

Impact of Gleason score of the tumor at the positive surgical margin as a prognostic factor

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Abstract. Although numerous studies have reported that a positive surgical margin (PSM) is the most important predictive factor for biochemical recurrence (BCR) of prostate cancer (PCa), only a small number of studies have evaluated the predictive value of the Gleason score (GS) of the tumor at the margin in radical prostatectomy (RP). The present study aimed to investigate the preoperative factors that predict PSM and the significant predictive factors for BCR in cases with PSM. In addition, it was examined whether documenting the GS of the tumor at the margin in pathological reports is useful as a predictive factor for BCR. Data of 241 patients with PCa who underwent RP at Kurume University Hospital (Kurume, Japan) between January 2007 and December 2011 were retrospectively reviewed. The median follow-up period was 72 months and 122 patients had at least one PSM. The time to BCR was significantly shorter in patients with PSM than in those with a negative surgical margin. Multivariate analysis demonstrated that >10 ng/ml prostate-specific antigen at diagnosis ($P=0.024$) and >25% positive core at biopsy ($P=0.041$) were independent prognostic preoperative factors for PSM. The GS of the tumor at the margin was equal, lower and higher than those of the main tumor in 74 (60.7%), 16 (13.1%) and 32 (26.2%) RPs, respectively. The BCR rates were 35.7, 55.1 and 82.1% in patients whose GS of the tumor at the margin was 6, 7 and 8-10, respectively ($P=0.0017$). The GS of the tumor at the PSM ($P=0.038$) and anatomic location of the PSM ($P=0.04$) were identified as independent prognostic preoperative factors for BCR, whereas the GS of the main tumor and margin length were not. These results suggest that documenting the GS at the margin in pathological reports is useful as a predictive factor for BCR.

Introduction

Prostate cancer (PCa) is the most common type of solid neoplasm in males (1). When radical prostatectomy (RP) is selected as a treatment for localized PCa, the prognosis is generally favorable (2). However, postoperative biochemical recurrence (BCR) occurs in 16-31% of patients within 5 years and in 25-53% within 10 years (3-5). Certain cases develop into castration-resistant PCa after clinical recurrence, frequently leading to poor outcomes. Thus, BCR is often used to justify the application of salvage therapies, such as endocrine therapy and radiotherapy.

Certain studies have identified various predictive factors for BCR. BCR after prostatectomy has been associated with multiple factors, including the preoperative prostate-specific antigen (PSA) score, positive surgical margins (PSM), the Gleason score (GS) at prostatectomy and pathological staging. Of these, PSM is the most important predictive factor for BCR (6-13). Certain patients with PSM have favorable prognosis after undergoing surgery alone, while others require salvage therapy immediately after surgery and have poor prognosis (14-16). Therefore, patients with PSM are considered to be a highly diverse group and the significance of PSM after RP remains controversial. This finding suggests the requirement for further subclassification of positive margins to identify patients with an elevated risk of BCR. However, only a small number of studies have reported on predictive factors for PSM and BCR in patients with PSM (17). In addition, studies evaluating the usefulness of the GS of the tumor at the margin in RP are currently scarce.

The present study aimed to investigate the preoperative factors that predict PSM and the significant predictive factors for BCR in cases with PSM. In addition, it was examined whether documenting the GS of the tumor at the margin in pathological reports is useful as a predictive factor for BCR.

Patients and methods

Patients and tissue samples. Patients (n=241) who underwent prostatectomy at Kurume University Hospital (Kurume, Japan) between January 2007 and December 2011 were

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enrolled in the present study. Most of the surgeries during this period were open procedures. Patients who had received preoperative hormone therapy and/or radiation therapy and those with pathological T stage 0 (pT0) were excluded. As a part of this study, the pathological diagnoses of the patients were re-examined. All patients were pathologically diagnosed with prostatic adenocarcinoma. Histopathological evaluations were performed by three pathologists (HK, KU and HY). Pathological diagnosis was made according to the 2016 World Health Organization Classification of Tumors of the Urinary System and Male Genital Organs (18).

The prostatectomy specimens were pinned to a paraffin block and fixed in 10% formalin for a minimum of 48 h and inked on the surface. Paraffin-embedded tissue samples were cut into sections of 4- μ m in thickness and examined on coated glass slides. A positive margin was defined as tumor cells abutting the inked surgical margin of the prostate apex, periphery and bladder neck. The GS of the tumor at the PSM was evaluated at the site in contact with the inked margin; when it was difficult to evaluate the GS at the PSM due to heat denaturation, it was evaluated using the continuous non-denaturing site GS (Fig. 1). PSM length was defined as the total length of the tumor in contact with the inked margin. When multiple PSMs were present, the added length of all margins was calculated.

The present study was approved by the Research Ethics Committee of Kurume University (Kurume, Japan) and conformed to the guidelines of the Declaration of Helsinki.

Statistical analysis. The associations between the margin status and GS of the tumor at the margin and clinicopathological characteristics were examined using the χ^2 test or Fisher's exact test. Cancer survival analysis was performed using the Kaplan-Meier method, log-rank test and Cox's proportional hazards model. The threshold for statistical significance was set at $P < 0.05$. BCR was defined as an increase in PSA level (>0.2 ng/ml) after two different measurements at least 3 months apart. For PSA, 10 ng/ml was used as the cutoff value that was classified as indicative of an intermediate risk in the D'Amico risk classification (7). For the positive core percentage and PSA density, the median was used as the cutoff value. JMP[®] Pro 14 software (SAS Institute, Inc.) was used to perform all statistical analyses.

Results

Association between surgical margin and clinicopathological characteristics. Of the 241 patients who had undergone RP, 122 had at least one PSM. The median follow-up period was 72 months. The characteristics of the entire RP cohort, the subset of patients with PSM and the subset with negative surgical margins (NSM) are provided in Table I. Higher PSA level at diagnosis, GS at prostatectomy and pathological T stage, as well as BCR, were more frequently identified in patients with PSM than in those with NSM (all $P < 0.05$).

Preoperative predictive factors for positive surgical margin in radical prostatectomy. Kaplan-Meier curves demonstrated that the time to BCR was significantly shorter in patients with PSM than in those with NSM (Fig. 2). Univariate and multivariate analyses for preoperative predictive factors for PSM in RP are

presented in Table II. Univariate analysis revealed that >10 ng/ml PSA at diagnosis, PSA density of >0.29 ng/ml/ml, GS at biopsy, clinical T stage, PSA density >0.29 and $>25\%$ positive core at biopsy were significant predictors for PSM. Furthermore, multivariate analysis demonstrated that >10 ng/ml PSA at diagnosis and $>25\%$ positive core at biopsy were independent prognostic preoperative factors for PSM.

Correlation of GS between the tumor at the margin and the main tumor. The GS of the tumor at the margin was 6 in 14 patients (11.5%), 7 in 69 patients (56.6%; 35 with GS 3+4 and 34 with GS 4+3), 8 in 30 patients (24.6%; all with GS 4+4), 9 in 8 patients (6.5%; 6 with GS 4+5 and 2 with GS 5+4) and 10 in 1 patient (0.8%). The GS of the tumor at the margin was equal, lower and higher than that of the main tumor in 74 (60.7%), 16 (13.1%) and 32 (26.2%) RPs, respectively (Table III).

Association of the GS of the positive surgical margin with other variables. The association of the GS of the tumor at the margin and other variables in 122 patients with PSM is presented in Table IV. The GS of the tumor at the margin was highly associated with PSA at diagnosis ($P=0.048$), pathological T stage ($P=0.0445$), the GS of the main tumor ($P < 0.0001$) and BCR ($P=0.0017$). Within a median follow-up of 72 months, BCR was observed in 75 (61.5%) of the 122 patients. The BCR rates were 35.7, 55.1 and 82.1% in patients whose GS of the tumor at the margin was 6, 7 and 8-10, respectively. The difference in recurrence-free survival among these three groups of patients was significant ($P=0.0053$; Fig. 3). In addition, the BCR rates were 52.7, 76.3 and 66.7% in patients whose anatomic locations at the PSM were apex, periphery and bladder neck, respectively. The difference in recurrence-free survival among the three groups (apex, periphery and bladder neck) of patients was also significant ($P=0.0032$; Fig. 4A). Among the 69 patients with GS 7 of the tumor at the margin, no significant difference was observed in recurrence-free survival between those 35 with GS 3+4 and those 34 with GS 4+3 ($P=0.537$; Fig. 4B).

Identification of the GS of the tumor at the margin as a prognostic factor of biochemical recurrence. The results of univariate and multivariate analyses for time to BCR are provided in Table V. Univariate analysis indicated that PSA level at diagnosis, pathological T stage, GS of the main tumor, GS of the tumor at the margin and anatomic location of PSM were strong predictive factors of BCR. On multivariate analysis, the GS of the tumor at the margin ($P=0.038$) and anatomic location of PSM ($P=0.040$) were identified as independent prognostic preoperative factors for BCR, whereas the GS of the main tumor was not ($P=0.661$).

Discussion

To date, several studies have demonstrated the usefulness of the GS of the tumor at the PSM as a predictor of BCR. Cao *et al* (17) indicated that both the GS of the main tumor and that of the tumor at the margin were predictors of BCR. However it was previously suggested that there was a difference between the two factors (17). In the present study, it was demonstrated that the GS of the main tumor is not a prognostic

Table I. Association between surgical margin and clinicopathological characteristics.

Parameter	Total (n=241)	Negative surgical margin (n=119)	Positive surgical margin (n=112)	P-value
Age at diagnosis, years	67 (50-77)	67 (53-77)	67 (50-76)	0.697
PSA level at diagnosis, ng/ml				
Total	7.90 (2.13-62.34)	6.44 (2.13-62.34)	9.42 (3.68-52.65)	0.015
<10	163 (67.6)	95 (79.8)	68 (55.7)	0.011
≥10	78 (32.4)	24 (20.2)	54 (44.3)	
Gleason score at prostatectomy				0.013
6≥	27 (11.2)	20 (16.8)	7 (5.7)	
3+4=7	103 (42.8)	49 (41.2)	54 (44.3)	
4+3=7	75 (31.1)	38 (31.9)	37 (30.3)	
8≤	36 (14.9)	12 (10.1)	24 (19.7)	
pT stage				<0.0001
T2	176 (73.0)	100 (84.0)	76 (62.3)	
T3a	46 (19.1)	15 (12.6)	31 (25.4)	
T3b	19 (7.9)	4 (3.4)	15 (12.3)	
Lymphatic invasion	12 (5.0)	4 (3.4)	8 (6.6)	0.067
Peripheral nerve invasion	111 (46.1)	41 (34.5)	70 (57.4)	0.081
Biochemical recurrence positive	120 (49.8)	45 (37.8)	75 (61.5)	<0.0001

Values are expressed as n (%) or the median (range) for age and total PSA. PSA, prostate-specific antigen.

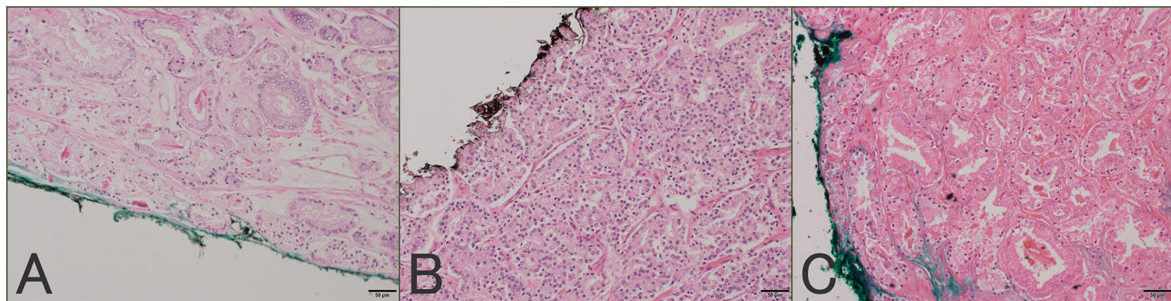


Figure 1. Photomicrographs displaying the GS of the tumor at the margin. (A) GS 3+3=6; (B) GS 4+4=8, (C) GS 3+3=6 heat denaturation. The GS of the tumor at the PSM was evaluated at the site in contact with the inked margin in A and B; when it was difficult to evaluate the GS at the PSM due to heat denaturation, it was evaluated using the continuous non-denaturing site GS in C (scale bars, 50 μ m; H&E). GS, Gleason score; PSM, positive surgical margin.

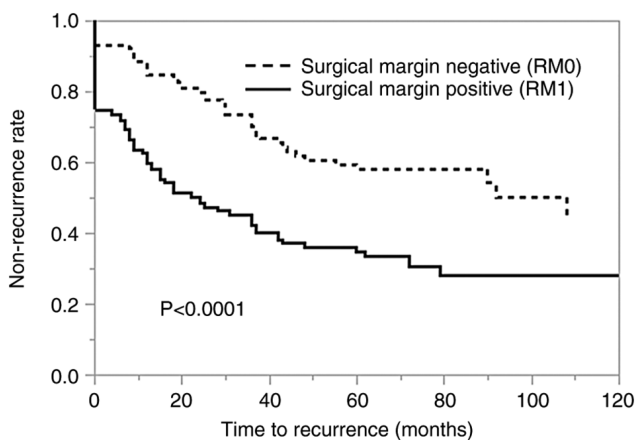


Figure 2. Kaplan-Meier curves for the time to biochemical recurrence compared between patients with positive surgical margin and those with negative surgical margin. RM, resection margin.

factor for BCR, whereas that of the tumor at the PSM is an independent prognostic predictor for BCR on multivariate analysis. This result suggested that GS of the tumor at the PSM is a more important factor than that at the main tumor.

PSM is considered the most significant risk factor for BCR after RP. Stephenson *et al* (19) reported that the PSM was a predictor for BCR based on the result of a multivariate analysis in a large-scale multicenter study involving >7,000 individuals. In addition, Wright *et al* (20) reported that in cases with PSM, the risk of BCR is 3.7 times higher and the risk of PCa-associated death is 1.7 times higher.

Among the predictors of PSM, identifying the preoperative risk factors may prevent BCR through the implementation of more careful surgical manipulation during surgery. Some preoperative factors have been reported previously, as in previous studies, PSA >10 ng/ml and a biopsy-positive rate of >25% were the factors identified in the present study.

Table II. Univariate and multivariate analysis for preoperative predictive factor for positive surgical margin in radical prostatectomy.

Parameter	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age at diagnosis, >67 years	1.05 (0.63-1.74)	0.857	1.04 (0.71-1.52)	0.840
PSA level at diagnosis, >10 ng/ml	3.14 (1.77-5.57)	<0.0001	2.28 (1.11-3.89)	0.024
CRP, mg/l	0.76 (0.37-1.58)	0.455	1.09 (0.65-1.81)	0.745
NLR, >1.58	1.67 (0.96-2.91)	0.069	1.22 (0.79-1.89)	0.368
Gleason score at biopsy				
6 \geq	1	0.0482	1	0.739
3+4=7	1.82 (0.96-3.44)		1.16 (0.73-1.84)	
4+3=7	1.22 (0.53-2.83)		1.21 (0.46-1.46)	
8 \leq	2.40 (1.18-4.88)		1.31 (0.61-1.83)	
Clinical T stage				
T2	1	0.017	1	0.425
T3a	2.01 (1.20-3.37)		1.77 (0.23-13.5)	
T3b	4.20 (0.42-41.5)		1.90 (0.28-18.6)	
PSA density >0.29 ng/ml/ml	2.81 (1.67-4.74)	<0.0001	1.48 (0.93-2.35)	0.103
Positive core at biopsy, >25%	2.16 (1.28-3.65)	0.0035	1.42 (0.96-2.10)	0.041

PSA, prostate-specific antigen; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; CI, confidence interval.

Table III. Correlation of GS between the tumor at the margin and the main tumor.

GS of the main tumor	GS of the tumor at the margin					Total
	6	7	8	9	10	
6	7	0	0	0	0	7
7	6	66	19	0	0	91
8	1	2	11	0	0	14
9	0	1	0	8	0	9
10	0	0	0	0	1	1
Total	14	72	30	8	1	122

Values are expressed as the number of patients. GS, Gleason score.

Preston *et al* (21) reported that among patients with localized PCa with a PSM, the disease-free survival in extraprostatic extension (EPE)+ patients with a negative resection margin was short. The importance of determining the appropriate dissection layer and resection site was confirmed. In the present study, the biochemical non-recurrent survival curves of 122 patients with PSM and 119 with NSM were compared and the incidence of BCR was indicated to be significantly higher in those with PSM.

The frequency of progression to clinical recurrence from BCR without treatment was 34% (22). In addition, hormone and radiation therapy were performed as salvage therapy for BCR. For radiotherapy in particular, improvement in cancer-specific survival has been reported (23,24). The results of the EORTC22911 trial reported improved clinical progression in

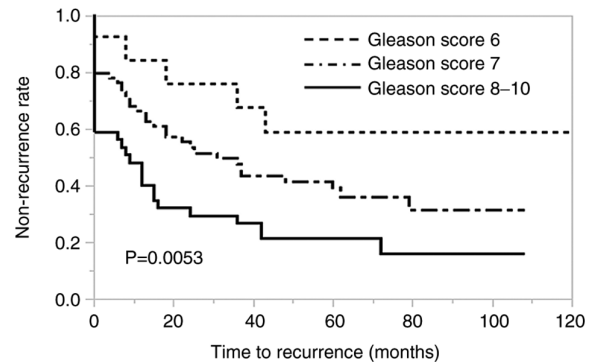


Figure 3. Kaplan-Meier curves for the time to biochemical recurrence stratified by the Gleason score of the tumor at the positive surgical margin.

the postoperative adjuvant radiotherapy group over a follow-up period of >5 years after RP (25). Furthermore, to identify the factors related to the effects of postoperative adjuvant radiotherapy, GS, seminal vesicular infiltration, pT stage, EPE and PSM were re-examined using isolated RP specimens of 522 individuals (26). They reported that only PSM was a prognostic factor. With this background, the present study examined risk factors for the purpose of extracting the PSM cases, particularly those that were highly likely to have BCR.

GS is generally used as an indicator of the grade of histopathological malignancy. GS in isolated specimens, in particular, exhibits a more accurate malignancy grade (7). Resnick *et al* (27) reported that GS in the excised specimen is a risk factor for BCR, even in PSM cases. In recent years, certain studies have reported that the GS of the tumor at the PSM is also a predictor for BCR (28,29). Udo *et al* (30) reported that the incidence of BCR

Table IV. Association of the GS of the positive surgical margin with other variables in the cohort (n=122).

Parameter	GS of 6 at the margin (n=14)	GS of 7 at the margin (n=69)	GS of 8-10 at the margin (n=39)	P-value
Age at diagnosis, years	68 (55-76)	67 (50-75)	63 (53-75)	0.216
PSA level at diagnosis, ng/ml	7.0 (4.16-16.5)	9.41 (4.05-52.6)	10.4 (3.68-50.1)	0.048
Pathological stage				0.0445
T2	13	40	23	
T3a	1	21	9	
T3b	0	8	7	
GS of the main tumor				<0.0001
6	7	0	0	
7	6	66	19	
8	1	3	20	
Biochemical recurrence	5 (35.7)	38 (55.1)	32 (82.1)	0.0017
Median FU time, months	58	69	72	0.081

Values are expressed as n, n (%) or the median (range) for age and total PSA. GS, Gleason score; RP, radical prostatectomy; PSA, prostate-specific antigen; FU, follow-up.

Table V. Univariate and multivariate analysis for time to biochemical recurrence.

Parameter	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at diagnosis >67 years	1.04 (0.99-1.08)	0.056	1.03 (0.99-1.09)	0.099
PSA level at diagnosis >10 ng/ml	1.02 (1.00-1.04)	0.026	2.61 (0.93-8.23)	0.063
Pathological T stage				
T2	1		1	
T3a	1.36 (0.78-2.29)	0.265	1.32 (0.68-2.56)	0.210
T3b	2.44 (1.21-4.55)	0.014	1.51 (0.63-3.63)	0.130
GS of the main tumor				
6	1		1	
7	3.09 (0.96-18.9)	0.137	2.22 (0.35-2.86)	0.678
8-10	5.15 (1.47-32.5)	0.029	1.94 (0.49-3.62)	0.661
GS of the tumor at the PSM				
6	1		1	
7	1.92 (0.82-5.58)	0.137	1.15 (0.36-3.98)	0.124
8-10	3.29 (1.39-9.66)	0.005	1.78 (0.43-5.22)	0.038
Linear length of tumor at the margin, >3 mm	1.31 (0.89-1.17)	0.656	1.08 (0.91-1.25)	0.359
Anatomic location of the positive margin				
Apex	1		1	
Periphery	2.12 (1.28-3.45)	0.003	2.24 (1.16-4.30)	0.040
Bladder neck	1.84 (0.79-3.77)	0.118	1.19 (0.47-3.06)	0.115

PSA, prostate-specific antigen; GS, Gleason score; PSM, positive surgical margin; HR, hazard ratio; CI, confidence interval.

increases when the PSM site contains Gleason grade 4 or higher tissues. In particular, cases with Gleason grade 4 tumors at the PSM have more BCRs than those with only grade 3 tumors (31).

In ~40% of the present cases, the GS of the tumor at the margin was different from that of the main tumor (lower in 13.1%

and higher in 26.2% of cases). The multivariate analysis indicated that the GS of the main tumor was not a prognostic factor for BCR, whereas that of the tumor at the PSM was an independent prognostic predictor for BCR. In addition, the GS at the site of a positive margin was significantly associated with the PSA value

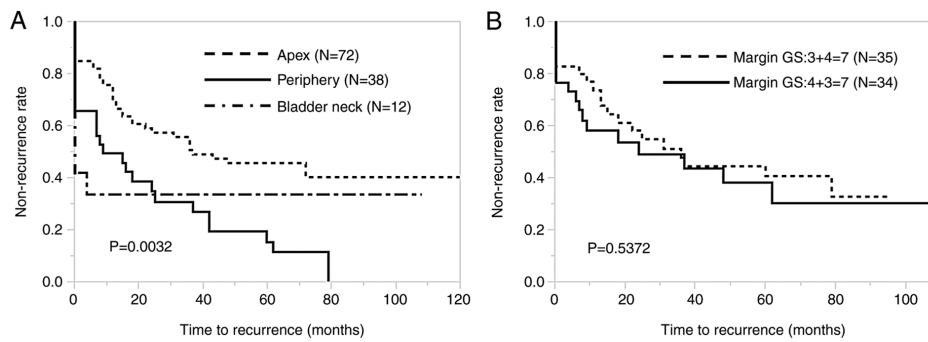


Figure 4. Kaplan-Meier curves for the time to biochemical recurrence stratified by (A) the anatomic location at the margin and (B) between patients with GS 3+4 and those with GS 4+3 at the positive surgical margin. GS, Gleason score.

and pT stage. The higher the GS at the positive margin, the earlier the BCR was observed. Evaluation of the GS of the tumor at the margin may be difficult; however, as no significant difference was observed in BCR-free survival between patients whose tumor at the margin had GS 3+4=7 and those whose tumor at the margin had GS 4+3=7, the GS of the tumor at the positive margin was simply classified into stages 6, 7 and 8 or more.

In addition, a positive margin site is more common in the apex of the tumor (32); in the present study, of all patients with a PSM, ~60% had a positive margin at the apex, which is almost equivalent to the proportion reported in a previous study (32). In the present study of positive sites, BCR occurred significantly earlier in patients with positive margins located laterally than in those with positive margins in the apex and bladder neck sites. PSM located laterally was an independent prognostic predictor of BCR in PSM cases alongside GS at the PSM. This finding demonstrated that documenting the GS of the tumor at the positive margin and at the PSM in the pathology report may accurately identify the presence of BCR.

According to the margin length, Marks *et al* (33) reported no significant difference between the extent of PSM and BCR. By contrast, Cao *et al* (34) indicated that the linear length of a PSM was an independent prognostic factor for BCR in stage pT2 cancers. Certain studies have reported a standard linear PSM length of 1 mm, while others have reported a standard length of 3 mm; the impact of the PSM length is still under debate. From the viewpoint of pathologists, measuring the length of multiple positive sites is time-consuming and labor-intensive. Even in the present study, the length of the positive margin site was not a predictor for BCR.

Several limitations of the present study should be acknowledged. First, in this study, PSM was present in 122/241 patients and this proportion is high. The reasons for this may be that about one-third of these cases were at high-risk according to the D'Amico classification and that most of the surgical procedures were open surgeries. Further studies on other surgical procedures (endoscopic/robot-assisted surgery) are required. Furthermore, the length of the tumor was evaluated; however, the width of the tumor was not considered when evaluating the GS of the tumor at the margin in the present study. At our hospital, the width is unified at 3.5 mm according to Japanese guidelines (35). As the width of all specimens was almost the same, the width was not considered in the present study.

In conclusion, the present study suggested that the GS of the tumor at the PSM in RP is a more significant prognostic

factor for BCR than the GS of the main tumor. For a PSM in RP, the GS of the tumor at the margin must be documented, in addition to the anatomic location.

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Availability of data and materials

The datasets used and/or analysis during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HK, KU, MM, SS and TI designed the study. HK, NO, KC, MN and KN performed the research. HK, JA and HY contributed to the pathological analysis. HK analyzed the data and wrote the manuscript. MM, SS, and TI agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated. HK and KU checked and approved the authenticity of the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics committee at Kurume University (Kurume, Japan). The Ethics Committee waived the requirement for obtaining written informed consent for the cases as the data of these patients were retrospectively analyzed.

Patient consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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