



# Prediction of biochemical failure using prostate-specific antigen half-life in patients with adverse pathologic features after radical prostatectomy

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## Abstract

**Purpose** Prostate-specific antigen nadir and time to prostate-specific antigen nadir are predictors of disease progression in patients who undergo radical prostatectomy. However, a mutually conflicting relationship exists between them. Thus, we compared postoperative prostate-specific antigen levels at the first follow-up with the expected levels while considering the half-life of prostate-specific antigen to improve the prediction of biochemical failure after radical prostatectomy in patients with adverse pathologic features.

**Methods** Patients treated with robot-assisted laparoscopic prostatectomy were enrolled. Patients with a follow-up duration of < 12 months or positive lymphadenectomy results were excluded. “Adverse prostate-specific antigen” was defined as a prostate-specific antigen level higher than the expected level at 6 weeks.

**Results** Among 450 patients, adverse pathologic features and adverse prostate-specific antigen were found in 260 (57.8%) and 245 (54.5%) patients, respectively. Analysis of patients with and without abnormal prostate-specific antigen level revealed significantly different biochemical failure-free survival outcomes. Patients with one adverse pathologic feature but without adverse prostate-specific antigen showed similar biochemical failure-free survival to those without adverse pathologic features. Adverse prostate-specific antigen was identified as an independent predictor for biochemical failure within 1 year after radical prostatectomy. The area under the curve when adding adverse prostate-specific antigen to the conventional factors was significantly higher than that for the conventional factors alone.

**Conclusion** The difference between postoperative prostate-specific antigen levels at the first follow-up visit after radical prostatectomy and the expected level while considering the half-life of prostate-specific antigen is a predictive factor for treatment efficacy following radical prostatectomy.

**Keywords** Patient outcome assessment · Prostate · Prostate cancer · Prostatectomy

## Introduction

Radical prostatectomy (RP) is the most widely chosen treatment option for localized prostate cancer [1, 2]. As approximately 30% of patients undergoing RP experience biochemical recurrence, postoperative radiotherapy should be offered in men with adverse pathologic features or detectable prostate-specific antigen (PSA) and no evidence of disseminated

disease [3]. Adjuvant radiotherapy (ART) is expected to yield better oncological outcomes for patients with adverse pathologic features [4–6]. Within 1 year after RP, improvement and stabilization of operative side effects such as incontinence and sexual dysfunction leads to the increased use of salvage radiotherapy (SRT) at the time of biochemical recurrence [5–8]. Moreover, recent clinical practice has demonstrated a declining trend in postoperative radiotherapy use within 6 months after surgery [9]. Although this clinical pattern could be related to multiple factors, including patient referral, physician and referral bias, concerns about toxicity, and lack of survival benefits in updated randomized trials [9], precise criteria should be provided to predict biochemical failure (BCF) in addition to the number of adverse pathologic features.

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Currently, PSA is used as the only indicator for monitoring BCF in patients undergoing RP. Theoretically, PSA, which has a half-life of 2–3 days, should decline to undetectable levels after RP except in patients with systemic micro-metastasis or residual prostate tissue (even benign) or in cases of incomplete RP [10–13]. Several studies have identified PSA nadir and time to PSA nadir as predictors of disease progression in patients who undergo RP [14, 15]. However, a mutually conflicting relationship exists between PSA nadir and time to PSA nadir. To overcome this limitation, we developed a novel parameter, adverse PSA, which compares the postoperative PSA level at the first follow-up visit with the expected level while considering PSA half-life. In this study, we aimed to evaluate the efficacy of adverse PSA for predicting BCF in patients with adverse pathologic features after RP.

## Materials and methods

### Study population and data collection

Institutional review board approval was obtained to retrospectively collect data on all patients treated with robot-assisted laparoscopic prostatectomy (RALP) at our institution. We reviewed 538 consecutive patients who underwent RALP procedures between May 2007 and March 2016. Of these patients, 88 with a follow-up duration of < 12 months, neoadjuvant androgen deprivation therapy, or positive lymphadenectomy results were excluded from the analysis, leaving 450 patients in the final analysis.

### Assessments of clinicopathological variables

Clinical variables relevant to the study included age, body mass index, Charlson comorbidity index, follow-up duration, preoperative PSA level, clinical stage, biopsy Gleason score, and pathologic results. Magnetic resonance imaging and whole-body bone scanning were routinely performed before RALP for all patients. The images were interpreted by radiological specialists in the urology department at our hospital. The final pathological diagnosis was determined using RP specimens by pathology specialists.

For preoperative risk analysis, the patients were categorized into low (PSA < 10 ng/mL, biopsy Gleason score ≤ 6, clinical stage < T2a), high (PSA > 20 ng/mL, biopsy Gleason score ≥ 8, clinical stage ≥ T3a), and intermediate (patients who did not meet the criteria for the high- or low-risk groups) risk groups. Adverse pathologic features were defined as pT3 disease, positive surgical margin (PSM), Gleason score 8–10, and seminal vesical invasion (SVI). BCF was defined as (1) a confirmed increase in the PSA level to more than the threshold of 0.2 ng/mL, (2) failure

of the PSA level to decrease to undetectable levels, or (3) the need for additional therapy, including radiotherapy, androgen deprivation therapy, or both for consecutive PSA increases despite not reaching the threshold of 0.2 ng/mL.

### Assessments of PSA level at 6 weeks

The patients were followed-up with PSA tests at 6 weeks, every 3 months for 3–5 years after surgery, and semiannually thereafter. The PSA levels of all patients were detected using an ultrasensitive photometric method with a Cobas C601 analyzer (Roche Diagnostics, Risch-Rotkreuz, Switzerland). PSA levels < 0.01 ng/mL were considered undetectable. Therefore, this study defined detectable PSA as a PSA level ≥ 0.01 ng/mL.

Adverse PSA was defined as a detectable PSA level at the initial follow-up visit after RP that was higher than the expected level. Patients with undetectable PSA were categorized as “without adverse PSA”. Considering a PSA half-life of 2.7 days, expected PSA was calculated using the following formula: (expected PSA) = (preoperative PSA) ×  $\left(\frac{1}{2}\right)^{\left(\frac{t}{2.7}\right)}$ , where  $t$  is time in days [13].

The time between the operative date and the first follow-up date after RALP was calculated.

### Statistical analysis

Continuous variables are expressed as the median (interquartile range). Categorical variables are reported as the number and frequency. Student’s  $t$  test and Pearson’s Chi-square test were used for statistical comparisons of continuous and categorical variables, respectively. Simple and multiple logistic regressions with forward selection were used. Survival curves were established using the Kaplan–Meier method and compared with the log-rank test. Prognostic factors were established using univariate analysis and those that were significant were entered into the multivariate analysis using the Cox stepwise regression method. Pairwise comparisons of receiver operating characteristic (ROC) curves were used to compare predictive performance. All statistical comparisons were conducted using IBM SPSS Statistics v. 23 (IBM Corporation, Armonk, NY, USA) and MedCalc v. 11.6 (MedCalc Software, Ostend, Belgium). A  $p$  value < 0.05 was considered statistically significant.

## Results

### Patient characteristics

Table 1 summarizes the clinicopathological characteristics of the study patients. Adverse pathologic features and adverse PSA were found in 260 (57.8%) and 245 (54.5%) patients, respectively. Of the 190 patients without adverse pathologic features, 91 (47.9%) had adverse PSA. Patients without adverse pathologic features had significantly lower PSA level, preoperative risk category, pathologic Gleason score, pathological T stage category, extracapsular extension, SVI, tumor volume, perineural invasion (PNI), and lymphovascular invasion (LVI) than those with adverse pathologic features. In our cohort, the time to initial assessment of PSA was 43 (30–51) days.

The patients with adverse pathologic features were further divided into two groups according to the presence of adverse PSA. Of the 260 patients with adverse pathologic features, 154 (59.3%) patients also had adverse PSA. The group with adverse PSA had a significantly higher risk category, pathologic Gleason score, SVI, and tumor volume.

No significant differences existed between the groups with respect to PSM and pathologic T stage.

### Adverse PSA in relation to the risk of BCF

The biochemical failure-free survival (BCFFS) outcomes of patients with and without adverse pathologic features stratified by adverse PSA are shown in Fig. 1. Patients with adverse pathologic features showed significantly lower BCFFS rates than those without adverse pathologic features (log-rank  $p=0.001$ ).

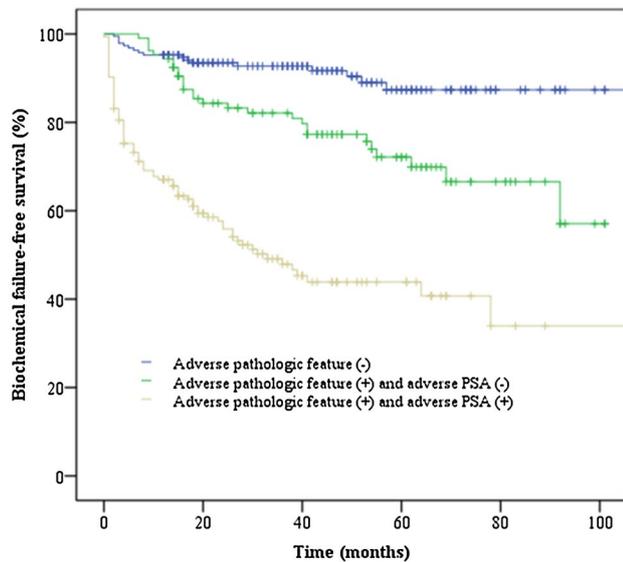
At a median follow-up of 47.0 (interquartile range, 26.8–67.0) months, patients with adverse pathologic features but without adverse PSA had significantly lower 5-year BCFFS rates than those without adverse pathologic features (66.4% vs. 87.2%;  $p<0.001$ ). However, patients with concomitant adverse pathologic features and adverse PSA showed significantly lower rates than both patients without adverse pathologic features (39.5% vs. 87.2%;  $p<0.001$ ) and patients with adverse pathologic features but without adverse PSA (39.5% vs. 66.4%;  $p<0.001$ ) (Table 2).

**Table 1** Clinicopathological characteristics of prostate cancer patients treated with radical prostatectomy, stratified by the presence of adverse pathologic features and adverse PSA among patients with adverse pathologic features

	Adverse pathologic feature (-)	Adverse pathologic feature (+)		<i>p</i> value	
		Adverse PSA (-)	<i>p</i> value		Adverse PSA (+)
Patients ( <i>n</i> )	190 (42.2)	106 (23.6)		154 (34.2)	
Age (years)	65.3 (60.2–69.0)	66.4 (60.5–69.7)	0.050	64.1 (59.2–68.5)	0.383
CCI ( $\geq 3$ )	1 (0.5)	2 (1.8)	0.823	1 (0.6)	0.623
BMI	24.0 (22.4–25.4)	24.0 (23.0–26.0)	0.437	24.0 (22.4–25.6)	0.418
PSA (ng/mL)	5.94 (4.59–8.73)	6.69 (5.25–9.67)	<0.001	9.71 (6.68–21.09)	<0.001
Risk category			<0.001		<0.001
Low	69 (36.3)	20 (18.9)		14 (9.1)	
Intermediate	103 (54.2)	63 (59.4)		66 (42.9)	
High	18 (9.5)	23 (21.7)		74 (48.1)	
Pathologic Gleason score			0.005		<0.001
$\leq 7$	190 (100.0)	89 (84.0)		107 (69.5)	
$\geq 8$	0 (0.0)	17 (16.0)		47 (30.5)	
Pathologic stage			0.850		<0.001
$\leq T2$	190 (100.0)	21 (19.8)		32 (20.8)	
T3	0 (0.0)	85 (80.2)		122 (79.2)	
Extracapsular extension	0 (0.0)	77 (72.6)	0.063	95 (61.7)	<0.001
Seminal vesicle invasion	0 (0.0)	8 (7.5)	0.013	27 (17.5)	<0.001
Positive surgical margins	0 (0.0)	42 (39.6)	0.180	74 (48.1)	<0.001
Tumor volume (cc)	1.0 (0.5–1.7)	2.4 (1.2–3.2)	0.009	2.5 (1.2–4.6)	<0.001
PNI	72 (37.9)	74 (69.8)	0.058	122 (79.2)	<0.001
LVI	5 (2.6)	10 (9.4)	0.321	20 (13.0)	<0.001

Data are presented as the mean (SD) or number (%)

BMI body mass index, CCI Charlson comorbidity index, LVI lymphovascular invasion, PNI perineural invasion, PSA prostate-specific antigen



**Fig. 1** Kaplan–Meier curves of biochemical failure-free survival in patients with and without adverse pathologic features stratified by adverse prostate-specific antigen (PSA)

### Univariate and multivariate analyses of predictors for BCFFS

The results of Cox proportional hazards regression analyses of the predictors for BCF are presented in Table 3. In the multivariate analysis, preoperative PSA, pathologic Gleason score ( $\geq 8$ ), pathologic stage ( $\geq T3$ ), SVI, PSM, LVI, and adverse PSA remained as independent predictors of BCF.

### Adverse PSA in relation to the number of adverse pathologic features for the prediction of BCF

The BCFFS outcomes according to the number of adverse pathologic features stratified by the presence of adverse PSA are presented in Fig. 2. The analysis according to the number of adverse pathologic features showed no significant difference in BCFFS between patients with one adverse pathologic feature and without adverse PSA and those with no adverse pathologic features but with adverse PSA (log-rank  $p = 0.288$ ). The BCFFS rate was similar

between the subgroups of patients with one adverse pathologic feature and with adverse PSA and patients with two adverse pathologic features but without adverse PSA (log-rank  $p = 0.808$ ).

### Efficacy of adverse PSA to identify patients with BCF within 1 year

In sub-analysis to identify parameters to precisely predict patients who required additional treatments after RP, univariate and multivariate logistic regression analyses were performed to identify the factors predicting BCF within 1 year after RP. Notably, preoperative PSA (odds ratio (OR) = 1.08 [95% confidence interval 1.037–1.117],  $p < 0.001$ ), pathologic stage ( $\geq T3$ ) (OR = 2.54 [1.031–6.271],  $p = 0.043$ ), PNI (OR = 8.93 [1.71–46.703],  $p = 0.010$ ), LVI (OR = 3.37 [1.269–8.925],  $p = 0.014$ ), and adverse PSA (OR = 3.37 [1.269–8.925],  $p = 0.015$ ) were identified as independent predictors of BCF within 1 year after RP in multivariate analysis, whereas PSM (OR = 1.79 [0.834–3.846],  $p = 0.135$ ) and pathologic Gleason score ( $\geq 8$ ) (OR = 1.15 [0.461–2.847],  $p = 0.769$ ) were not identified as predictors of BCF. There was no harmful collinearity among these variables confirmed by coefficients of variance inflation factors of  $< 3.8$ .

For predicting the development of BCF within 1 year after RP in the entire cohort, the sensitivity, specificity, positive predictive value, and negative predictive value of adverse PSA were 90.6%, 51.6%, 23.7%, and 97.1%, respectively. The results of ROC curve analysis for BCF within 1 year after RP in patients with adverse pathologic features are shown in Fig. 3. The area under the curve (AUC) of the conventionally used perioperative factors was 0.800 (95% confidence interval 0.727–0.874). The AUC when adding adverse PSA to the conventional factors was 0.834 (0.740–0.814), which was significantly higher than that of the conventional factors alone ( $p = 0.0048$ ). We found significant differences in 1-year BCFFS according to the number of adverse pathologic features (0 vs. 1 vs. 2 vs. 3 vs. 4: 93.4% vs. 85.6% vs. 55.6% vs. 35.0% vs. 0.0%; log-rank  $p < 0.001$ ).

**Table 2** Biochemical failure outcomes of prostate cancer patients treated with radical prostatectomy, stratified by adverse pathologic features and adverse PSA among patients with adverse pathologic features

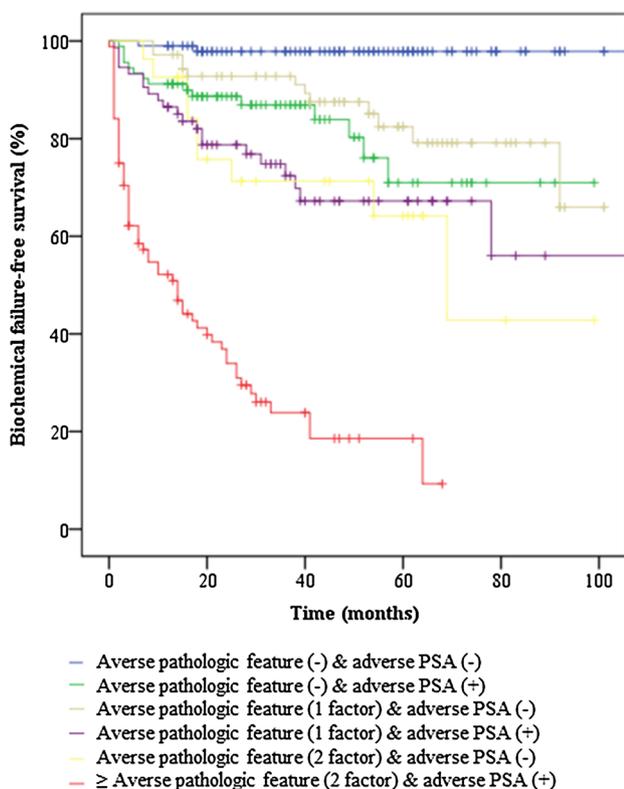
	Adverse pathologic features (–)	Adverse pathologic features (+)		<i>p</i> value
		Adverse PSA (–)	Adverse PSA (+)	
BCF	17 (8.9)	28 (28.4)	77 (50.0)	<0.001
Time to BCF	28.0 (13.5–34.5)	18.0 (14.0–41.0)	6.0 (2.0–18.5)	<0.001
5-year BCFFS	87.20%	66.40%	39.50%	<0.001
Follow-up	41.0 (22.0–61.0)	57.5 (40.0–71.8)	45.0 (28.0–69.0)	0.053

BCF biochemical failure, BCFFS biochemical failure-free survival, PSA prostate-specific antigen

**Table 3** Association of various clinicopathological factors with biochemical failure in patients treated with radical prostatectomy

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	<i>p</i> value	Hazard ratio (95% CI)	<i>p</i> value
Age	1.00 (0.972–1.026)	0.919		
CCI ( $\geq 3$ )	1.05 (0.835–1.314)	0.689		
BMI	0.99 (0.917–1.073)	0.839		
PSA	1.06 (1.046–1.069)	<0.001	1.03 (1.014–1.054)	0.001
Prostate volume	1.00 (0.978–1.007)	0.312		
Pathologic Gleason score ( $\geq 8$ )	4.20 (2.838–6.214)	<0.001	2.03 (1.234–3.340)	0.005
Pathologic stage ( $\geq T3$ )	4.30 (2.844–6.488)	<0.001	2.35 (1.371–4.031)	0.002
Extracapsular extension	1.83 (1.282–2.609)	0.001		
Seminal vesicle invasion	6.28 (4.11–9.572)	<0.001	2.58 (1.477–4.515)	0.001
Tumor volume	1.22 (1.165–1.267)	<0.001	1.02 (0.947–1.093)	0.642
Positive surgical margins	4.51 (3.099–6.561)	<0.001	2.61 (1.668–4.082)	<0.001
PNI	3.32 (2.050–5.385)	<0.001	1.81 (0.926–3.518)	0.083
LVI	3.33 (1.997–5.559)	<0.001	1.51 (0.841–2.710)	0.168
Adverse PSA	3.74 (2.461–5.668)	<0.001	2.17 (1.30–3.624)	0.003

BMI body mass index, CCI Charlson comorbidity index, CI confidence interval, LVI lymphovascular invasion, PNI perineural invasion, PSA prostate-specific antigen



**Fig. 2** Kaplan–Meier curves of biochemical failure-free survival in patients without vs. with adverse pathologic features stratified by adverse prostate-specific antigen (PSA)

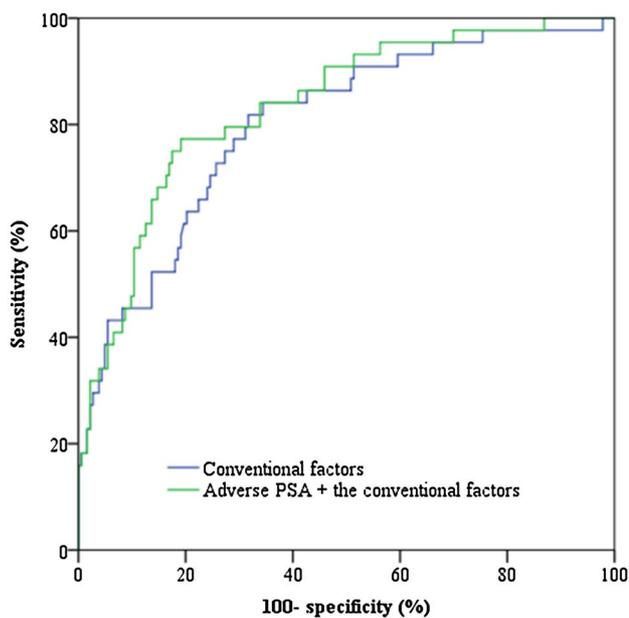
## Discussion

In this study, we detected differences in the prognosis of

BCF according to the number of adverse pathologic features and the presence of adverse PSA. A higher number of adverse pathologic features was associated with worse BCFFS (Fig. 2). Notably, adverse PSA precisely stratified prognoses among patients with adverse pathologic features. Moreover, our findings will be useful for physicians when attempting to create individualized follow-up treatment plans for patients with one adverse pathologic feature. Patients with one adverse pathologic feature and without adverse PSA showed no difference in BCFFS compared to those with no adverse pathologic features but with adverse PSA. In sub-analysis, we identified patients who required additional treatment, including ART, to predict BCF within 1 year after RP. Adverse PSA was identified as a significant predictor. The AUC when adding adverse PSA to the conventional factors was higher than that of the conventional factors alone.

PSA nadir and time to PSA nadir were identified as predictors of BCF in previous studies [14, 15]. However, a mutually conflicting relationship exists between these two variables. Patients whose first follow-up visit was earlier than the exact postoperative time to reach PSA nadir were stratified into the undetectable PSA and later PSA nadir groups. In contrast, those who visited later than the exact time were classified into a group with later PSA nadir even with undetectable PSA. Although the usefulness of PSA monitoring dichotomized at 6 weeks after RP has been reported, analyses in previous studies were not based on the biological features of tumor markers [10, 14].

Tumor biomarkers are molecules produced by cancer cells or released by an organism in response to the presence of cancer [16]. The identification of a specific predictive time



**Fig. 3** Comparison of the area under the receiver operating characteristics (ROC) curve for predicting biochemical failure within 1 year after radical prostatectomy for adverse prostate-specific antigen (PSA) added to the conventional factors vs. conventional factors alone

point has been a common strategy to discriminate between patients with favorable and unfavorable tumor biomarker reduction curves [17]. The minimum titer observed at time  $t$  is considered as a predictor for treatment efficacy in non-urological diseases [18–20]. For prostate cancer, the efficacy of PSA nadir for predicting disease progression using different thresholds has been demonstrated in patients treated with RP [21–23]. However, predictive strategies based on a single time point have not been investigated. Moreover, there is no consensus regarding the optimal timing of the first follow-up visit after RP. At our institution, the first follow-up visit in patients treated with RP is at 6 weeks. Mathematical analysis showed that preoperative PSA should be  $>480$  ng/mL for the PSA level at the 6-week follow-up visit to be higher than the undetectable value (0.01 ng/mL). However, the time of initial assessment of PSA varies depending on individual circumstances; for example, it was 43 (30–51) days in this cohort. To resolve this limitation, this study introduced adverse PSA as an original concept based on a mathematical equation including PSA half-life.

Our results revealed that adverse PSA was a significant prognostic factor for BCF in both the entire cohort and in patients stratified by the presence of adverse pathologic features (Table 2). This finding has two meaningful implications. First, physicians can use our equation as a powerful prognostic tool for planning individualized follow-up and treatment plans. In cases with both adverse pathologic features and

adverse PSA, physicians may design additional treatment and future schedules based on postoperative PSA kinetics, such as PSA doubling time or PSA velocity. In cases with adverse pathologic features and without adverse PSA, clinical decision-making between ART and SRT may vary according to the preferences of the physicians and patients in terms of the patients' quality of life because the median time to BCF in patients with BCF was  $>1$  year. Second, the absence of adverse pathologic features does not necessarily guarantee that the patients will not experience BCF at some point in the future. Among patients without adverse pathologic features, patients with adverse PSA had worse BCFFS than those without adverse PSA. This finding is similar to that in patients with one adverse pathologic feature and without adverse PSA. In patients with one adverse pathologic feature, the absence of adverse PSA might reflect successful surgery. On the contrary, the prognostic effects of the potential parameters, excluding adverse pathologic features but including preoperative PSA and LVI, triggered adverse PSA in patients without adverse pathologic features.

Surgery aims to cure the disease through resection of organs containing cancer lesions. Although adverse pathologic features were observed in specimens, verification of the efficacy of surgery takes time. PSA at the first follow-up visit after RP was a significant predictor of BCF. However, in addition to the small sample size and retrospective design, this study had several limitations. First, inconsistent values for PSA half-life have been reported (2–3 days) [11–13]. Therefore, future studies using a PSA half-life of 2.7 days might show different results. Second, patients with a detectable PSA level in the early postoperative period often do not show disease progression. However, the first follow-up visit in patients treated with RP is the earliest time at which it is possible to detect the PSA level consecutively rising as the first sign of recurrent disease. Physicians will be able to design future plans based on the prediction of BCF at the first follow-up visit using adverse PSA. Our planned future investigation of prognostic effects will address these problems.

## Conclusions

In conclusion, the difference between postoperative PSA level at the first follow-up visit after RP and the expected level while considering PSA half-life is a predictive factor for treatment efficacy following RP. Based on our results, physicians can more accurately predict BCF in patients with adverse pathologic features and adverse PSA.

**Author contributions** KSL: project development, manuscript writing; KCK: manuscript writing/editing; BHC: project development, manuscript writing.

## Compliance with ethical standards

**Conflict of interest** There is no potential conflict of interest.

**Human and animal rights** Clinical research involving human participants but no animals.

**Ethical approval** The study was approved by our institutional review board.

**Informed consent** Due to the retrospective nature of the study, written informed consent was waived.

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