

# Outcomes of pathologically localized high-grade prostate cancer treated with radical prostatectomy

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## Abstract

Adjuvant radiation therapy (ART) is recommended without consideration of radical prostatectomy Gleason score (RP GS) for cases with adverse features. We compared the outcomes of pathologically localized high-grade (GS 8–10) prostate cancer (PC) with those of pT3 GS 7 PC.

A total of 1585 men who underwent RP between 1995 and 2015 comprised the cohort, which was divided into group 1 (RP GS 7 (3+4) and pT3; n=760), group 2 (RP GS 7(4+3) and pT3; n=565), and group 3 (RP GS 8–10 and pT2; n=260). Biochemical recurrence (BCR), all-cause mortality (ACM), and PC-specific mortality (PCSM) risk were compared among groups using Cox regression and competing risk analysis.

At a median follow-up of 58 months (interquartile range: 37–85), 721 men experienced BCR and 84 died (22 due to PC). BCR-free survival rates were lower in group 3 than in group 1 ( $P < .001$ ); nevertheless, no difference was observed between groups 2 and 3 ( $P = .638$ ). Furthermore, no difference in ACM was noted among groups. PCSM rates were higher in group 3 than in groups 1 and 2 ( $P = .001$  and  $P = .005$ , respectively). This association persisted in multivariate models after adjustment for clinicopathological variables.

Patients with RP GS 8–10 and pT2 PC had higher BCR and PCSM rates than those with RP GS 7 and pT3 PC. Localized high-grade PC should be considered in decision-making for ART.

**Abbreviations:** ACM = all-cause mortality, ADT = androgen-deprivation therapy, ART = adjuvant radiation therapy, BCR = biochemical recurrence, BCRFS = biochemical recurrence-free survival, CRPC = castration-resistant prostate cancer, EPE = extraprostatic extension, GS = Gleason score, LNI = lymph node invasion, PC = prostate cancer, PCSM = prostate cancer-specific mortality, PSA = prostate-specific antigen, PSM = positive surgical margin, RP = radical prostatectomy, SVI = seminal vesicle invasion.

**Keywords:** biochemical recurrence, Gleason score, mortality, prostate cancer, radical prostatectomy

## 1. Introduction

The prostate cancer (PC) grading system had undergone 2 major updates since its introduction in 1974 by Gleason and Mellinger,<sup>[1]</sup> with the current application of Gleason score

(GS) differing from that of the original system. Despite revisions, biopsy GS 8–10 remains to be considered to denote high risk and is one of the most important prognostic indicators in the evaluation and treatment of men with PC.<sup>[2]</sup>

Clinical staging of PC involves the assessment of disease extent using pretreatment variables and includes digital rectal examination, measurement of prostate-specific antigen (PSA) level, biopsy GS, and radiologic imaging. Pathological staging of PC after radical prostatectomy (RP) is determined by histologic identification of tumor extent in the prostate, seminal vesicles, and pelvic lymph nodes, if lymphadenectomy is performed. Pathological staging more accurately estimates disease burden and is more useful than clinical staging in predicting outcomes.<sup>[3]</sup> GS, surgical margin status, T stage (extraprostatic extension [EPE], seminal vesicle invasion [SVI]), and pelvic lymph node invasion (LNI) are the most important pathological criteria used in predicting prognosis after RP.<sup>[3–7]</sup> Both biochemical recurrence-free survival (BCRFS) and PC-specific mortality (PCSM) are associated with these pathological features of the disease.<sup>[8]</sup> As expected, pathologically localized disease (pT2) shows significantly better outcomes than locally advanced disease (pT3).<sup>[9]</sup>

The current guidelines recommend adjuvant androgen-deprivation therapy (ADT) for patients with LNI and adjuvant radiation therapy (ART) for patients with other adverse pathological features (positive surgical margin [PSM], EPE, or SVI) or detectable PSA after RP without consideration of RP GS.<sup>[10–12]</sup> Whether adjuvant therapy is necessary when RP GS is high (8–10) remains controversial.<sup>[13–15]</sup> Several studies analyzed

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predictors of biochemical recurrence (BCR) after adjuvant therapy to identify patients who might benefit from radiotherapy; nonetheless, the predictive impact of high RP GS was not consistent.

In the event of discord between RP GS and pathological T stage as regards risk classification, the oncological outcomes and application of ART are questionable. We hypothesized that the survival outcomes of men with localized (pT2) high-grade PC might be worse than or similar to those of men with RP GS 7 and locally advanced (pT3) PC. The present study aimed to evaluate whether oncological and survival outcomes of men with RP GS 8–10 and pT2 would be different from those of men with RP GS 7 and pT3.

## 2. Patients and methods

This retrospective study received approval from the institutional review board (IRB) of Yonsei University Severance Hospital (IRB number: 4–2018–0206) for the collection of data on all patients who underwent RP for PC at our institution between 1995 and 2015.

A total of 1585 men with RP GS 7 and pT3 or RP GS 8–10 and pT2 were identified. Patients who received neoadjuvant therapy, had metastatic disease at initial diagnosis or LNI during RP, and had incomplete clinicopathological or follow-up data were excluded. Considering that GS 7(3+4) and GS 7(4+3) show different prognosis,<sup>[16]</sup> the cohort was divided into the following 3 groups according to RP GS and pT stage: group 1, which comprised 760 men with RP GS 7(3+4) and pT3; group 2, which consisted of 565 men with RP GS 7(4+3) and pT3; and group 3, which comprised 260 men with RP GS 8–10 and pT2.

Pathological stages were assigned in accordance with the American Joint Committee on Cancer staging system.<sup>[4]</sup> Pathological analysis of RP specimens was performed by an experienced uropathologist at our institute.<sup>[17]</sup> Briefly, the entire surface of the resected prostate specimens was coated with India ink, fixed in neutral buffered formalin, and embedded in paraffin blocks. Whole-mount step sections were transversely cut at regular intervals from the apex of the prostate to the tips of the

seminal vesicles. Each section was examined for SVI, EPE, and PSM.

Postoperative PSA follow-up was undertaken at 3-month intervals for the first 2 years and at 6-month intervals for the subsequent 3 years; annual PSA follow-up was recommended thereafter. Adjuvant or salvage radiotherapy was administered at the discretion of the surgeon.

BCR was defined as detectable PSA after RP, 2 consecutive increases of  $\geq 0.2$  ng/ml in PSA level with undetectable PSA after RP, or any secondary treatment after surgery.<sup>[18,19]</sup> BCRFS was defined as the time from RP to the occurrence of BCR. Data on mortality and cause of death were collected from medical records in the Cancer Registry Center database at our institution. PCSM was defined as death due to PC or death attributable to castration-resistant PC (CRPC) in patients. CRPC was defined as biochemical, radiologic, or clinical progression in a low-testosterone environment.<sup>[20]</sup>

Baseline characteristics and pathological outcomes were compared using Chi-Squared test for categorical data and Kruskal–Wallis test for continuous data. BCRFS and all-cause mortality (ACM) were estimated using the Kaplan–Meier method, and log-rank test was used to compare these estimates among groups. Multivariate Cox regression analyses were performed to identify predictive factors for BCR and ACM. PCSM was calculated and compared among groups using a competing risk model. A cumulative incidence function was generated for each group. Multivariate competing risk regression analysis of PCSM was performed with death from other causes as the competing event.<sup>[21]</sup> The level of significance was set at 0.05 in all analyses. All statistical analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org>) and its `cmprsk` and `rms` packages.

## 3. Results

Baseline characteristics of patients are summarized in Table 1. Significant differences in age, PSA level, year of surgery, and PSM were observed across groups (all  $P < .005$ ). Groups 2 and 3 had

**Table 1**  
Patient characteristics.

	Group 1*	Group 2†	Group 3‡
No. patients	760	565	260
Age, years (median [IQR])	66 (61–70)	67 (62–71)	67 (61–72)
PSA, ng/ml (median [IQR])	8.65 (5.83–13.48)	10.65 (6.75–18.31)	10.65 (6.54–19.03)
Year of surgery (median [IQR])	2011 (2009–2013)	2010 (2008–2012)	2012 (2009–2014)
Surgical method			
Open	153 (20.1)	135 (23.9)	55 (21.2)
Robotic	594 (78.2)	421 (74.5)	202 (77.7)
Laparoscopic	13 (1.7)	9 (1.6)	3 (1.2)
PSM	454 (59.7)	365 (64.6)	93 (35.8)
EPE	687 (90.4)	451 (79.8)	–
SVI	73 (9.6)	114 (20.2)	–
Follow-up, months, (median [IQR])	58 (36–82)	61 (39–90)	48.5 (35–79)
BCR	269 (35.4)	309 (54.7)	143 (55.0)
PCSM	5 (0.7)	7 (1.2)	10 (3.8)
ACM	32 (4.2)	35 (6.2)	17 (6.5)

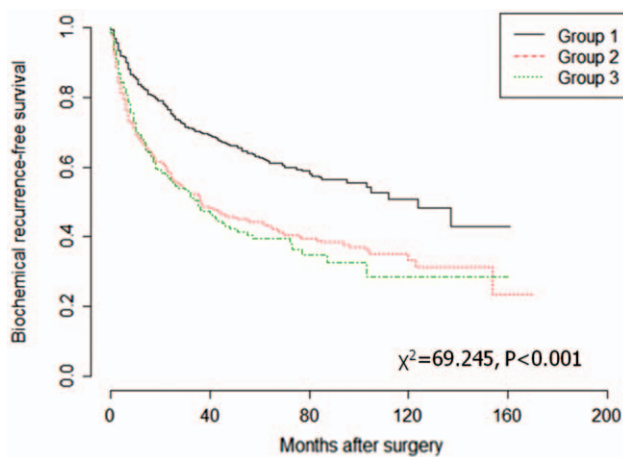
\* Radical prostatectomy Gleason score 7(3+4) and pathological T3.

† Radical prostatectomy Gleason score 7(4+3) and pathological T3.

‡ Radical prostatectomy Gleason score 8 and pathological T2.

Data are expressed as N (%) unless otherwise specified.

ACM = all-cause mortality, BCR = biochemical recurrence, EPE = extraprostatic extension, IQR = interquartile range, PCSM = prostate cancer-specific mortality, PSA = prostate-specific antigen, PSM = positive surgical margin, SVI = seminal vesicle invasion.

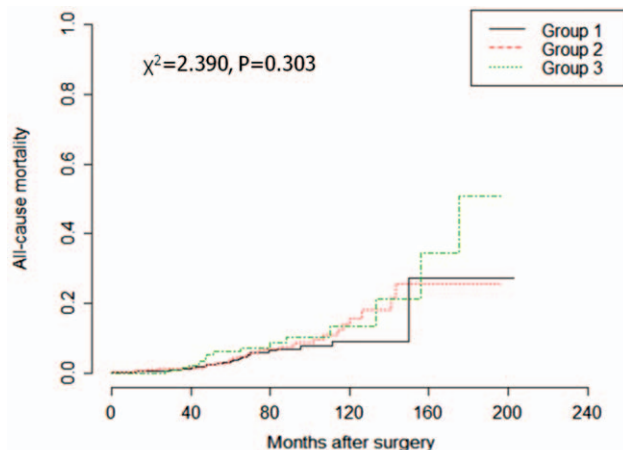


At Risk	760	389	123	21	1	Group 1
	565	210	80	20	2	Group 2
	260	74	21	1	1	Group 3

Figure 1. Kaplan-Meier plots of biochemical recurrence-free survival.

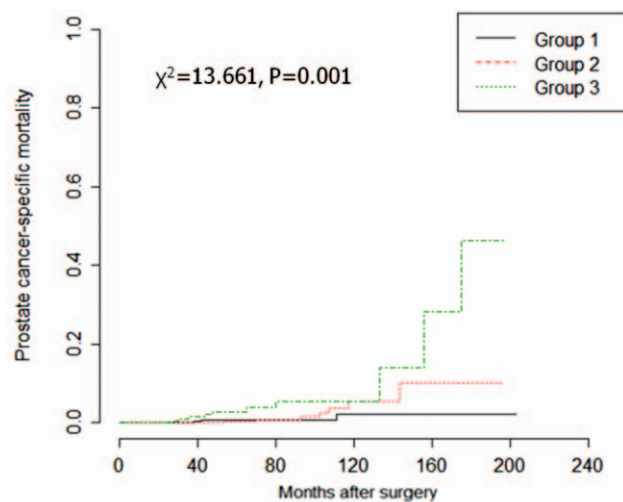
higher preoperative PSA level than group 1. Group 3 showed lower PSM rate than the other groups. There is no difference in proportion of surgical methods among the 3 groups (groups 1 and 2:  $P=.259$ , groups 1 and 3:  $P=.784$ , groups 2 and 3:  $P=.590$ , overall:  $P=.536$ ).

Of 1585 men, 721 experienced BCR and 84 died (22 due to PC) at a median follow-up of 58 months (interquartile range: 37–85). The 10-year BCRFS rates were 50.9%, 33.2%, and 28.6% in groups 1, 2, and 3, respectively. BCRFS was worse in group 3 than in the other groups (group 1:  $P<.001$ , group 2:  $P=.638$ , overall:  $P<.001$ ; Fig. 1). No significant difference in ACM was noted among groups (Fig. 2). The 15-year ACM rates were 27.2%, 25.6%, and 50.8% in groups 1, 2, and 3, respectively. PC-specific survival rates were significantly lower in group 3 than in groups 1 and 2 ( $P=.001$ ,  $P=.005$ , respectively; Fig. 3). Specifically, the 15-year PCSM rates were 2.1%, 8.9%, and 42.6% in groups 1, 2, and 3, respectively.



At Risk	760	555	213	49	2	1	Group 1
	565	422	188	50	9		Group 2
	260	164	65	19	5		Group 3

Figure 2. Kaplan-Meier plots of all-cause mortality.



At Risk	760	555	213	49	2	1	Group 1
	565	422	188	50	9		Group 2
	260	164	65	19	5		Group 3

Figure 3. Cumulative incidence functions of prostate cancer-specific mortality.

In multivariate models, BCR was higher in group 2 (adjusted hazard ratio [AHR], 1.625; 95% confidence interval [CI]: 1.305–2.022;  $P<.001$ ) and group 3 (AHR, 1.928; 95% CI: 1.387–2.679;  $P<.001$ ) than in group 1 (Table 2). Nevertheless, our group classification was not associated with ACM (Table 3). PCSM was higher in group 2 (AHR, 1.187; 95% CI: 0.336–3.850;  $P=.770$ ) and group 3 (AHR, 5.306; 95% CI: 1.517–18.560;  $P=.009$ ) than in group 1 (Table 4).

#### 4. Discussion

Pathological features including RP GS, surgical margin status, EPE, SVI, and LNI status are the strongest prognostic factors for predicting postoperative outcomes. Approximately 30% of patients treated with RP exhibit PSM, EPE, and SVI.<sup>[22]</sup> Post-RP recurrence rates in patients with these pathological findings may be greater than 60% at 5 years.<sup>[23]</sup> Therefore, most current guidelines recommend that ART should be offered to patients with adverse features (PSM, EPE, SVI, or detectable PSA), as ART has been shown to reduce BCR, local recurrence, and clinical progression. However, these guidelines do not take RP GS into account in the decision-making for patient selection for ART.<sup>[10,12]</sup>

ADT is recommended when PSA is persistently detected despite ART.<sup>[10]</sup> Although ADT is initially effective in hindering tumor growth, the disease may progress to an androgen-independent state. This state, which is also known as CRPC, is generally characterized by poor prognosis and an average survival ranging from 10 to 20 months.<sup>[24]</sup> Thus, identifying patients who may benefit from ART is crucial.

Several clinicians differ in their opinions and practice with respect to the adoption of ART, notwithstanding the guidelines.<sup>[25]</sup> This variability results from the concern about functional complications (e.g., incontinence, sexual dysfunction), as well as its oncological benefit that may not be clinically significant, even uncertain.<sup>[26,27]</sup> Swanson et al concluded that the risk of BCR in men with locally advanced disease varies widely depending on the preoperative PSA level (<10 vs  $\geq 10$  ng/ml) and

**Table 2**

**Cox regression analysis of predictors of biochemical recurrence.**

	Univariable model			Multivariable model		
	HR	(95% CI)	P value	AHR	(95% CI)	P value
Age	1.009	(0.998–1.020)	.102	1.014	(0.999–1.029)	.076
PSA	1.007	(1.006–1.009)	<.001	1.005	(1.002–1.007)	<.001
Year of surgery	1.021	(0.995–1.047)	.113	1.025	(0.990–1.060)	.164
Surgical margin						
Negative	1	(reference)		1	(reference)	
Positive	2.193	(1.868–2.576)	<.001	2.098	(1.614–2.727)	<.001
Group*						
1	1	(reference)		1	(reference)	
2	1.833	(1.556–2.159)	<.001	1.625	(1.305–2.022)	<.001
3	1.945	(1.587–2.384)	<.001	1.928	(1.387–2.679)	<.001

\* Group 1—radical prostatectomy Gleason score 7(3+4) and pathological T3, group 2—radical prostatectomy Gleason score 7(4+3) and pathological T3, group 3—radical prostatectomy Gleason score 8 and pathological T2.

AHR=adjusted hazard ratio, CI=confidence interval, PSA=prostate-specific antigen.

RP GS (<7 vs ≥7).<sup>[22]</sup> In addition, Kang et al evaluated patients with adverse features who qualified for ART based on the current American Urological Association and American Society for Radiation Oncology guidelines. They reported that only 16.6% of these patients who had adverse features developed BCR and that BCR occurred in only 3 out of 87 patients with preoperative

PSA level < 6.35 ng/ml and GS < 8. Thus, they recommended that patient selection for ART should be more customized to avoid significant overtreatment.<sup>[28]</sup>

Previous studies have indicated the association between RP GS and BCR after RP. Menon et al analyzed the oncological outcomes of patients undergoing robot-assisted RP and reported

**Table 3**

**Cox regression analysis of predictors of all-cause mortality.**

	Univariable model			Multivariable model		
	HR	(95% CI)	P value	AHR	(95% CI)	P value
Age	1.108	(1.068–1.150)	<.001	1.114	(1.071–1.158)	<.001
PSA	1.002	(0.998–1.006)	.357	1.001	(0.996–1.006)	.679
Year of surgery	0.925	(0.862–0.992)	.029	0.926	(0.862–0.996)	.038
Surgical margin						
Negative	1	(reference)		1	(reference)	
Positive	1.398	(0.884–2.221)	.152	1.177	(0.720–1.923)	.516
Group*						
1	1	(reference)		1	(reference)	
2	1.258	(0.777–2.037)	.350	1.042	(0.640–1.697)	.868
3	1.576	(0.871–2.852)	.133	1.346	(0.720–2.517)	.351

\* Group 1—radical prostatectomy Gleason score 7(3+4) and pathological T3, group 2—radical prostatectomy Gleason score 7(4+3) and pathological T3, group 3—radical prostatectomy Gleason score 8 and pathological T2.

AHR=adjusted hazard ratio, CI=confidence interval, PSA=prostate-specific antigen.

**Table 4**

**Competing risks analysis of predictors of prostate cancer-specific mortality.**

	Univariable model			Multivariable model		
	HR	(95% CI)	P value	AHR	(95% CI)	P value
Age	1.070	(0.996–1.140)	.067	1.054	(0.978–1.140)	.170
PSA	1.000	(0.997–1.010)	.430	0.996	(0.989–1.000)	.280
Year of surgery	0.895	(0.791–1.010)	.077	0.923	(0.811–1.050)	.230
Surgical margin						
Negative	1	(reference)		1	(reference)	
Positive	3.030	(1.040–8.860)	.043	2.065	(0.669–6.370)	.210
Group*						
1	1	(reference)		1	(reference)	
2	1.500	(0.486–4.620)	.480	1.187	(0.336–3.850)	.770
3	5.460	(1.888–15.79)	.002	5.306	(1.517–18.560)	.009

\* Group 1—radical prostatectomy Gleason score 7(3+4) and pathological T3, group 2—radical prostatectomy Gleason score 7(4+3) and pathological T3, group 3—radical prostatectomy Gleason score 8 and pathological T2.

AHR=adjusted hazard ratio, CI=confidence interval, PSA=prostate-specific antigen.

that one of the strongest predictors of BCR was RP GS 8–10 (HR, 5.37; 95% CI: 2.99–9.65;  $P < .0001$ ).<sup>[5]</sup> Similarly, Eisenberg et al evaluated the outcomes of patients with pT3aN0 PC and observed that RP GS was significantly associated with BCR (HR, 1.84; 95% CI: 1.6–2.1;  $P < .0001$ ).<sup>[6]</sup> Furthermore, Suardi et al investigated BCRFS in patients treated with robot-assisted RP; they reported that the 3-, 5-, and 7-year BCRFS rates for RP GS 8–10 were lower than those for RP GS  $\leq 7$  and that RP GS 8–10 was an independent predictor of BCR (HR, 5.14;  $P = .004$ ).<sup>[29]</sup>

Comparable to the relationship between BCR and RP GS, PCSM was higher in patients with RP GS 8–10 than in those with RP GS  $\leq 7$ , with high RP GS being a significant risk factor for PCSM. Freedland et al analyzed PCSM in men who exhibited BCR after RP and reported that RP GS was one of the independent predictors of time to PCSM following BCR (HR, 2.26; 95% CI: 1.35–3.77;  $P = .002$ ).<sup>[7]</sup> Abdollah et al reported that RP GS  $\geq 8$  was an independent predictor of PCSM (HR, 5.62; 95% CI: 3.08–10.23;  $P < .001$ ).<sup>[30]</sup> Collectively, these findings indicated that RP GS was strongly associated with prognosis.

Nonetheless, there has been controversy as to whether adjuvant therapy is necessary when RP GS is  $\geq 8$ . Van der Kwast et al analyzed pathological data on specimens from participants in the randomized controlled European Organisation for Research and Treatment of Cancer trial 22,911 and identified no statistically significant predictive impact of RP GS ( $P > .1$ ).<sup>[13]</sup> Kamat et al investigated BCRFS in patients who received ART for PSM and reported that GS  $\geq 7(4+3)$  was predictive of BCR in univariate analysis, but not in multivariate analysis.<sup>[14]</sup> Conversely, Taille et al evaluated ART failure in patients with BCR after RP and showed that GS ( $P = .0395$ ) was an independent predictive factor.<sup>[31]</sup>

In the present study, we evaluated whether survival outcomes (BCRFS, ACM, and PCSM) of men with RP GS 8–10 and pT2 would be different from those of men with RP GS 7 and pT3. In addition, we aimed to identify whether patients with high RP GS could be considered for ART, despite having localized PC. We observed decreasing trends for both BCRFS and cancer-specific survival with increasing RP GS, irrespective of pathological stage. Specifically, group 1 showed significantly higher BCRFS than the other groups; however, no significant difference in BCRFS rates was noted between groups 2 and 3. PCSM rates were not significantly different between groups 1 and 2, with PCSM being higher in group 3 than in the other groups. Moreover, PSA, PSM, and our group classification were predictors of BCR in multivariate Cox regression analysis. Preoperative PSA level was used for risk classification, and PSM was one of the adverse features to consider ART.<sup>[10]</sup> In our group classification, groups 2 and 3 showed higher BCR than group 1, with the AHR for group 3 being higher than that for group 2. Additionally, group 3 was the only predictor of PCSM in multivariate competing risk analysis. Overall, high RP GS was associated with aggressive tumor behavior, which increased BCR and PCSM. These findings implied that RP GS might have more impact on survival outcomes than pathological T stage; hence, high RP GS should be included as one of the criteria for selecting patients who might benefit from ART. Moreover, ART can be used less aggressively for low or intermediate RP GS disease, even though the disease is not localized.

This study has several limitations. First, all data from a single institution were retrospectively reviewed; therefore, our results may not be generalizable. Second, data on adjuvant or salvage therapy were not presented because only a few men received ART

and salvage therapy could act as a surrogate marker of BCR.<sup>[32,33]</sup> Further studies evaluating oncological outcomes after ART in a large number of patients with localized high-grade PC and locally advanced low-grade PC are required to confirm our results. Third, the present study cohort was not reclassified in accordance with the updated Gleason grading system because our institution adopted the system in 2016. A major change in the 2014 update by the International Society of Urological Pathology was a restrictive definition of grade pattern 3. As some cases of RP GS 7 might have shifted up to RP GS 8, updated RP GS 8 disease may have a better prognosis than what our study results implied. However, Gleason pattern 5 has remained unchanged in the updated Gleason grading system.<sup>[16]</sup> Therefore, the current results should be reassessed in accordance with the updated Gleason grading system. Finally, comorbidity variables and a tertiary Gleason pattern in RP GS were not included in the model.

## 5. Conclusion

Patients with RP GS 8–10 and pT2 PC had higher BCR and PCSM rates than those with RP GS 7 and pT3 PC. These findings suggest that worse oncological outcomes despite localized disease could be attributed to high RP GS. Thus, high RP GS should be considered in decision-making for adjuvant treatment. ART can be more aggressive for localized high-grade PC but less aggressive for locally advanced low-grade PC.

## Author contributions

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**Writing – original draft:** Ji Eun Heo.

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