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Biochemical Recurrence After Radical Prostatectomy: The Distinct Prognostic Role of ISUP Grade 5

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Abstract

Background:

Biochemical recurrence (BCR) after radical prostatectomy (RP) is an important indicator of disease progression in prostate cancer. Although several clinicopathological factors have been associated with postoperative recurrence, the relative prognostic contribution of individual pathological features remains incompletely defined. Therefore, this study aimed to evaluate the clinicopathological predictors of BCR after RP.

Methods:

A total of 183 prostate cancer patients who underwent RP were evaluated. Biopsy and pathological International Society of Urological Pathology (ISUP) grades, pathological T stage, lymph node involvement, positive surgical margins (PSM), seminal vesicle and lymphovascular invasion (LVI), and tumor volume were examined. BCR was defined as two consecutive postoperative prostate specific antigen (PSA) values ≥ 0.2 ng/mL after an initially undetectable postoperative PSA level. Logistic regression and Cox proportional hazards analyses were used to determine independent predictive factors of BCR and progression-free survival.

Results:

BCR occurred in 18.0% of patients during follow-up. Higher biopsy and pathological ISUP grades, advanced pathological T stage, LVI, and PSM were significantly associated with BCR. In multivariable analysis, pathological ISUP grade 5 emerged as the strongest independent predictor of BCR (OR 7.17, 95% CI 2.02–25.43). In Cox regression analysis, ISUP grade 5 was also associated with a significantly higher hazard of recurrence (HR 9.33, 95% CI 4.28–20.31) and shorter progression-free survival.

Conclusions:

Pathological ISUP grade 5 is the strongest predictor of BCR and may contribute to improved postoperative risk stratification.

Background

Prostate cancer (PCa) is the second most frequent malignancy among men worldwide [1]. The incidence of PCa varies across geographic areas, revealing differences in prostate-specific antigen (PSA) level [2]. The Tumor–Node–Metastasis (TNM) staging system and the European Association of Urology (EAU) risk group classification are widely used for risk stratification between urologists. These classification systems stratify patients according to the risk of biochemical recurrence (BCR) following radical prostatectomy (RP) [3].

Tumor grade represents a key factor of pathological assessment in PCa. The Gleason score (GS) reflects the cumulative extent of tumor grade in all prostate biopsy cores. In 2014, the International Society of Urological Pathology (ISUP) introduced a standardized five-stage grading system, which was subsequently updated in 2019 to improve prognostic accuracy [4]. The EAU risk group classification, largely derived from the D'Amico classification system, integrates clinical tumor stage, PSA level, and pathological findings obtained from prostate tissue [5].

BCR following RP is a well-established indicator of oncological outcomes [6]. PSA levels are typically measured every six months during the first three postoperative years and annually thereafter; however, evidence giving specific follow-up intervals remains limited [7]. This follow-up strategy is largely based on observations that early BCR is likely to be associated with recurrence of PCa [8]. In addition, elevated postoperative PSA levels, especially in the presence of adverse clinicopathological features such as higher ISUP grade and positive surgical margins (PSM), may predict subsequent BCR and assist in determining surveillance [9]. Furthermore, an increased PSA level after RP has been defined as an indicator of BCR and metastatic potential [10].

The prognostic value of individual pathological parameters in predicting BCR following RP remains unclear. A deeper understanding of these factors may improve postoperative risk stratification and guide surveillance strategies. Therefore, this study aimed to identify the clinicopathological predictors of BCR and to determine whether specific pathological features, particularly ISUP grade 5, represent a distinct prognostic entity.

Methods

Study design

This study was conducted at a single center and included patients who underwent open RP and pelvic lymph node dissection when indicated between 2011 and 2025 for clinically localized PCa. Institutional data were reviewed to identify eligible patients. A total of 251 patients were identified, of whom 68 were excluded due to incomplete clinicopathological data (n = 2), lack of postoperative PSA follow-up (n = 3), and a follow-up duration of less than 12 months (n = 63). A total of 183 patients were included. Postoperative PSA levels were obtained every three months during the first postoperative year, every six months until the third year, and annually thereafter, according to follow-up protocols.

RP specimens were evaluated by a dedicated genitourinary pathologist according to standard pathological protocols. Assessed pathological variables included prostate and tumor volume, ISUP grade (all specimens were evaluated according to the 2014 ISUP grading system), pathological T stage, pelvic lymph node involvement (LNI), extraprostatic extension, PSM, seminal vesicle invasion (SVI), perineural invasion, lymphovascular invasion (LVI), and the presence of high-grade prostatic intraepithelial neoplasia.

BCR was accepted as two consecutive postoperative PSA measurements ≥ 0.2 ng/mL following an undetectable PSA level after RP.

Statistical Analysis

Categorical variables were summarized as frequencies and percentages, whereas continuous variables were expressed as means with standard deviations or medians with ranges, depending on the distribution of the data. Normality was assessed using the Shapiro–Wilk test. Comparisons between patients with and without BCR were performed using the Pearson chi-square test or Fisher's exact test for categorical variables, and the independent-samples t-test or Mann–Whitney U test for continuous variables. Agreement between biopsy ISUP grade and final pathological ISUP grade was evaluated using the weighted kappa coefficient.

Variables that were statistically significant in univariate analyses, along with clinically relevant variables, were included in multivariable logistic regression models to identify predictors of BCR. Given the lack of independent association between intermediate ISUP grades and BCR in univariate analyses, ISUP grades 1–4 were grouped and compared with ISUP grade 5 to specifically assess the prognostic impact of the highest-grade disease. Progression-free survival was estimated using the Kaplan–Meier method, and differences between groups were evaluated using the log-rank test. Cox proportional hazards regression analysis was used to identify independent predictors of time to BCR. Hazard ratios were reported with corresponding 95% confidence intervals (CIs). IBM SPSS Statistics (version 20.0; IBM Corp., Armonk, NY, USA) was used, and a two-sided p-value < 0.05 was considered statistically significant.

Results

Patient characteristics, including age, PSA levels, and follow-up duration, are summarized in Table 1. During follow-up, BCR occurred in 33 of 183 patients (18.0%). Higher biopsy ISUP grades were associated with an increased risk of BCR. Higher pathological ISUP grades, advanced pathological T stage (≥ T3), LVI, and PSM were significantly more common in patients who developed BCR.

Table 1
Patient characteristics

Variable	**Non-BCR (n = 150)**	**BCR (n = 33)**	***p-value***
Age (years)	62.1 ± 5.8	62.1 ± 6.1	0.963
PSA (ng/mL)	11.6 ± 9.4 (2.4–64.9)	15.8 ± 18.1 (5.2–106)	**0.048**
Follow-up time (months)	45.7 ± 32.3 (1–142)	59.5 ± 32.1 (12–132)	**0.009**
PSA: prostate specific antigen; BCR: biochemical recurrence			

Pathological ISUP grade, pathological T stage, LNI, PSM, SVI, LVI, capsule invasion, and tumor volume were associated with BCR in univariate logistic regression analyses. However, pathological ISUP grades 2–4 did not demonstrate an independent association with this finding. Therefore, ISUP grades 1–4 were

grouped and compared with ISUP grade 5 in subsequent multivariable models. Pathological ISUP grade 5 emerged as the strongest independent predictor of BCR, conferring a 7.17-fold increased risk (95% CI: 2.02–25.43) in multivariable logistic regression analysis. LVI was also independently associated with BCR, revealing a 3.26-fold increased risk (95% CI: 1.19–8.93). Tumor volume was also significantly associated with BCR. Patients with tumor volumes greater than the mean value (20.94 cc) demonstrated significantly shorter progression-free survival compared to patients with smaller tumor volumes (86.9 vs. 115.5 months; p = 0.004) **(**Table 2**).**

Table 2
Pathological characteristics

Variable	**Non-BCR (n = 150)**	**BCR (n = 33)**	***p-value***
Prostate volume (cm³)	55.5 ± 23.1 (20–134)	57.6 ± 25.4 (10–130)	0.496
Pathological ISUP grade			**< 0.001**
1	24 (16%)	1 (3%)	
2	46 (31%)	7 (21%)	
3	50 (33%)	7 (21%)	
4	25 (17%)	8 (24%)	
5	5 (3%)	10 (30%)	
Pathological T stage			**0.002**
≤T2	62 (41%)	4 (12%)	
≥T3	88 (59%)	29 (88%)	
Lymph node involvement	9 (6%)	8 (24%)	**0.004**
Positive surgical margin	50 (33%)	19 (58%)	**0.009**
Seminal vesicle invasion	20 (13%)	13 (39%)	**< 0.001**
Perineural invasion	135 (90%)	33 (100%)	0.077
Lymphovascular invasion	15 (10%)	13 (39%)	**< 0.001**
HGPIN	146 (97%)	32 (97%)	0.999
Capsule invasion	116 (77%)	31 (94%)	**0.030**
Tumor volume (cm³)	18.7 ± 18.7 (1–90)	30.9 ± 26.2 (2–83)	**0.006**

PSA: prostate specific antigen; ISUP: International Society of Urological Pathology; HGPIN: high-grade prostatic intraepithelial neoplasia; BCR: biochemical recurrence

Kaplan–Meier analysis showed significantly shorter progression-free survival among patients with high-risk clinicopathological features, including biopsy ISUP grade 4, pathological ISUP grade 5, LNI, PSM, SVI,

and LVI **(Fig. 1).** In Cox proportional hazards regression analysis, pathological ISUP grade 5 consistently emerged as the strongest independent predictor of time to BCR. Patients with ISUP grade 5 disease had a 9.33-fold increased hazard of BCR (95% CI: 4.28–20.31) compared with those with lower-grade disease **(**Table 3**).**

Table 3
Time to biochemical recurrence according to clinicopathological variables

Variable	**Mean time (months)**	**95% CI**	***p-value***
Pathological ISUP grade			**< 0.001**
1–4	114.8	104.3–125.2	
5	32.8	20.0–45.5	
Lymph node involvement	63.9	44.7–83.0	**0.006**
Positive surgical margin	92.6	77.5–107.7	0.034
Seminal vesicle invasion	82.7	62.9–102.5	**0.004**
Lymphovascular invasion	60.8	45.1–76.5	**< 0.001**
ISUP: International Society of Urological Pathology			

Discussion

BCR after RP remains a clinically important indicator of subsequent disease progression. Although surgical techniques and perioperative risk stratification have improved over time, a considerable proportion of patients still develop BCR during long-term follow-up. Multiple clinicopathological factors have been linked to recurrence risk, among which preoperative PSA remains one of the most widely recognized predictors. Descazeaud et al. showed that when PSA exceeded 10 ng/mL, the 5-year progression rate rose from 18% to 40% compared with patients whose PSA levels were below 10 ng/mL [11]. Likewise, Naselli et al. reported a higher recurrence risk in patients with PSA values above 20 ng/mL [12]. In this study, preoperative PSA was also significantly associated with BCR, with a mean preoperative PSA level of 15.8 ng/mL among patients who developed recurrence. These findings support the established relationship between elevated PSA and increased recurrence risk. In contrast, Kim et al. found no significant predictive value for preoperative PSA in their cohort [13]. In that series, all patients had LNI-positive disease, and mean PSA levels in both recurrence and non-recurrence groups were approximately 30 ng/mL, suggesting that the prognostic utility of PSA may decline at very high values. Although preoperative PSA has been extensively studied, the optimal threshold for predicting BCR remains uncertain.

Follow-up duration is another important factor in the detection of BCR. While longer surveillance increases the likelihood of identifying recurrence, there is still no consensus regarding the ideal postoperative monitoring period. Descazeaud et al. reported a mean time to BCR of approximately four

years, with a 5-year progression rate of 25% [11]. Similarly, in our cohort, mean follow-up was approximately four years in patients without BCR and five years in those with recurrence. These findings suggest that at least five years of follow-up may be necessary for adequate postoperative surveillance after RP. Further research is needed to define the most appropriate monitoring duration. Refined risk stratification tools may play an important role in postoperative surveillance. Porcaro et al. demonstrated that the 2012 Briganti nomogram can independently predict disease progression even after adjusting for tumor upgrading, thereby identifying prognostic subgroups that may require more intensive follow-up [14]. These findings further suggest that the first five years after RP represent a critical period for the detection of BCR.

Tumor grade has long been recognized as a cornerstone of prognostication in PCa. Large cohort studies and established nomograms have shown that higher ISUP grades are associated with BCR and cancer-specific mortality. Porcaro et al. reported that adverse tumor grades (ISUP > 3) were associated with both BCR and cancer-specific mortality following definitive treatment and identified tumor grade as an important determinant of progression-free survival in patients with PCa [14]. Similarly, Meijer et al. reported that a prostate biopsy ISUP grade ≥ 4 is an independent predictor of early BCR [15]. Patients with ISUP grade ≥ 4 in prostate biopsy specimens are at increased risk of BCR after surgery, which may have implications for radical treatment decisions. In our study, pathological ISUP grade 5 showed a strong association with BCR. Moreover, our findings suggest that not all high-grade disease confers equal prognostic significance. While intermediate ISUP grades showed limited independent predictive value in multivariable analyses, ISUP grade 5 was associated with a higher risk of BCR compared with other clinicopathological parameters. These findings suggest that ISUP grade 5 should be considered a distinct pathological category rather than being grouped with other high-grade tumors.

LNI and other adverse pathological findings, including SVI and PSM, have shown variable associations with BCR across previous studies. These features may reflect either residual local disease or occult micrometastatic spread present at the time of surgery. Kim et al. found that patients with persistent PSA had significantly higher rates of LNI, whereas PSM was not significantly associated with BCR [13]. This suggests that nodal micrometastatic disease may be a stronger determinant of recurrence than residual local tumor at the surgical margin. In our cohort, both LVI and LNI were significantly more frequent in patients with BCR. In multivariable analysis, LVI independently increased BCR risk by 3.26-fold. Prior studies have likewise identified pathological stage as an important predictor of recurrence. Naselli et al. reported the pT3a/b stage as a strong independent predictor of persistently detectable PSA [12]. Our findings are in agreement with these observations: 88% of patients with BCR in our study had ≥T3 disease, compared with 59% in the non-BCR group.

In addition, although LNI, SVI, and PSM were associated with shorter BCR-free survival, none demonstrated an independent prognostic effect comparable to that of ISUP grade 5. These findings further underscore the prognostic importance of pathological ISUP grade 5 and support its role in postoperative risk stratification. ISUP grade 5 may therefore represent a distinct high-risk subgroup among patients undergoing RP.

This study has limitations. It was designed as a retrospective single-center study and may introduce selection bias and restrict generalizability. The moderate sample size limited detailed subgroup analyses based on established postoperative risk classifications. In addition, variation in follow-up duration constrained assessment of long-term endpoints such as metastasis-free survival and cancer-specific survival. Molecular and genetic biomarkers like PSA doubling time were not included in the analysis.

Conclusion

BCR following RP is dependent on various clinicopathological factors, with pathological ISUP grade 5 recognized as the most significant independent predictor among these. Identifying this high-risk adverse pathological feature may enhance postoperative risk assessment, allowing for more precise follow-up strategies and treatment options in this group of patients.

Abbreviations

BCR
Biochemical recurrence
RP
Radical prostatectomy
PSA
Prostate-specific antigen
ISUP
International Society of Urological Pathology
LVI
Lymphovascular invasion
LNI
Lymph node involvement
PSM
Positive surgical margin
SVI
Seminal vesicle invasion

Declarations

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Conflict of Interests

The authors declare that there are no conflicts of interest.

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Figures

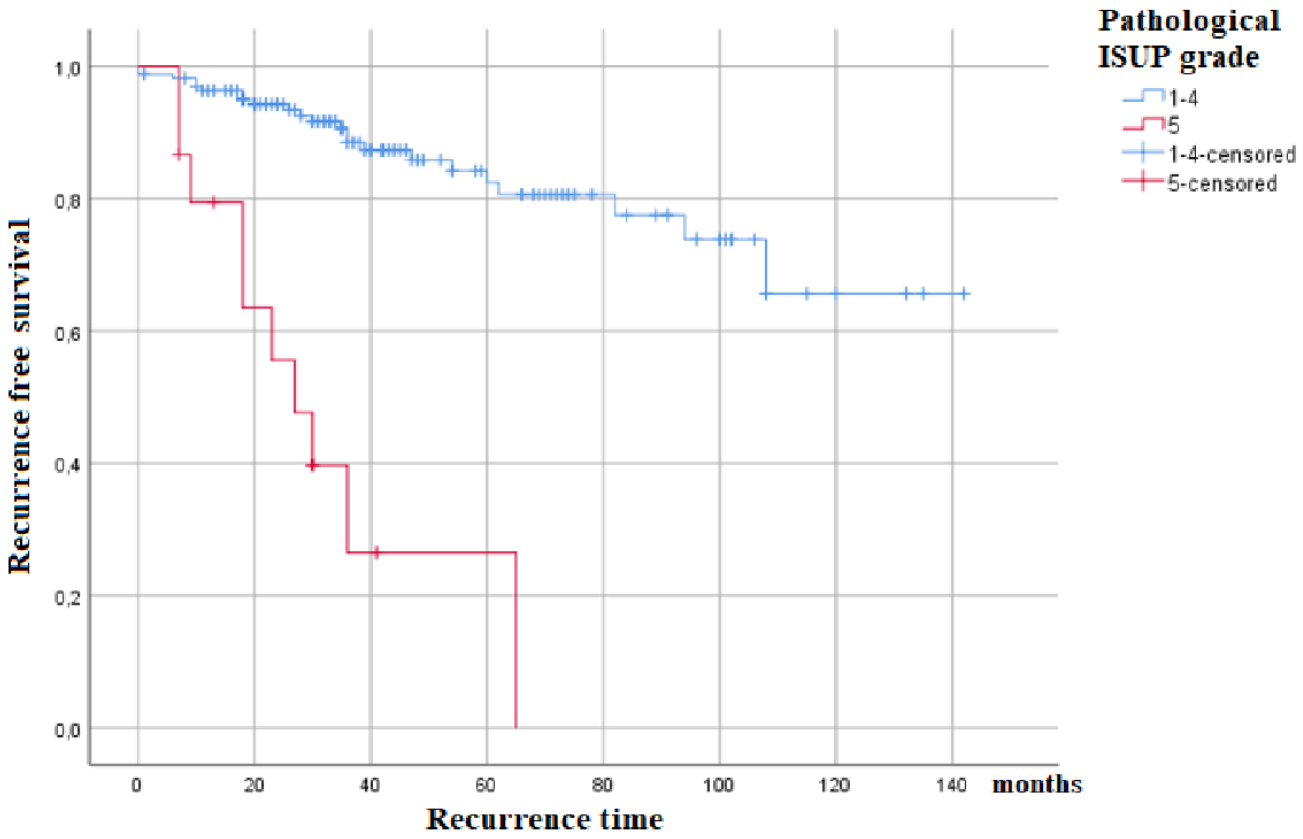


Figure 1. Kaplan–Meier analysis of time to biochemical recurrence stratified by pathological ISUP grade 1–4 / ISUP grade 5

Figure 1

See image above for figure legend

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