

Research Article

Conditional biochemical recurrence-free survival after radical prostatectomy in patients with high-risk prostate cancer

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ABSTRACT

Background: Conditional survival is defined as the likelihood of subsequent survival given the precondition of having already survived a certain length of time. Most analyses of conditional survival in prostate cancer are not clinically applicable because they do not analyze outcomes conditioned on the durability of cure after treatment. We evaluated the conditional probability of biochemical recurrence (BCR)-free survival (C-BCRFS) after radical prostatectomy (RP) for prostate cancer according to the National Comprehensive Cancer Network risk classification and prognostic factors in patients who survived several years without BCR.

Methods: Between January 2009 and December 2018, 877 patients with complete clinicopathologic and follow-up data were included. Using the Kaplan–Meier estimation, the probabilities of C-BCRFS after RP were estimated in patients who did not experience BCR at 0–4 years. C-BCRFS was analyzed according to the National Comprehensive Cancer Network risk classification and compared using the log-rank test. Prognostic factors at each year without BCR were evaluated using multivariable Cox regression analysis.

Results: The median follow-up duration and patient age were 48 months and 67 years, respectively. As the BCR-free interval increased (baseline, 1, 2, 3, and 4 years after RP), the 5-year C-BCRFS rates improved marginally (74.8%, 83.2%, 89.1%, 93.6%, and 98.5%, respectively). However, the 5-year C-BCRFS rates in the high/very high-risk group rose from 54.0% at baseline to 67.6%, 80.3%, 88.6, and 97.8% after 1–4 years free of BCR, respectively. In patients with a BCR-free duration more than 1 year, only seminal vesicle invasion and pathological Gleason score were significant predictive factors of BCR thereafter.

Conclusion: In the high/very high-risk group, the C-BCRFS markedly improved as the interval without BCR increased. In patients who were BCR-free for several years, seminal vesicle invasion and pathological Gleason score were prognostic factors of continued BCRFS. This is useful not only for patient counseling but also to optimize postoperative follow-up strategies.

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1. Introduction

For patients who undergo radical prostatectomy (RP) for prostate cancer (PCa), there are multiple prediction tools to assess expected oncologic outcomes after treatment.^{1–4} However, there is a relative paucity of data to inform prognosis in patients who undergo RP and have had undetectable prostate-specific antigen (PSA)

for a certain duration. In other words, the conditional survival (CS) after RP based on the duration of freedom from biochemical recurrence (BCR) is unknown. CS is a survival probability estimate that depends on the precondition of having already survived for a certain length of time.^{5–14} CS analysis can lead to more accurate prognostic information compared with initial estimates⁸ and has the potential to impact surveillance and secondary treatment strategies after RP. Therefore, although the absolute number of men with potentially durable freedom from BCR after RP is quite large, they remain at risk for adverse oncologic outcomes. Being able to identify CS after RP may be quite useful for this large cohort, especially patients at high risk of recurrence.

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CS in patients with PCa has been previously assessed in studies using population-based cancer registry data.^{6,7,15} However, most of these analyses are not readily clinically applicable because they do not analyze outcomes conditioned on the durability of cure after treatment. In men who undergo RP, CS analysis using BCR instead of cancer-specific survival can be more realistic because BCR is a reliable surrogate to evaluate survival after RP. To our knowledge, only two studies have reported the conditional estimation of BCR-free survival (C-BCRFS) after RP using BCR as a conditional event.^{16,17} One study reported that the time from RP is associated with recurrence-free survival.¹⁶ The risk of BCR decreases with increasing survivorship, mainly in patients with adverse pathologic factors.¹⁶ The other study integrated the time elapsed from surgery into a nomogram for survival rate thereafter.¹⁷ They concluded that CS can provide patients an updated risk of subsequent recurrence or survival.¹⁷

In this study, we evaluated the 5-year C-BCRFS in patients without BCR up to 4 years after RP using Kaplan–Meier estimation. These C-BCRFS rates were stratified according to the National Comprehensive Cancer Network (NCCN) risk classification¹⁸ to inform more precise prognoses. In addition, we examined important prognostic factors for men with each elapsed interval without BCR.

2. Materials and methods

We evaluated 1,016 patients with PCa treated with RP at our institution from January 2009 to December 2018 who had complete clinical follow-up data. We excluded patients with pathological lymph node metastasis ($n = 23$), persistently high PSA (>0.2 ng/mL) after RP ($n = 39$), and neoadjuvant or adjuvant therapy ($n = 77$). All evaluated patients gave their informed consent to be included in our institutional review board–approved RP database. The final study cohort included 877 men with clinically localized PCa.

All surgical specimens were processed according to standard pathologic procedures using 3-mm whole-mount sections. Tumor grade was assigned according to the 2005 International Society of Urologic Pathology Gleason grading system.¹⁹ Pathological staging was assessed using the 7th American Joint Committee on Cancer TNM staging system.²⁰ Pelvic lymph node dissection was performed if the estimated risk of lymph node metastasis exceeded 8% based on Partin tables. After surgery, we checked PSA every 3 or 6 months for 5 years and then every year. BCR was defined as a single postoperative PSA reading of 0.2 ng/mL or higher.²¹

C-BCRFS was defined in the present study as the probability that a patient will survive BCR free, given that the patient has already survived BCR free for a certain number of years.²² The CS was estimated using multiplicative law of probability.⁸ The 5-year C-BCRFS represents the probability of surviving additional 5 years, given that the person has already survived x years ($x =$ time elapsed since surgery).¹⁶ For example, for a patient who is alive after a 3-year follow-up, the 5-year C-BCRFS rate is calculated by using the 8-year survival rate divided by the 3-year survival rate.¹⁶ All survival analyses were based on the Kaplan–Meier method. Each C-BCRFS was calculated up to 4 years after RP by excluding men who experienced recurrence or who were lost to follow-up. The probabilities of 5-year C-BCRFS were analyzed according to the NCCN classification (low/very low, intermediate, and high/very high)¹⁸ and compared using the log-rank test. Survival data were censored at the last follow-up or the date of death from any cause in the absence of BCR. In addition, prognostic factors of BCRFS in each cohort after surviving a certain number of years free from BCR were evaluated using multivariable Cox regression analysis. All statistical analysis was performed using SPSS, version 26.0 (SPSS Corp;

College Station, TX, USA), with a p value less than 0.05 considered significant.

3. Results

Clinicopathologic characteristics and follow-up results of the study cohort are shown in Table 1. There were 245 (27.9%), 343 (39.1%), and 289 (33.0%) patients in the NCCN low/very low-, intermediate-, and high/very high-risk groups, respectively. The median age was 67 years (IQR 62–72 years). Extracapsular extension and seminal vesicle invasion were diagnosed in 273 (31.1%) and 103 (11.7%) patients, respectively. Pelvic lymph node dissection with negative pathological diagnosis was performed in 263 (30.0%) patients. Two hundred and ten patients (23.9%) had positive surgical margins. During a mean follow-up of 48 months (range 12–129 months), 158 patients (18.0%) experienced BCR. Ten (1.1%) and 13 (1.5%) patients experienced metastasis and local recurrence, respectively. Four (0.5%) and 20 (2.3%) patients died of PCa and any cause, respectively.

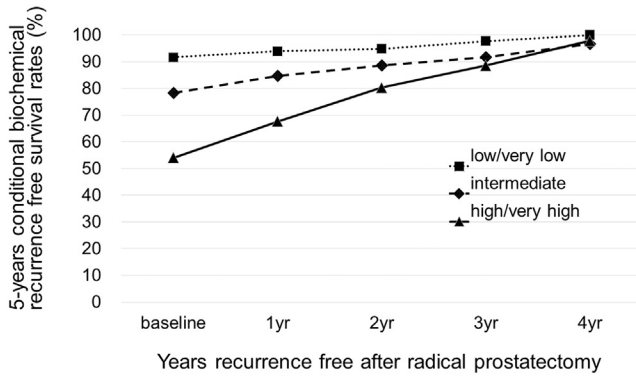
Fig. 1 shows the 5-year C-BCRFS rates depending on the duration of the BCR-free interval after RP stratified by the NCCN risk group. The C-BCRFS increased as the BCR-free interval after RP increased; however, the 5-year C-BCRFS curves among the different NCCN risk groups overlapped at 4 years after RP. As the BCR-free interval increased (baseline, 1, 2, 3, and 4 years after RP), the 5-year C-BCRFS rates in the entire cohort improved marginally (74.8%, 83.2%, 89.1%, 93.6%, and 98.5%, respectively). However, the improvement in 5-year C-BCRFS rates with increasing BCR-free interval was more pronounced in the high/very high-risk group (54.0%, 67.6%, 80.3%, 88.6%, and 97.8%, respectively). After 3 years of BCR-free follow-up, there was no significant difference in C-BCRFS between the intermediate- and high/very high-risk groups ($p = 0.296$, log-rank test). In addition, there was no significant difference in C-BCRFS among all the NCCN risk groups after 4 years of BCR-free follow-up ($p = 0.127$, log-rank test).

Fig. 2 shows the Kaplan–Meier curves for C-BCRFS according to the duration of survivorship stratified by the following prognostic

Table 1
Clinical and pathological characteristics.

Variable/Value	N = 877
Age, years, median (IQR)	67 (62, 72)
Surgery type, No	
Open	179 (20.4)
Laparoscopic	212 (24.2)
Robotic	486 (55.4)
Preoperative PSA, ng/ml, median (IQR)	7.8 (5.3, 12.0)
PSA, No (%)	
<10	583 (66.5)
10–20	205 (23.4)
≥20	89 (10.1)
Prostate volume, ml, median (IQR)	32.9 (25.9, 43.3)
NCCN risk, No (%)	
Low/very low	245 (27.9)
Intermediate	343 (39.1)
High/very high	289 (33.0)
Pathological Gleason grade, No (%)	
6	220 (25.1)
7	510 (58.2)
8–10	147 (16.8)
Positive surgical margin, No (%)	210 (23.9)
Organ confined disease, No (%)	587 (66.9)
Extracapsular extension, No (%)	273 (31.1)
Seminal vesicle invasion, No (%)	103 (11.7)
Pelvic lymph node dissection, No (%)	263 (30.0)
Tumor volume, %, median (IQR)	13 (6, 22)

IQR, interquartile range; PSA, prostate-specific antigen.



No. of yr from surgery	baseline	1yr	2yr	3yr	4yr
overall	74.8	83.2	89.1	93.6	98.5
low/very low	91.7	93.9	94.9	97.7	100
intermediate	78.4	84.7	88.7	91.7	96.7
high/very high	54.0	67.6	80.3	88.6	97.8

No. of yr from surgery	baseline	1yr	2yr	3yr	4yr
overall	877	616	478	340	238
low/very low	245	201	184	148	111
intermediate	343	233	164	110	75
high/very high	289	182	130	82	52

Fig. 1. The 5-year conditional biochemical recurrence-free survival depending on duration of biochemical recurrence-free interval after radical prostatectomy, stratified by NCCN risk group. As duration of biochemical recurrence-free interval increased (1, 2, 3, and 4 year after radical prostatectomy), 5-year conditional biochemical recurrence-free survival rates improved: 74.8%, 83.2%, 89.1%, 93.6%, and 98.5%, respectively.

parameters: NCCN risk group, Gleason score, pathological T stage, and PSA level. C-BCRFS improved mainly for patients without BCR with adverse pathologic factors. For example, among patients with high/very high risk, the 5-year C-BCRFS increased from 54.0% at baseline to 88.6% (+34.6%) for patients surviving 3 years without BCR. The corresponding improvements in C-BCRFS were +13.3% and +6.0% in the intermediate- and low/very low-risk groups, respectively. Similar findings were observed for pathological T stage, Gleason score, and PSA level.

Table 2 shows predictive factors of BCRFS according to time elapsed from RP using proportional hazard ratios in multivariable Cox regression analysis. The predictive factors of BCRFS after RP at baseline were PSA level, extracapsular extension, seminal vesicle invasion, pathological Gleason score, and surgical margin status.

Table 2
Proportional hazard ratios in multivariable Cox regression analysis for prediction of biochemical recurrence-free survival after radical prostatectomy.

	Baseline		1-year		2-year		3-year		4-year	
	HR	P value	HR	P value	HR	P value	HR	P value	HR	P value
Prostate-specific antigen, ng/ml										
<10	Reference		Reference		Reference		Reference		Reference	
10-20	1.450	0.049	1.744	0.028	1.270	0.501	0.933	0.893	0.454	0.400
≥20	1.744	0.018	1.376	0.374	1.069	0.897	0.988	0.987	-	0.986
Extracapsular extension, yes										
1.463	0.048		1.201	0.501	1.195	0.634	1.300	0.631	1.385	0.771
Seminal vesicle invasion, yes										
1.755	0.007		2.094	0.012	2.357	0.036	3.758	0.012	7.254	0.041
Pathological Gleason score										
6	Reference		Reference		Reference		Reference		Reference	
7	2.936	<0.001	2.754	0.005	3.670	0.005	3.375	0.047	17.846	0.029
8-10	5.106	<0.001	5.508	<0.001	4.672	0.008	6.857	0.007	27.338	0.024
Positive surgical margin, yes										
1.574	0.010		1.400	0.182	1.448	0.284	0.743	0.573	0.349	0.342

HR; hazard ratio.

However, only seminal vesicle invasion and pathological Gleason score were important predictive factors of BCRFS in patients who were BCR free for more than 1 year. Interestingly, Gleason score became the most important predictive factor of BCRFS over time.

4. Discussion

Patients who have experienced durable survival after diagnosis and treatment of various malignancies may have favorable prognoses.^{5,8,9,23-26} CS estimates survival probabilities that depend on criteria such as prior survival. The first CS report in PCa showed that the median survival increased from 24 months at baseline to 34 months after 5 years of cancer-specific survival.⁶ A study using data from the United States Surveillance, Epidemiology, and End Results database showed that CS in localized PCa did not vary by clinical stage, although CS for men with metastatic PCa increased significantly with time (33% to 56% over 5 years).⁷ Multiple population-based studies have had similar results, with CS not changing appreciably by clinical stage for localized PCa but increasing markedly for men with metastatic PCa (17% to 54% over 5 years in Australia and 39% to 49% over 5 years in Japan).^{11,12} Because PCa has a diverse prognosis depending on the disease status, each study has reported various results. However, it appears that CS is not very useful in early-stage PCa, which has low mortality, but has a clear benefit in aggressive malignancies such as late-stage PCa.

Our results showed a definite increase in C-BCRFS among men with localized PCa, particularly in the high/very high-risk group. The 5-year C-BCRFS rates in the entire cohort after RP increased to 83.2% (+8.4%), 89.1% (+14.3%), 93.6% (18.8%), and 98.5% (+23.7%) for men without BCR 1, 2, 3, and 4 years after RP, respectively. The 5-year C-BCRFS rates in the high/very high-risk group increased from 54.0% to 97.8% (43.8%) over 4 years of freedom from BCR. It is consistent with those of two previous similar studies using BCR as a conditional event after RP.^{16,17} Ploussard et al.¹⁶ reported that the 5-year C-BCRFS rate in the entire cohort after RP increased to 77.4% (+8.7%), 82.1% (+15.3%), 88.0% (+23.6%), and 94.0% (+32.0%) in patients surviving without recurrence for 1, 2, 3, and 4 years after RP, respectively.

They also found that the risk of BCR decreases with increasing survivorship, mainly in patients with adverse pathologic factors, such as high Gleason scores (8-10), pT3b-4 disease, high PSA level, and positive surgical margin.¹⁶ They also assessed the impact of parameters on CS over time by multivariable Cox regression analysis. Gleason score 8-10 and pT3b-4 stage PCa were shown to have a

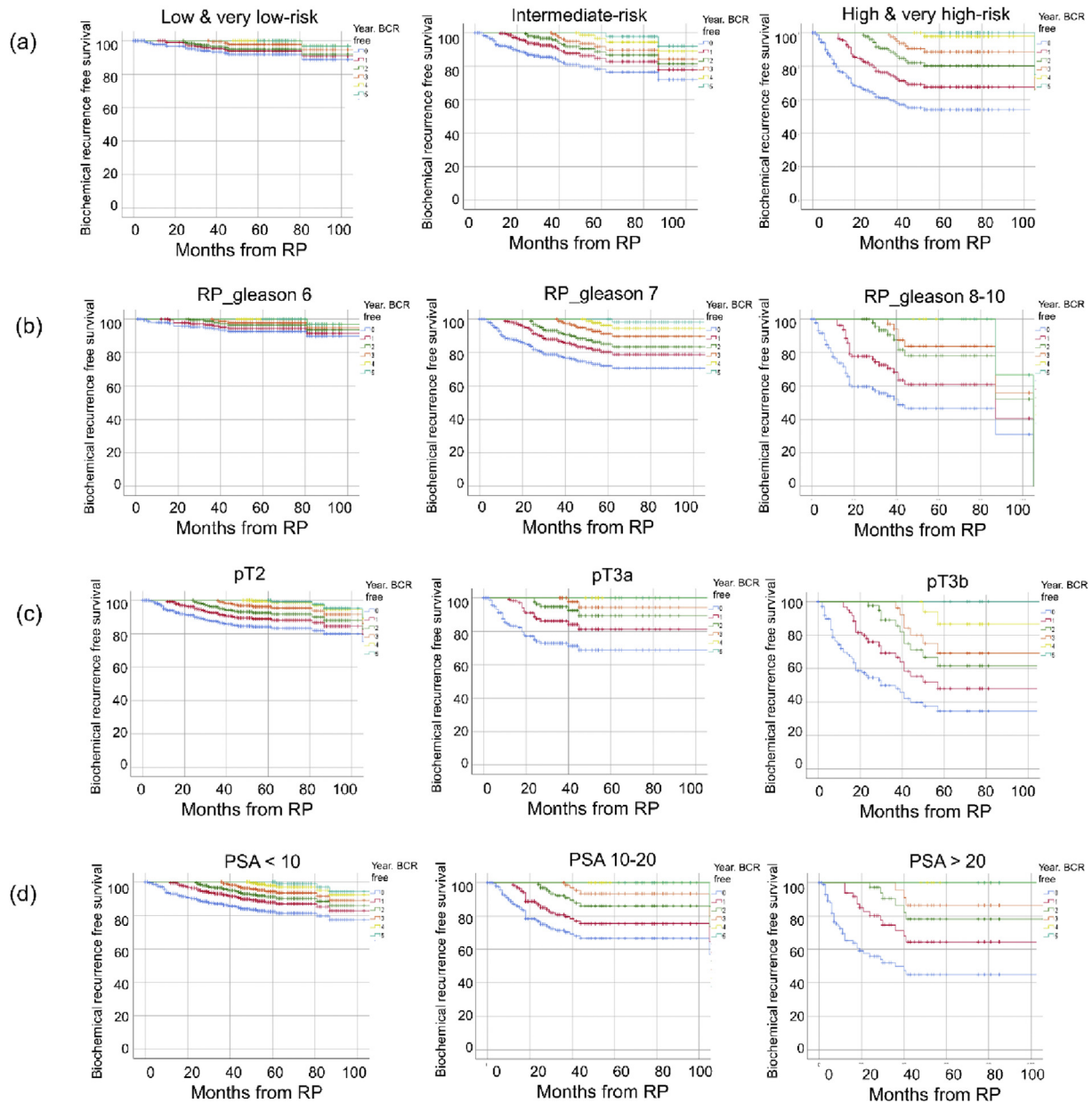


Fig. 2. The 5-year conditional biochemical recurrence-free survival improves mainly for biochemical recurrence-free surviving patients with adverse pathologic factors. Kaplan–Meier curves for biochemical recurrence-free survival according to duration of survivorship were then stratified by prognostic parameters: (a) NCCN risk group, (b) Gleason score, (c) pathological T stage, and (d) prostate-specific antigen level. RP, radical prostatectomy; BCR, biochemical recurrence; NCCN, National Comprehensive Cancer Network.

stable impact on CS over time.¹⁶ Conversely, the effect of high PSA level and positive surgical margin on CS rates decreased over time (PSA >20 ng/mL: hazard ratio, 1.79 to 1.43; positive surgical margin status: hazard ratio 1.89 to 1.48).¹⁶ In the present study, the impacts of Gleason score (8–10) and pT3b stage on CS estimates increased over time. However, the impacts of high PSA levels and positive margins disappeared in CS estimates longer than 1 year without BCR.

Our results and others indicate that a longer BCR-free interval is a significant positive prognostic factor after curative radical treatment for localized PCa. This may help guide surveillance and follow-up strategies for PCa survivors, e.g., less frequent follow-up examinations and PSA checks over time. In our study cohort, most patients who relapsed experienced BCR within the first few years, and C-BCRFS among high/very high-risk patients increased

markedly from 54.0% at RP to 88.6% after 3 years of freedom from BCR. The BCRFS rate at RP in the low/very low-risk group was 91.7%; therefore, if patients in the high/very high-risk group survived without BCR for 3 years, they would have a BCRFS rate similar to that of the low/very low-risk group at RP.

The results of this study are limited by several factors. First, there may have been a surgical selection bias, as the cohort was composed of men who underwent RP at a single tertiary referral center. Not every patient underwent RP by the same modality (open versus laparoscopic versus robotic), and there were multiple treating surgeons. Second, the study design is retrospective. Adjuvant treatments were usually administered to patients in the high/very high-risk group. However, these patients were excluded from the present study. Fifty-two patients in the high/very high-risk group underwent neoadjuvant or adjuvant therapy compared

with 289 who did not. If patients undergoing therapy had been included in this analysis, the gap in C-BCRFS rates in this risk group may have been bigger than what we observed in the present analysis.

To summarize, C-BCRFS increases significantly among patients with high/very high risk after RP as the BCR-free interval increases. CS after RP may be quite useful in patients with a high risk of recurrence to guide prognosis after RP, alter the frequency of follow-up examinations and PSA tests, and shift the balance of secondary treatment toward observation in men who have increasing BCR-free intervals after their initial treatment. In addition, Gleason score and presence of seminal vesicle invasion become more important prognostic factors over time. Conversely, preoperative PSA and margin status are important prognostic factors only immediately after RP.

Ethics statement

This retrospective, single-center study was approved by the Pusan National University Yangsan Hospital Institutional Review Board (05-2016-007). As all data were analyzed retrospectively after deidentification, the requirements for review and informed consent were waived.

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Conflicts of interest

None of the contributing authors have any conflicts of interest, including specific financial interests, relationships, or affiliations relevant to the subject matter or materials discussed in the manuscript.

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