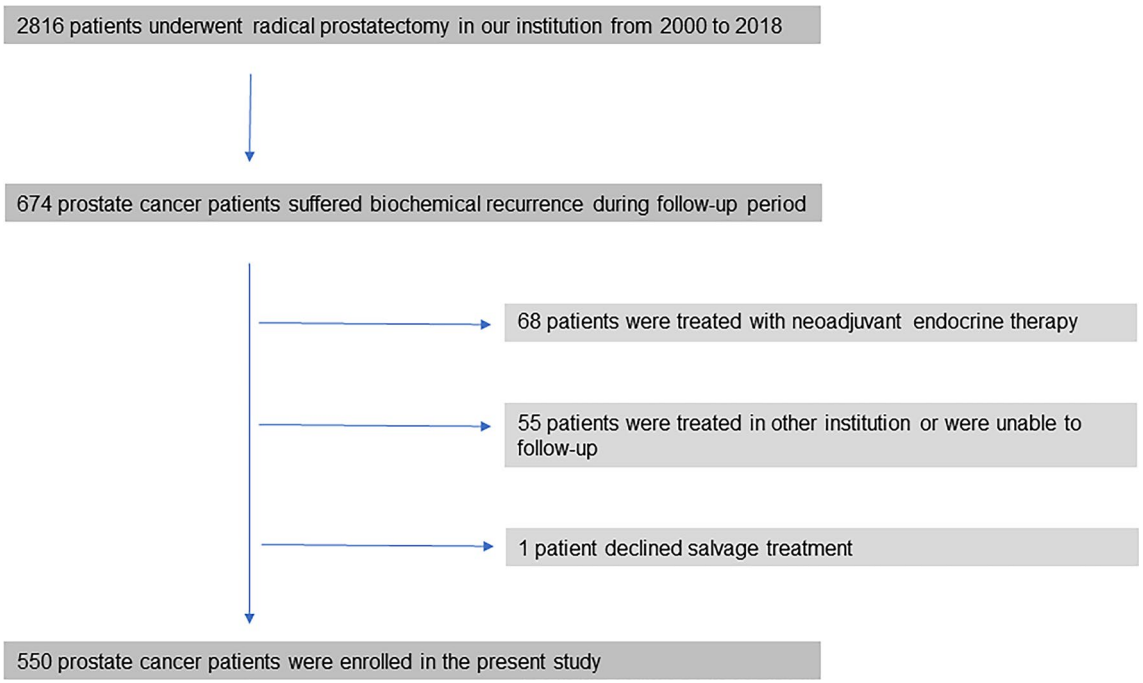


**Fig. 1** The design and inclusion criteria of the present study

of soft tissue lesion [5]. Imaging examinations were performed when an attending doctor suspected disease progression. In addition, the indication of salvage EBRT depended on each attending surgeon and patient. In principle, salvage EBRT was performed after arising the PSA level to 0.2 g/mg or higher in patients with BCR. PSA velocity and PSA doubling time were defined as follows in the present study. Namely, PSA doubling time was calculated by log(2) divided by the slope of the linear regression of log(PSA) over time. PSA velocity was calculated using linear regression analysis. Calculation was performed using three consecutive values of PSA test just before BCR diagnosis during postoperative PSA follow-up.

Univariate and multivariate Cox proportional hazards regression analyses were used to clarify predictive indicators for progression to CRPC-free survival. The actuarial probabilities of the progression to CRPC-free survival rate were calculated using the Kaplan–Meier method. To obtain a multivariate model with maximum accuracy for the significant variables, we used a stepwise selection procedure. To establish a risk stratification model, we dichotomized each variable. The cut-off value for each variable was set as previously reported [6]. That is, the value that was best for discriminating between good and poor outcomes according to the most significant $p$ value by the log–rank test, which was determined by investigating all the available cut-off value. The relative risk (RR) of progression to CRPC was calculated using the significant variables in the multivariate Cox regression analysis, and patients were classified into group according to the RR of the progression to CRPC [7]. Harrell's concordance index (C-index) was used as a means of prognostic discernment [8]. A $p$ value $< 0.05$ was considered statistically significant. All statistical analyses were performed using Stata software (ver. 11.0; Stata Corp, College Station, TX, USA).

## Results

Patient characteristic are described in Table 1. Of 550 patients, 140 were treated by androgen deprivation therapy (ADT) after BCR, 280 were initially, treated by EBRT, 27 were treated by concurrent EBRT and ADT as the first salvage treatment after BCR. In addition, 103 patients were under only observation without salvage therapy during the follow-up periods. Of 280 patients treated by EBRT without concomitant ADT, 105 patients required ADT after EBRT due to PSA rising during study period. Fifty prostate cancer patients died during the study period for some reason. Of those patients, 12 died from prostate cancer. The mean follow-up period after prostatectomy was 78.2 ± 49.3 months, and that after BCR was 58.8 ± 45.5 months. Fifty-two patients (9.5%) progressed to CRPC during the follow-up period. The mean time from surgery to BCR was 19.4 ± 22.9 months in the entire cohort. The mean time from BCR to progression to CRPC in the 52 patients whose prostate cancer developed to CRPC was 55.1 ± 43.9 months. 12 patients had metastatic disease at the time of CRPC. In addition, 36 patients of 52 have metastatic disease during study period.

**Table 1** Patients' characteristics

| | |
|---|---|
| Age at surgery (mean ± SD) | 66.0 ± 6.3 |
| Preoperative PSA ng/ml (mean ± SD) | 14.8 ± 13.3 |
| Clinical stage, *n* (%) | |
| T1c | 321 |
| T2 | 208 |
| T3 | 21 |
| Biopsy Gleason score | |
| ≤6 | 73 |
| 7 | 246 |
| 8 | 101 |
| ≥9 | 130 |
| Pathological T stage | |
| T2 | 256 |
| T3a | 163 |
| T3b | 121 |
| T4 | 10 |
| Pathological Gleason score | |
| ≤6 | 32 |
| 7 | 266 |
| 8 | 84 |
| ≥9 | 168 |
| Surgical margin, *n* (%) | |
| Positive | 207 |
| Negative | 343 |
| Lymph node invasion | |
| Positive | 32 |
| Negative/not resected | 518 |
| Lymphovascular invasion | |
| Presence | 298 |
| Absence | 252 |
| Time to BCR from surgery (mean ± SD) | 19.4 ± 22.9 |
| Number of salvage radiation therapy | 294 |
| PSA doubling time (mean ± SD) | 9.5 ± 13.9 |
| PSA doubling time < 6 months, n | 264 |
| PSA doubling time ≥ 6 months, n | 286 |
| PSA velocity (mean ± SD) | 2.4 ± 9.1 |
| PSA velocity < 0.4 ng/ml/year, n | 264 |
| PSA velocity ≥ 0.4 ng/ml/year, n | 286 |
| Number of developing CRPC | 52 |
| Number of developing metastasis | 56 |

*SD* standard deviation, *PSA* prostate-specific antigen, *BCR* biochemical recurrence, *CRPC* castration-resistant prostate cancer

The progression to CRPC-free survival rates after BCR at 5, 7, and 10 years were 90.3%, 88.0%, and, 76.8%, respectively. Preoperative variables (preoperative PSA, clinical T stage, and biopsy Gleason score) and postoperative variables (pathological T stage, surgical margin status, pathological Gleason score, lymph node invasion, lymphovascular invasion [LVI], time to BCR from surgery, PSA velocity, PSA doubling time, and salvage radiation) were included in Cox univariate analysis. In univariate analysis, a biopsy Gleason score ≥ 9, pathological T stage ≥ 3b, pathological Gleason score ≥ 9, lymph node invasion, LVI, PSA doubling time < 6 months, and PSA velocity ≥ 0.4 ng/mL/year were significantly associated with progression to CRPC (Fig. 2a–g). In multivariate analysis, a pathological Gleason score ≥ 9 (hazard ratio [HR] 3.398; 95% confidence interval [CI] 1.887–6.120; $p < 0.001$), LVI (HR 2.362; 95% CI 1.275–4.373; $p = 0.006$), and PSA velocity ≥ 0.4 ng/mL/year (HR 6.480; 95% CI 2.311–18.171; $p < 0.001$) were independent predictive factors for progression to CRPC (Table 2).

The RR of progression to CRPC was calculated by incorporating those three significant factors obtained from the multivariate analysis into the following formula: RR = exp ([1.223 × pathological Gleason score] + [0.860 × LVI] + [1.869 × PSA velocity]). In this equation, pathological Gleason score was assigned a value of 1 or 0 for scores of ≥ 9 or ≤ 8, respectively, LVI was assigned a value of 1 or 0 for presence or absence, respectively, and PSA velocity was assigned a value of 1 or 0 for velocities of ≥ 0.4 ng/mL/year or < 0.4 ng/mL/year, respectively. The patients were classified into three groups according to the RR of progression to CRPC. The low-risk group was defined as patients with an RR of 1.000 (zero risk factors, $n = 139$), the intermediate-risk group was defined as patients with an RR of 2.362–22.021 (one or two risk factors, $n = 326$), and the high-risk group was defined as patients with an RR of 52.039 (three risk factors, $n = 85$). The 10-year progression to CRPC-free survival rates were 96.7% in the low-risk group, 84.7% in the intermediate-risk group, and 24.5% in the high-risk group (Fig. 3). The progression to CRPC-free survival rate differed significantly between the groups. The C-index of this stratification model was 0.7650.

## Discussion

RP is very effective in many localized prostate cancer patients. However, approximately 15–40% of patients who undergo RP will experience BCR within 5 years [3, 7, 9]. There are possible treatment options after BCR; observation, salvage radiation ± ADT, and ADT alone. However, the patients initially selected observation or salvage radiation only, may have a need for subsequent ADT. Among them, some patients progress to CRPC and eventually die from prostate cancer. Therefore, it is urgently needed to identify patients with lethal prostate cancer after BCR.

In the present study, we demonstrated that a biopsy Gleason score ≥ 9, pathological T stage ≥ 3b, pathological Gleason score ≥ 9, LVI, PSA doubling time < 6 months, and PSA velocity ≥ 0.4 ng/mL/year were significantly associated with progression to CRPC on univariate analysis. Further, we identified pathological Gleason score ≥ 9, PSA velocity ≥ 0.4 ng/mL/year, and LVI as independent predictive factors for progression to CRPC in patients with BCR.

First independent factor, pathological Gleason score has been shown to be significantly associated with second BCR after salvage EBRT [10]. In addition, Yang et al. reported that Gleason 9–10 prostate cancer derives less survival benefit from ADT than Gleason 8 prostate cancer and that a higher Gleason score predicts lower benefit [11]. In this way, the Gleason score has been considered to be a universal prognostic factor of castration resistance. In the present study, the prognosis worsened as the Gleason score increased, as has been seen in previous studies. However, a clear threshold for progression to CRPC was seen in patients with a Gleason score of 9 or higher.

Second independent factor, PSA velocity, which is one of the indices of PSA kinetics, has been reported to be a significant marker for prostate cancer-specific mortality [5]. Further, long-term PSA velocity improves risk assessment of prostate cancer mortality [12]. Freedland et al. reported that PSA doubling time was a significant risk factor for cancer-specific mortality [2]. The Prostate Cancer Working Group advises recording PSA doubling times and particular paying attention on those patients with shorter PSA doubling times, as these patients have the greatest risks of developing detectable metastatic disease and death from prostate cancer [13, 14]. In the present study, PSA doubling time and PSA velocity were both significant factors associated with progression to CRPC in univariate analysis. However, PSA velocity was more significant than PSA doubling time for predicting progression to CRPC in the multivariate analysis.

Third independent factor, LVI, has been demonstrated to be an independent prognostic factor for BCR [15–18]. However, no study to date has reported the clinical implication of LVI as a prognostic factor from BCR to CRPC. In addition, very few reports investigated the association of LVI and prostate cancer mortality. LVI has been shown to be a general prognostic factor in urological cancers, especially in urothelial carcinoma [18–20]. It has been suggested that LVI is an essential step toward metastasis in urologic cancers [21]. We previously reported that microvascular invasion is associated with failure of salvage radiotherapy after BCR in patients who underwent RP [20]. The presence of LVI might be associated with possible micro metastases and may indicates a need for subsequent ADT. Taken together, these

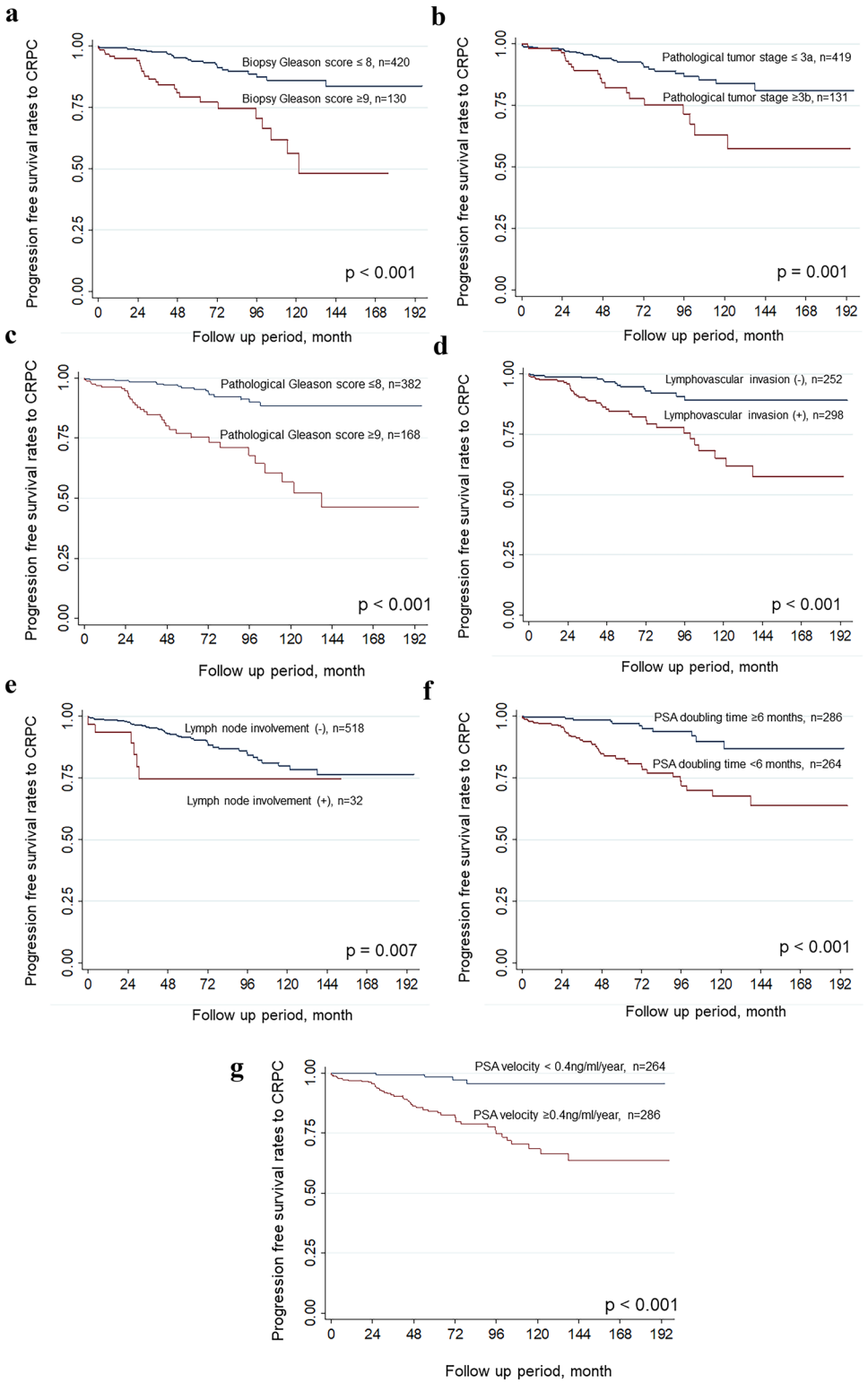


**Fig. 2** **a** Kaplan–Meier analysis according to the biopsy Gleason score. Significance: $p < 0.05$. Biopsy Gleason score $\leq 8$ vs. biopsy Gleason score $\geq 9$. **b** Kaplan–Meier analysis according to pathological tumor stage. Significance: $p < 0.05$. Pathological tumor stage $\leq 3$a vs. pathological tumor stage $\geq 3$b. **c** Kaplan–Meier analysis according to the pathological Gleason score. Significance: $p < 0.05$. Pathological Gleason score $\leq 8$ vs. pathological Gleason score $\geq 9$. **d** Kaplan–Meier analysis according to lymphovascular invasion. Significance: $p < 0.05$. Presence of lymphovascular invasion vs. absence of lymphovascular invasion. **e** Kaplan–Meier analysis according to PSA doubling time. Significance: $p < 0.05$. PSA doubling time $< 6$ months vs. PSA doubling time $\geq 6$ months. **f** Kaplan–Meier analysis according to PSA velocity. Significance: $p < 0.05$. PSA velocity $< 0.4$ ng/ml/year vs. PSA velocity $\geq 0.4$ ng/ml/year

findings suggest that prostate cancer with LVI not only have metastatic ability, but also increase the risk of progression to CRPC.

In the present study, using above three independent factors, we finally developed novel risk stratification model for progression to CRPC in patients with BCR following RP. The patients were classified into three groups according to the risk of progression to CRPC. The 10-year progression to CRPC-free survival rates in the low-, the intermediate-, and the high-risk group were 96.7%, 84.7%,

**Table 2** Results of univariate and multivariate analyses

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | 95% CI | HR | *p* value | 95% CI | HR | *p* value |
| Preoperative PSA, < 8 ng/ml vs. ≥ 8 ng/ml | 0.868–3.157 | 1.656 | 0.126 | | | |
| Time from surgery to BCR, < 3 months vs. ≥ 3 months | 1.047–3.139 | 1.813 | 0.034 | | | |
| Clinical T stage, ≤ 1c vs. ≥ 2a | 0.634–1.910 | 1.101 | 0.733 | | | |
| Biopsy Gleason score, ≤ 8 vs. ≥ 9 | 2.260–6.739 | 3.903 | < 0.001 | | | |
| Pathological T stage, ≤ 3a vs. ≥ 3b | 1.480–4.494 | 2.579 | 0.001 | | | |
| Surgical margin status, positive vs. negative | 0.959–3.372 | 1.799 | 0.067 | | | |
| Pathological Gleason score, ≤ 8 vs. ≥ 9 | 3.049–9.598 | 5.409 | < 0.001 | 1.887–6.120 | 3.398 | < 0.001 |
| Lymph node invasion, positive vs. negative | 1.379–7.661 | 3.250 | 0.007 | | | |
| Lymphovascular invasion, presence vs. absence | 2.118–7.049 | 3.864 | < 0.001 | 1.275–4.373 | 2.362 | 0.006 |
| Salvage radiation therapy, irradiated vs. non-irradiated | 0.783–2.362 | 1.360 | 0.276 | | | |
| PSA doubling time, < 6 months vs. ≥ 6 months | 2.352–8.926 | 4.582 | < 0.001 | | | |
| PSA velocity, < 0.4 ng/ml/year vs. ≥ 0.4 ng/ml/year | 3.521–27.090 | 9.766 | < 0.001 | 2.311–18.171 | 6.480 | < 0.001 |

*CI* confidence interval, *HR* hazard ratio, *PSA* prostate-specific antigen, *BCR* biochemical recurrence

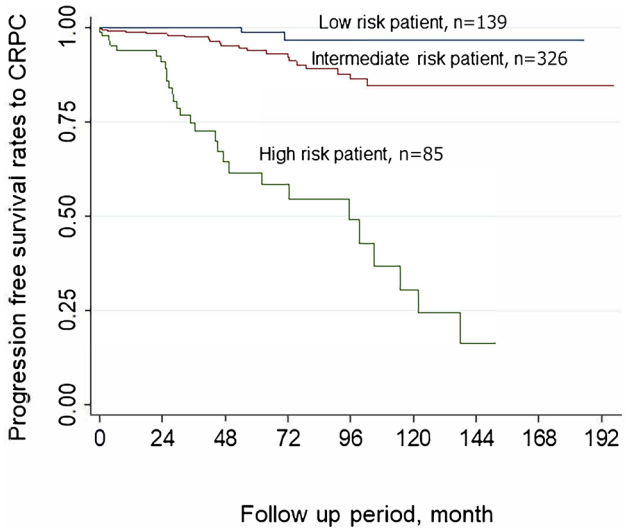


**Fig. 3** Kaplan–Meier analysis of the CRPC-free survival rate according to the risk stratification model. The CRPC-free survival rate differed significantly between each group ($p < 0.001$)

and 24.5%, respectively. Early detection of recurrent disease is important, but not all patients with BCR after RP will develop metastatic and require salvage treatment. If patients undergo salvage therapy too early, they may suffer by receiving unnecessary treatment. In the present study, 48 of 139 low-risk patients initially had selected observation. However, none of the patients received subsequent ADT. The patients with low-risk may be a good candidate for observation or differed salvage therapy. On the other hand, the rate of CRPC progression in the high-risk patients treated with ADT or EBRT alone as first salvage treatment were 41.2% and 35.1% during the study period, respectively. However, the rate of CRPC progression in the high-risk patients treated with ADT + EBRT was 16.7%. The high-risk patients in the present model may progress to lethal prostate cancer, which was quite likely to die. Therefore, the early aggressive and maximum treatment may be necessary to those high-risk patients. It is suggested that salvage ADT plus EBRT may be possible to suppress progression to CRPC in high-risk patients. In addition, these high-risk patients might be possible candidate for clinical trial of new therapeutic agents those were developed in recent years. In this way, the risk model we established in the present study can be easily introduced into clinical practice.

The present study had several limitations. It was a retrospective study that involved the analysis of data collected from patients who underwent RP at a single institution. Second, we excluded some patients during the study period because the patient or attending physician relocated. Third, we used progression to CRPC as a surrogate endpoint of prostate cancer-specific mortality because it takes considerable time to estimate cancer-specific mortality or overall survival in patients with BCR after surgery. Further studies on cancer-specific mortality and overall survival are needed. Despite the limitations, the risk factors identified in this study could help to identify patients at a high risk of progression to CRPC and could be useful in counseling patients before salvage treatment. Further prospective studies will be expected to confirm our findings. We believe that our results could help physicians make better decisions about treatment after BCR in prostate cancer patients who underwent RP. The risk stratification model established in the present study could be useful for patient counseling and in identifying patients with a poor prognosis who might be candidates for clinical trials of alternative management strategies, such as novel adjuvant therapies.

The present results suggest that the pathological Gleason score, LVI, and PSA velocity are independent prognostic factors for progression to CRPC. The risk stratification model established using these three prognostic factors could be useful for patient counseling and in identifying patients with a poor prognosis. This study provides important information for patients with localized prostate cancer undergoing RP regarding to predicting progression to CRPC.

## Compliance with ethical standards

**Conflict of interest** No author has any conflict of interest.

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