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Development of Novel Nomograms to Predict 5- and 7-Year Biochemical-Recurrence-Free Survival in High-Risk Prostate Cancer Patients After Carbon-Ion Radiotherapy and Androgen Deprivation Therapy

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Featured Application: Nomograms were developed to estimate 5- and 7-year biochemical recurrence-free survival in patients with high-risk prostate cancer treated with carbon-ion radiotherapy and androgen deprivation therapy.

Abstract: Background: The aim of this study was to develop nomograms predicting 5- and 7-year biochemical-recurrence (BCR)-free survival in high-risk prostate cancer (PCa) patients treated with carbon-ion radiotherapy (CIRT) and androgen deprivation therapy (ADT). Methods: We retrospectively evaluated 785 high-risk PCa patients treated with CIRT and ADT. Based on the least absolute shrinkage and selection operator model, two nomograms predicting 5- and 7-year BCR-free survival were developed and internally validated. The ability of each nomogram to predict BCR-free survival was determined by calculating the area under the survival curve (AUC). Results: The 5- and 7-year BCR-free survival rates were 92.1% and 89.3%, respectively. Age, prostate-specific antigen level, clinical T stage, and Gleason score were incorporated into the nomogram predicting 5-year BCR-free survival. In addition to these variables, the percentage of positive biopsy cores was also added to the nomogram predicting 7-year BCR-free survival. The AUC value of each nomogram showed suboptimal-to-good discrimination. Conclusions: We developed the first nomograms accurately predicting BCR-free survival in high-risk PCa patients treated with CIRT and ADT. These nomograms will enable adequate understanding and explanation of BCR-free survival to patients when clinicians use them.

Keywords: prostate cancer; high-risk; nomogram; carbon-ion radiotherapy; androgen deprivation therapy

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1. Introduction

Prostate cancer (PCa) represents one of the most common malignancies affecting males globally [1,2]. The global incidence of PCa is increasing with the aging of the population [3,4]. Because of the heterogeneity of PCa in terms of severity, ranging from indolent to highly aggressive, PCa patients are usually classified into risk groups (low-, intermediate-, and high-risk) before definitive treatment. According to the D'Amico and the National Comprehensive Cancer Network (NCCN) risk criteria, the risk classification is based on the prostate-specific antigen (PSA) level, clinical T (cT) stage, and biopsy Gleason score (GS) [5,6]. Both radiotherapy (RT) and radical prostatectomy (RP) have played an important role in the definitive treatment of non-metastatic localized or locally advanced PCa and can decrease the cause-specific mortality (CSM) rate [7]. High-risk PCa cases, which account for 20–30% of PCa diagnoses, are associated with biochemical recurrence (BCR), metastases, and CSM [8–10]. Although RT with androgen deprivation therapy (ADT) and RP with or without adjuvant therapy are the main treatments for high-risk PCa, no clear consensus has been reached yet on the optimal treatment recommendations in clinical guidelines [6,11].

Carbon-ion radiotherapy (CIRT) was first used for localized prostate cancer in 1995 by the National Institute for Quantum Science and Technology in Chiba, Japan (formerly known as the National Institute of Radiological Science) [12]. The unique physical and biological properties of CIRT offer potential advantages over conventional RT, including enhanced cytotoxic effects on cancer cells and superior dose distribution [12–17]. Favorable clinical outcomes, such as lower rates of BCR and CSM, have been observed in high-risk PCa patients treated with CIRT in combination with ADT [13–17]. Furthermore, CIRT combined with long-term ADT has yielded more favorable treatment outcomes compared with treatments involving RT and RP in high-risk PCa patients [14]. Despite these promising results, a subset of high-risk PCa patients remains at elevated risk for BCR, a critical clinical concern due to its strong correlation with overall mortality [14,18–20]. Consequently, more precise risk stratification for high-risk PCa beyond the conventional D'Amico and NCCN criteria is required to accurately assess BCR risk in individual patients. Conventional high-risk PCa classifications encompass a diverse spectrum of disease, necessitating refined predictive tools. Previously, we examined whether the Candiolo nomogram, which was originally developed to predict 10-year BCR risk in all-risk PCa patients treated with conventional RT, can also predict outcomes after CIRT [13,21–23]. Although our previous study showed better discrimination even in high-risk PCa patients treated with CIRT based on the Candiolo risk classification, the risk categories and modality used differ between the Candiolo classification and our studies [13].

Therefore, a novel prediction model is needed to predict BCR-free survival in high-risk PCa patients after CIRT and ADT. The aim of this study was to develop a new tool for predicting 5- and 7-year BCR-free survival in high-risk PCa patients after CIRT.

2. Materials and Methods

2.1. Patients

We performed a retrospective analysis of a database acquired from prospective clinical trials conducted at the Research Center for Charged Particle Therapy, QST Hospital. This research was sanctioned by the institutional review board at QST Hospital (approval no. N21-005), and the study details have been disclosed on our institutional website; potential participants were given the chance to opt out of being enrolled. The patients in this study were diagnosed with high-risk PCa and treated with CIRT combined with ADT between April 2000 and May 2018. The inclusion criteria were pathologically confirmed prostate adenocarcinoma, stage T1–T3N0M0, no concomitant primary malignancies, and no history

of PCa treatment. TNM staging was conducted by digital rectal examination, ultrasound, computed tomography, magnetic resonance imaging, and isotope bone scanning, according to the TNM Classification of Malignant Tumors [24]. The definition of high-risk PCa at QST Hospital, which has been modified from those in conventional risk classifications [5,6], is an initial prostate-specific antigen (PSA) level $\geq$ 20 ng/mL, cT3a/b disease, and/or a Gleason score (GS) $\geq$ 8, corresponding to high-risk and very-high-risk disease (excluding cT4 stage) based on the NCCN risk classification [6]. All prostate biopsy specimens were re-evaluated by a single pathologist (M.H.) to determine the percentage of positive biopsy cores (%PC) and assign a Gleason score. Of 929 patients in total, 785 (84.5%) were included in this study. Since %PC is a clinically important predictor, multivariate imputation by chained equations was used to supplement missing %PC values in this study. No other variable had missing values from the beginning.

2.2. CIRT

Patients received CIRT at QST Hospital, Japan, following a detailed treatment protocol described previously [12–14]. Briefly, CIRT was administered to the prostate gland and seminal vesicle once daily 4 days a week. The radiation dose was expressed in Gy (RBE) (physical carbon ion dose [Gy] $\times$ RBE). The RBE value for CIRT was estimated to be 3.0 at the distal portion of the spread-out Bragg peak, based on previous studies [12–14]. The present study utilized the following dose fractionation schemes: 66.0 Gy (RBE)/20 fractions (91 cases), 63.0 Gy (RBE)/20 fractions (98 cases), 57.6 Gy (RBE)/16 fractions (301 cases), and 51.6 Gy (RBE)/12 fractions (295 cases).

2.3. ADT

All patients received neoadjuvant and concomitant ADT for 2–6 months prior to CIRT. ADT was administered via subcutaneous injection of a luteinizing-hormone-releasing hormone analogue, with or without an oral anti-androgen. No patients underwent surgical castration. Post-CIRT adjuvant ADT was recommended for a minimum of 24 months, including the neoadjuvant period. To exclude the masking effects of prolonged ADT on BCR, patients who received ADT for more than 36 months were excluded from the analysis.

2.4. Assessment

Patients were monitored at 3-month intervals for the first 5 years following CIRT and subsequently at 3- to 6-month intervals. Follow-up duration was defined as the time from CIRT initiation to the last recorded follow-up. Clinical records were updated as of August 2022. The primary endpoint was BCR, defined as a PSA level $\geq$ 2.0 ng/mL above the nadir in accordance with the Phoenix definition [25]. BCR-free survival was calculated from the date of CIRT initiation.

The following variables were analyzed as candidate predictors: age, PSA level, cT stage, biopsy GS, and %PC. First, log-rank tests were used to compare Kaplan–Meier curves for BCR-free survival and to evaluate the clinical predictors in our patients. Second, a nomogram was developed by randomly selecting 60% of the patients (n = 470) to construct the model, with the remaining 40% (n = 315) reserved for validation. Due to the non-normal distribution of the PSA level and %PC data, the Box–Cox transformation was performed. After transformation, the distributions were relatively normalized. The least absolute shrinkage and selection operator (LASSO) regression approach was used because it efficiently handles multicollinearity among predictors and selects the most relevant variables for the model, ensuring simplicity and interpretability. After using this model to select predictive variables meeting the criteria for minimal binomial deviance, nomograms for 5- and 7-year BCR-free survival in high-risk PCa patients after CIRT and ADT were developed. Third, the ability of these nomograms to predict 5- and 7-year BCR-free survival

was calculated using Heagerty's area under the survival curve (AUC) method for internal validation [26]. Lastly, using the median probability values derived from each nomogram as cut-off thresholds (0.93 for 5-year and 0.90 for 7-year predictions), patients with high versus low probabilities of BCR-free survival were compared using the log-rank test. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using the R software (http://www.r-project.org/, accessed on 25 January 2024) and the EZR software (https://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html, accessed on 25 January 2024) [27]. The R packages utilized included glmnet for LASSO regression, survival for survival analysis, and pROC for receiver operating characteristic curve analysis.

3. Results

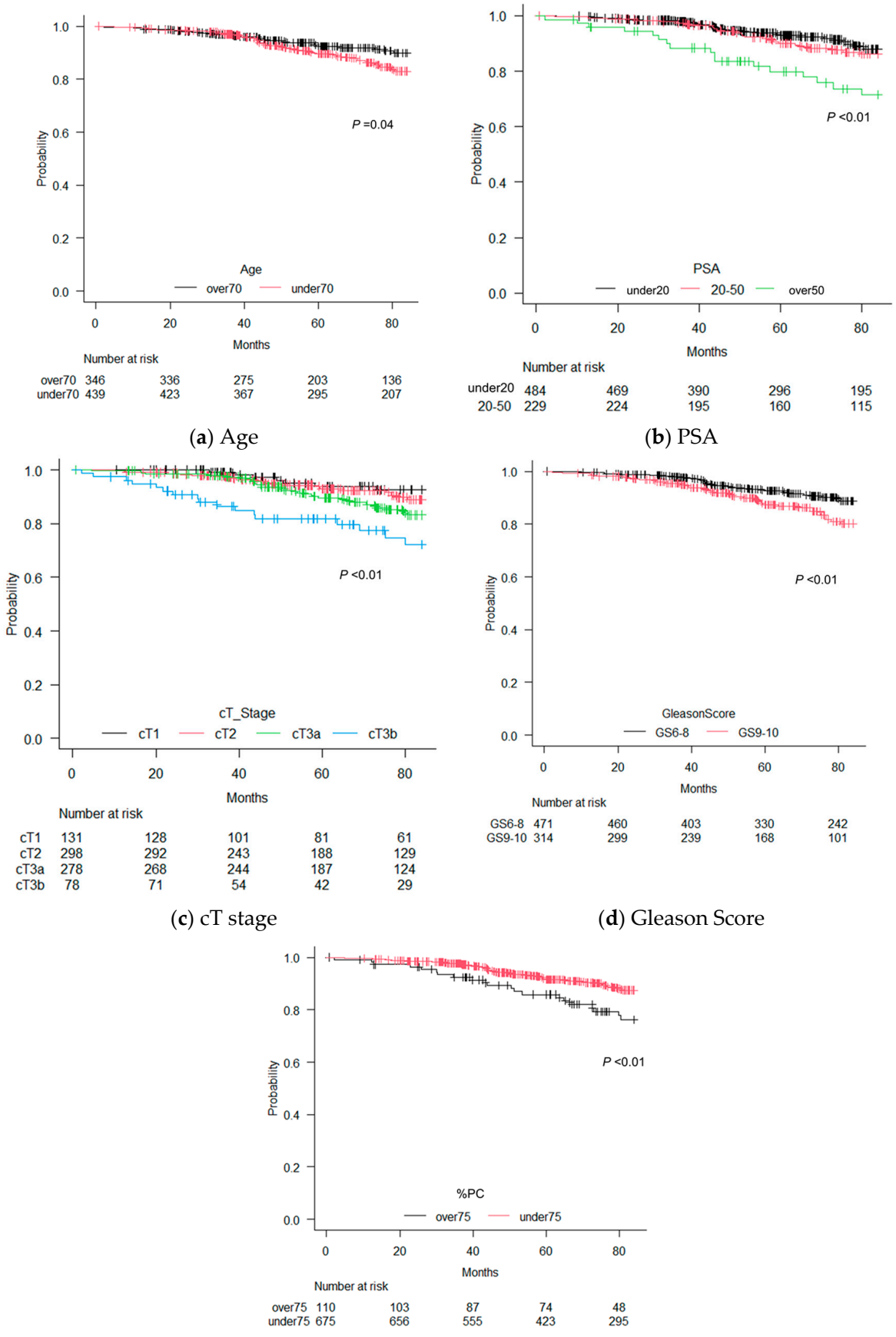
Table 1 presents the characteristics of the 785 patients diagnosed with high-risk PCa included in the analysis. The median age of the patients (interquartile range [IQR]) was 69.0 (IQR, 64.0–73.0) years. The median PSA level was 14.4 (IQR, 7.7–26.4) ng/mL. The cT stage was cT1 in 131 (16.7%) patients, cT2 in 298 (38.0%) patients, cT3a in 278 (35.4%) patients, and cT3b in 78 (9.9%) patients. The GS was 6 in 39 (5.0%) patients, 7 in 245 (31.2%) patients, 8 in 187 (23.8%) patients, 9 in 311 (39.6%) patients, and 10 in 3 (0.4%) patients. The median %PC was 40.0% (IQR, 25.0–58.3%) after using multivariate imputation by chained equations for the missing values. The median follow-up interval was 87.0 (IQR, 57.4–129.2) months, and the median duration of ADT was 25.0 (IQR, 23.7–27.9) months. The 5- and 7-year BCR-free survival rates were 92.1% and 89.3%, respectively.

Table 1. Patients' characteristics in the present study.

Variables	N = 785
Age (year) Median (IQR)	69.0 (64.0, 73.0)
PSA (ng/mL) Median (IQR)	14.4 (7.7, 26.4)
cT stage	cT1: 131(16.7%), cT2: 298 (38.0%), cT3a: 278 (35.4%), cT3b: 78 (9.9%)
Gleason Score	GS6: 39 (5.0%), GS7: 245 (31.2%), GS8: 187 (23.8%), GS9: 311 (39.6%), GS10: 3 (0.4%)
Positive core (%) Median (IQR)	40.0 (25.0, 58.3)
Duration of ADT (Months) Median (IQR)	25.0 (23.7, 27.9)
Dose of CIRT	66.0 Gy (RBE)/20 fractions: 91 (11.6%), 63.0 Gy (RBE)/20 fractions: 98 (12.5%), 57.6 Gy (RBE)/16 fractions: 301 (38.3%), 51.6 Gy (RBE)/12 fractions: 295 (37.6%)

ADT: androgen deprivation therapy, CIRT: carbon-ion radiotherapy, GS: Gleason score, PSA: prostate-specific antigen.

The Kaplan–Meier curves in Figure 1 show BCR-free survival according to each clinical variable evaluated. Age, PSA level, cT stage, biopsy GS, and %PC were significantly associated with BCR-free survival. The dose of CIRT was not identified as a significant predictor of BCR-free survival in the Kaplan–Meier analysis. The LASSO regression multivariate model was used to construct the nomograms shown in Figure 2a,b (5- and 7-year BCR-free survival rates, respectively). The LASSO coefficient solution path graphically represents how each variable's coefficient changed as the penalty term (lambda) was varied. Based on the LASSO coefficient solution path (Figure S1), age, PSA level, cT stage, and biopsy GS were input into the 5-year BCR-free survival nomogram. These same predictors plus %PC were input into the 7-year BCR-free survival nomogram. Points were assigned to each category and then summed to calculate the overall probability of each outcome. The points in each category were summed to calculate the overall probability of each outcome, as described previously [28].

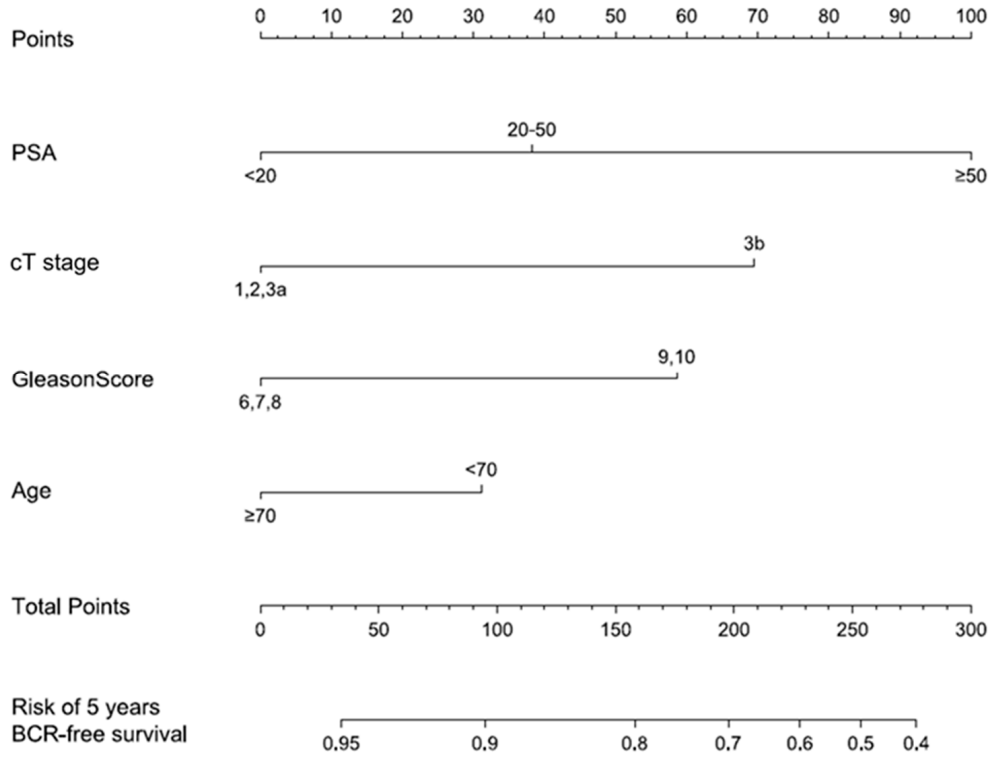


(**a**) Age (**b**) PSA

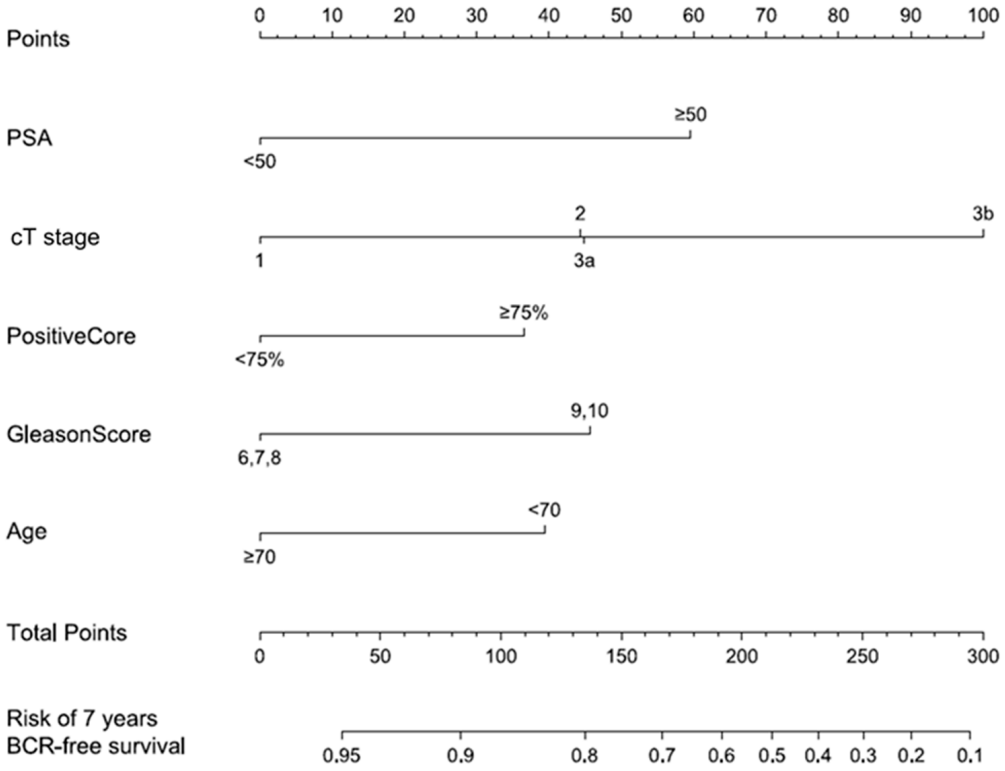
(**c**) cT stage (**d**) Gleason Score

(**e**) %PC

Figure 1. Kaplan–Meier curves for BCR-free survival according to each clinical variable. BCR: biochemical recurrence, PSA: prostate-specific antigen, %PC: percentage of biopsy positive cores.



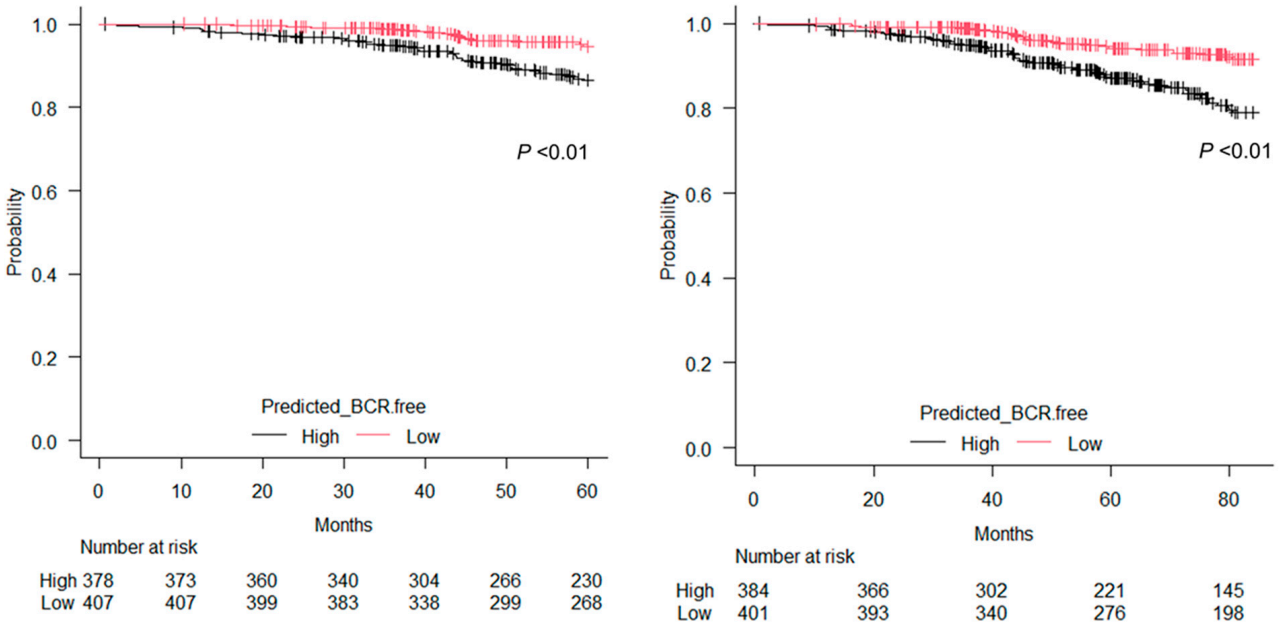
(**a**) 5-year BCR-free survival



(**b**) 7-year BCR-free survival

Figure 2. Nomograms predicting BCR-free survival after CIRT with ADT. Directions: A line was drawn upwards to the number of points in each category. The points were summed, and then a line of total points was drawn downwards to determine the probability on the bottom line. ADT: androgen deprivation therapy, BCR: biochemical recurrence, CIRT: carbon-ion radiotherapy, PSA: prostate-specific antigen.

To determine the predictive accuracy of the nomograms, training, validation, and entire datasets were used. Based on the training, validation, and entire datasets, the AUC values for the 5-year BCR-free survival rate were 0.71, 0.60, and 0.66, respectively, and those for the 7-year BCR-free survival rate were 0.73, 0.62, and 0.68, respectively. The AUC values indicated suboptimal-to-good performance. The median likelihoods of achieving BCR-free survival at 5 and 7 years were 0.93 and 0.90, respectively. The entire dataset was divided into two distinct categories: patients exhibiting a high probability of BCR-free survival, and patients with a low probability, based on the aforementioned cut-off values. The 5- and 7-year BCR-free survival nomograms revealed significant differences, as indicated by the Kaplan–Meier curves (Figure 3). Each calibration plot was smoothed using the training, validation, and entire datasets with local regression non-parametric lines. According to the calibration plots, the nomograms slightly underestimated the actual probability in each dataset (Figure S2).



(**a**) 5-year BCR-free Nomogram (**b**) 7-year BCR-free Nomogram

Figure 3. Kaplan–Meier survival curves stratified by risk group, defined by calculated cut-off values. BCR: biochemical recurrence.

4. Discussion

Based on a systematic review and meta-analysis to compare the efficacies of RT and RP, Cheng et al. showed better overall survival after RP-based treatment and better BCR-free survival after external beam RT-based treatment. However, there was no significant difference in CSM between the two treatments [7]. The current guidelines do not provide clear recommendations regarding the selection criteria for high-risk PCa patients for RT or RP [6]. Previously, we showed that CIRT combined with long-term ADT for high-risk PCa patients showed relatively favorable outcomes compared with those after RT and RP in previous studies [14]. Also, compared with another study population [19], our high-risk PCa patients showed better BCR-free survival overall. However, a number of conventional high-risk PCa patients show poor outcomes after any definitive treatment, because high-risk PCa is thought to consist of a broad mix of diseases [13,14]. Although the NCCN and D'Amico risk classifications are very simple and easy to utilize in daily clinical practice, clinicians would like to identify high-risk PCa patients using a more precise predictive model. Therefore, several prognostic models for PCa were developed

and validated to evaluate certain endpoints, such as CSM and metastasis, using a very large database [29,30]. The Candiolo nomogram was overall more successful in predicting BCR in patients treated with RT combined with or without ADT compared with the D'Amico risk classification [21,22]. Although we previously showed that reclassification of high-risk PCa patients after CIRT and ADT using the Candiolo nomogram was better than that using the NCCN classification for predicting BCR [13], the Candiolo nomogram was originally developed based on very-low- to very-high-risk PCa patients treated with conventional RT, not CIRT. Therefore, in the present study, we aimed to more precisely re-evaluate high-risk prostate cancer patients identified by conventional classification systems and to develop a novel nomogram. Our developed nomogram was very useful in predicting BCR-free survival after CIRT combined with ADT to reduce ADT duration in high-risk PCa patients with a relatively low-risk of recurrence and to prescribe more intensive treatments for patients with a very high risk of recurrence.

Generally, predictive models incorporating more variables tend to have higher prediction accuracy. However, including too many unique variables can render a model impractical for routine clinical use. Although the factors included in our novel nomograms partially overlapped with those in previous reports (i.e., PSA level, cT stage, and biopsy GS) [5,6,21], our nomograms additionally incorporated age and %PC in addition to the variables included in simpler models. Our nomograms exhibited significant differences compared to other predictive models in the distribution of constituent predictors. As our nomograms are based on data obtained from high-risk PCa patients, highly aggressive predictors such as PSA level $\geq$ 50 ng/mL, cT3b, and biopsy GS $\geq$ 9 were assigned greater weights (Figure 2). Despite the efficacy of CIRT combined with ADT in controlling the majority of high-risk PCa patients, those with more severe and aggressive forms of the disease may be susceptible to BCR after CIRT and ADT.

The contributions of age, PSA level, cT stage, and biopsy GS differed between the 5-year and 7-year nomograms. This divergence stemmed from the LASSO regression model, which selects predictors and assigns variable weights based on their specific predictive power within the designated time frame. Although both nomograms share fundamental predictors, the statistical significance and weighting of each variable vary due to differences in underlying survival dynamics and the influence of time-dependent factors on BCR-free survival. For instance, age may exert a greater impact on long-term outcomes (7 years), as the cumulative effects of comorbidities and physiological aging become increasingly pronounced over time.

The AUC values derived from our nomograms indicated suboptimal-to-good performance. Furthermore, when using the cut-off value of each variable, utilization of the nomograms revealed significant differences in 5- and 7-year BCR-free survival rates, as shown by the Kaplan–Meier curves (Figure 3). The variables age and %PC may have contributed to the good discriminative performance of our nomograms for high-risk PCa patients. In our patient cohort, age, cT stage, biopsy GS, and %PC were all significantly associated with BCR-free survival (Figure 1). The dose fractionation of CIRT and the duration of ADT were not significantly associated with BCR-free survival.

While the impact of age on PCa outcomes remains controversial, some studies have demonstrated that advanced age may be correlated with better treatment outcomes in PCa patients who receive RT, including CIRT, with lower incidences of BCR, metastases, and CSM [13,31]. This suggests that older patients may have less aggressive PCa, such as variations in hormone levels at different ages and more comorbidities [13,31]. In the present study, we also found that our high-risk PCa patients over 70 years old also showed significantly better BCR-free survival compared with younger patients (Figure 1a). Although age was integrated into both nomograms to predict 5- and 7-year BCR-free survival, the

impact of advanced age on BCR-free events increased with prolonged observation periods (Figure 1a). Given that the number of healthy aged patients undergoing CIRT combined with ADT is increasing, BCR-free survival may improve further in the future. Because CIRT combined with ADT is as effective and safe in the elderly as it is in young patients with high-risk PCa [13,14], it may be the optimal treatment for high-risk PCa, especially in the elderly. %PC was selected as a variable in the 7-year BCR-free survival nomogram according to the LASSO coefficient solution path. The addition of %PC, along with the three routine risk factors, to the nomogram has the potential to enhance the overall accuracy of predictive models. %PC provides an estimation of the PCa volume [32]. Furthermore, %PC has been shown to be a valuable predictor of lymph node metastases in patients undergoing RP and extended pelvic lymph node dissection [33].

Our study has several limitations. First, this study was retrospectively analyzed using a database derived from prospective clinical trial data conducted at a single institution. Although the retrospective nature of the study might have affected the data quality, all data were uniformly reviewed and re-examined in this study. Second, the predictors utilized to create the two nomograms were slightly different between the Kaplan–Meier curves and LASSO regression multivariate model. To develop a better predictive model, LASSO selects a set of variables for which cross-validation will result in a smaller prediction error. Third, given that early recurrence after CIRT and ADT occurs rarely, the 5-year predictive model may have little practical value in clinical settings. Nonetheless, it proves valuable in identifying high-risk PCa patients susceptible to aggressive early recurrence. Fourth, the validity of the nomograms was not evaluated through external validation. To ensure their predictive accuracy, external validation should be conducted in diverse populations, irrespective of the satisfactory internal validation results. Given that the patients in this study were predominantly Japanese, external validation in other ethnic cohorts could enhance the generalizability of the nomograms. Moreover, external validation is necessary to compare the utility of our nomogram with other predictive models, such as the Candiolo nomogram. Lastly, the predictive factors evaluated in this study are conventional markers; however, future models integrating novel metabolic and inflammatory markers with substantial predictive potential may be developed. Metabolic factors significantly influence treatment outcomes in prostate cancer, potentially expanding the scope of risk assessment [34,35].

5. Conclusions

We developed the first nomograms that accurately predict BCR-free survival in high-risk PCa patients treated with CIRT combined with ADT. These nomograms allow for more detailed risk classification of high-risk PCa patients. Moreover, when clinicians perform CIRT combined with ADT in high-risk PCa patients, the present nomograms will enable precise understanding and explanation of BCR-free survival to patients.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app15020804/s1, Figure S1: LASSO coefficient solution paths to identify predictors. (a) Five-year BCR-free survival and (b) seven-year BCR-free survival.; Figure S2: Calibration plots of the nomograms using the training, validation, and entire datasets. (a) Five-year BCR-free survival and (b) seven-year BCR-free survival.

Author Contributions: Conceptualization, H.S. and H.I.; methodology, T.U.; software, T.U.; validation, M.W., K.K., A.O., M.N., S.A. and T.S.; formal analysis, T.U.; investigation, M.W.; resources, H.I.; data curation, M.W., K.K., A.O., M.N., S.A. and T.S.; writing—original draft preparation, T.U.; writing—review and editing, H.S. and H.I.; visualization, T.U.; supervision, T.I., K.A., H.T. and S.Y.; project administration, H.S. and H.I.; funding acquisition, H.S. and H.I. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study secured approval from the institutional review board at QST Hospital (approval no. N21-005).

Informed Consent Statement: The potential participants were given the opportunity to opt out of being enrolled.

Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

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Conflicts of Interest: Hiroyoshi Suzuki reports personal fees from Astellas, Janssen, AstraZeneca, Bayer, and Sanofi and scholarship donations from MSD, Janssen, Nippon Shinyaku, and Kissei.

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