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Research Article

Factors affecting biochemical recurrence of prostate cancer after radical prostatectomy in patients with positive and negative surgical margin

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ABSTRACT

Purpose: To investigate the clinical and pathological predictive factors affecting biochemical recurrence (BCR) after radical prostatectomy (RP) in patients with positive and negative surgical margin (SM).
Methods: Patients who underwent RP were retrospectively reviewed for the study. Demographic, clinical, pathological and oncological data were evaluated. All data were compared between patients with positive SM and negative SM to detect factors associated with SM status. Later, patients were divided into two groups as BCR-negative and BCR-positive groups. Data were separately compared between BCR groups for all patients, SM-negative and SM-positive patients, respectively.
Results: A total of 254 patients with a mean age of 63.5 years and the mean prostate-specific antigen of 10.9 ng/ml were evaluated in the study. SM positivity was found to be an independent prognostic factor for BCR ($p = 0.013$, Odds Ratio (OR): 0.267, 95% Confidence Interval (CI): 0.094-0.755). In SM-positive patients, biopsy Gleason Score and International Society of Urological Pathology grade were found to be independent predictive factors for BCR ($p < 0.05$). However, only tumor to SM distance (TSMD) was found to be an independent risk factor for BCR ($p = 0.024$) in SM-negative patients. The predictive cutoff value of the TSMD was found to be 75 μm for BCR (100% sensitivity and 63.9% specificity) (AUC = 0.803, $p = 0.024$). Although all of 46 patients with >75 μm TSMD were recurrence free, 5 of 31 patients with <75 μm TSMD had BCR ($p = 0.009$; OR: 0.839 CI: 0.719–0.979).
Conclusion: High Gleason Score and International Society of Urological Pathology grade of biopsy were found to be associated with BCR in SM-positive patients. For SM-negative patients, only TSMD was found to be associated with BCR after RP.

1. Introduction

Prostate cancer (PCa) is the most common malignancy and is the second cause of cancer-related deaths among men.[1] However, most patients are diagnosed with localized PCa. In the treatment of localized PCa, active surveillance, watchful waiting, radical prostatectomy (RP) or radiotherapy (RT) can be recommended based on life expectancy and risk status of the patients.[2] Among the treatment modalities, RP shows significant cancer-specific survival benefit in patients with clinically localized PCa.[3] However, biochemical recurrence (BCR) develops in nearly 30% of patients after surgery.[4] In these patients with BCR after surgery, unfavorable pathological features are seen as possible predictive factors for BCR. Among these pathological features, surgical margin (SM) positivity is one of the most important factors for BCR and for adjuvant radiotherapy decisions after surgery. However, BCR can be observed in SM-negative patients. In these patients, other unfavorable pathological features, especially high T stage and Gleason Score (GS), can be more important predictive factors for BCR.[5]

Therefore, in this study, we aimed to investigate the clinical and pathological predictive factors affecting BCR after surgery in SM-positive and SM-negative patients who underwent RP due to clinically localized PCa.

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2. Materials and methods

Patients who underwent RP due to clinically localized PCa in our referral center were retrospectively reviewed for the study. Among these, patients with clinical, pathological and oncological data were included in the study. Demographic data, prostate-specific antigen (PSA) value, clinical stage, prostate needle biopsy (biopsy GS, International Society of Urological Pathology (ISUP) grade, number of positive core and percentage of tumor), RP pathological data (RP GS, ISUP grade, extraprostatic extension (EPE), seminal vesicle invasion (SVI), perineural invasion, lymphovascular invasion, SM positivity, tumor volume, tumor density, lymph node positivity, and tumor to SM distance [TSMD]) and oncological data (adjuvant treatment and BCR) were evaluated. TSMD was measured from the site closest from the margin regardless of multifocality or location.

Patients were divided into two groups as BCR negative (Group 1) and BCR positive (Group 2) in accordance with the increase from the nadir to >0.2 ng/ml PSA level in serial measurements after RP. Positive BCR was defined as a PSA level of >0.2 ng/mL, two values at 0.2 ng/mL, or secondary treatment for elevated PSA level in the present study. All data were compared between Group 1 and Group 2. In addition, recurrence-free survival of the groups was evaluated. In accordance with SM status, patients were divided into two groups as SM negative and SM positive, and all data were compared between the groups. Then, patients were evaluated in the two subgroups as SM negative and SM positive. Data from the SM-positive and SM-negative groups were compared between Group 1 and Group 2 in accordance with BCR status, separately. Data detected as significant after the analysis were also evaluated by receiver operating characteristic (ROC) curve analysis to determine cutoff value and sensitivity and specificity ratios.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.1. Statistical analysis

Data of all patients were compared between BCR-negative and BCR-positive groups, then between SM-negative and SM-positive groups by using the Mann–Whitney U test and Pearson χ^2 test analyses. In addition, the data from the SM-positive and SM-negative patient groups were comparatively evaluated between BCR-negative and BCR-positive groups separately with the Mann–Whitney U test and Pearson χ^2 test. For significant data after univariate analysis, logistic regression analysis was performed to detect independent predictive factors. In addition, all patients were assessed with Kaplan–Maier survival analysis and log rank test in accordance with SM status to research recurrence-free survival. ROC curve analysis was performed to determine cutoff value and sensitivity and specificity ratios. For statistical analysis, the Statistical Package for the Social Sciences (SPSS, version 20.0; SPSS, Chicago, III) was used, and a p value $\leq$ 0.05 was accepted as significant.

3. Results

A total of 260 patients who had complete clinical and pathological data were evaluated. Among these, 254 patients with known BCR status were included in the study. Mean age and PSA of all patients were 63.5 years and 10.9 ng/ml. Patients were divided into two groups as BCR negative (−) (Group 1) and BCR positive (+)

Table 1
Analysis results of demographic, clinical, and pathological findings between Group 1 (BCR negative) and Group 2 (BCR positive) in all patients.

All patients		Group 1 (BCR negative) (n = 223)	Group 2 (BCR positive) (n = 31)	p*
Age (year)		63.4 ± 5.9 (45–84)	63.7 ± 6.5 (48–78)	0.759
PSA (ng/ml)		10.8 ± 11.4 (1.4–100)	11.1 ± 7.5 (3.4–34)	0.922
Clinical T stage, n (%)	T1c	134 (60.1)	12 (38.7)	0.078
	T2a	59 (26.5)	15 (48.4)	
	T2b	18 (8.1)	2 (6.5)	
	T2c–T3	12 (5.4)	2 (6.5)	
Prostate biopsy GS		6.4 ± 0.65 (6–9)	6.9 ± 0.82 (6–9)	**0.008**
Prostate biopsy positive core number		1.9 ± 2.1 (1–14)	2.1 ± 2.1 (1–9)	0.703
Percentage of tumor in positive cores		29 ± 25.3 (5–100)	42.9 ± 29.7 (5–90)	**0.041**
Prostate biopsy ISUP grade, n (%) (n = 252)	1	142 (65.7)	11 (36.7)	**0.001**
	2	39 (18.1)	7 (23.3)	
	3	16 (7.4)	6 (20)	
	4	18 (8.3)	5 (16.7)	
	5	1 (0.5)	1 (3.3)	
RP GS		6.85 ± 0.9 (6–9)	7.4 ± 1 (6–9)	**0.004**
RP ISUP grade, n (%)	1	87 (39)	7 (22.6)	**0.002**
	2	66 (29.6)	4 (12.9)	
	3	27 (12.1)	6 (19.4)	
	4	23 (10.3)	8 (25.8)	
	5	16 (7.2)	5 (16.1)	
EPE, n (%)		54 (24.2)	13 (43.3)	**0.026**
SVI, n (%)		23 (10.3)	8 (27.6)	**0.008**
PNI, n (%)		31 (13.9)	6 (20)	0.393
LVI, n (%)		4 (1.8)	1 (3.4)	0.463
SM positivity, n (%)		64 (28.8)	18 (58.1)	**0.001**
Tumor volume (cc)		3.8 ± 4.4 (0.04–24)	5.7 ± 6.2 (0.08–23)	0.253
Tumor density		10.7 ± 13.3 (0.02–90)	15.9 ± 14.6 (0.3–51.8)	0.063
LN positivity, n (%)		5 (3.7)	4 (12.9)	**0.014**
Adjuvant RT, n (%)		35 (15.7)	10 (32.3)	0.432

BCR = biochemical recurrence, PSA = prostate-specific antigen, GS = Gleason score, ISUP = International Society of Urological Pathology, RP = radical prostatectomy, EPE = extraprostatic extension, SVI = seminal vesicle invasion, PNI = perineural invasion, LVI = lymphovascular invasion, SM = surgical margin, LN = lymph node, RT = radiotherapy.
Significant p values were given as bold.
* Mann–Whitney U test and Pearson χ^2 test were used.

Table 2
Analysis of demographic, clinical, and pathological findings between negative and positive SM patients.

All patients		Negative SM (n = 171)	Positive SM (n = 83)	p*
Age (year)		62.9 ± 6.1 (45–75)	64.6 ± 5.6 (50–84)	0.084
PSA (ng/ml)		9.7 ± 8.3 (1.4–60)	13.3 ± 14.9 (2.9–100)	0.01
Clinical T stage, n (%)	T1c	106 (62)	40 (48.2)	0.2
	T2a	44 (25.7)	30 (36.1)	
	T2b	13 (7.6)	7 (8.4)	
	T2c–T3	8 (4.7)	6 (7.2)	
Prostate biopsy GS		6.3 ± 0.59 (6–8)	6.8 ± 0.8 (6–9)	**<0.001**
Prostate biopsy positive core number		1.6 ± 1.6 (1–14)	2.6 ± 2.6 (1–12)	**0.004**
Percentage of tumor in positive cores		23.9 ± 23.4 (5–90)	42.8 ± 26.6 (5–100)	**<0.001**
Prostate biopsy ISUP grade, n (%) (n = 252)	1	121 (70.8)	32 (38.6)	**<0.001**
	2	27 (15.8)	19 (22.9)	
	3	10 (5.8)	12 (14.5)	
	4	10 (5.8)	13 (15.7)	
	5	0 (0)	2 (2.4)	
RP GS		6.7 ± 0.8 (6–9)	7.4 ± 1 (6–9)	**<0.001**
RP ISUP grade, n (%)	1	82 (47.9)	17 (20.5)	**<0.001**
	2	50 (29.2)	20 (24.1)	
	3	18 (10.5)	15 (18.1)	
	4	16 (9.4)	15 (18.1)	
	5	5 (2.9)	16 (19.3)	
EPE, n (%)		13 (7.6)	54 (65.1)	**<0.001**
SVI, n (%)		3 (1.8)	28 (33.7)	**<0.001**
Tumor volume (cc)		3 ± 3.2 (0.04–17.5)	6.6 ± 6.5 (0.08–24)	**<0.001**
Tumor density		8 ± 9.7 (0.02–60)	18.2 ± 17.1 (0.4–90)	**<0.001**
LN positivity, n (%)		0 (0)	9 (10.8)	**<0.001**
BCR, n (%)		13 (7.6)	18 (21.7)	**<0.001**
Adjuvant RT, n (%)		5 (2.9)	40 (48.2)	**<0.001**

SM = surgical margin, PSA = prostate-specific antigen, GS = Gleason score, ISUP = International Society of Urological Pathology, RP = radical prostatectomy, EPE = extraprostatic extension, SVI = seminal vesicle invasion, LN = lymph node, BCR = biochemical recurrence, RT = radiotherapy.
Significant p values were given as bold.
* Mann–Whitney U test and Pearson χ^2 test were used.

(Group 2). In the groups, there were 223 and 31 patients in Group 1 and Group 2, respectively. Analysis results of demographic, clinical, and pathological findings between Group 1 and Group 2 for all patients are given in Table 1. For preoperative predictive factors for

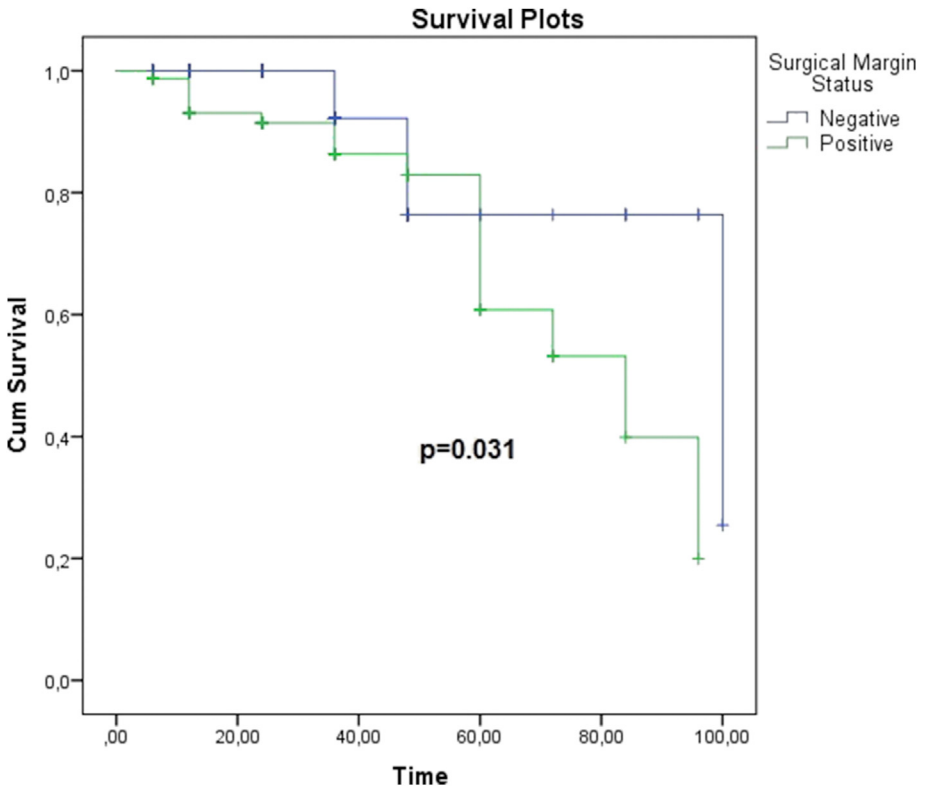

Fig. 1. Kaplan–Meier survival plots for recurrence-free survivals of SM-positive and SM-negative patients.

Table 3
Analysis results of demographic, clinical, and pathological findings between Group 1 (BCR negative) and Group 2 (BCR positive) in SM-positive patients.

SM-positive patients		Group 1 (BCR negative) (n = 65)	Group 2 (BCR positive) (n = 18)	p
Age (year)		64.6 ± 5.5 (50–84)	64.6 ± 6.4 (54–78)	0.948
PSA (ng/ml)		14.1 ± 16.6 (2.9–100)	10.3 ± 4.9 (4.1–19.4)	0.976
Clinical T stage, n (%)	T1c	33 (50.8)	7 (38.9)	0.769
	T2a	22 (33.8)	8 (44.4)	
	T2b	5 (7.7)	2 (11.1)	
	T2c–T3	5 (7.7)	1 (5.6)	
Prostate biopsy GS		6.7 ± 0.75 (6–9)	7.2 ± 0.83 (6–9)	**0.01**
Prostate biopsy positive core number		2.7 ± 2.6 (1–12)	2.4 ± 2.5 (1–9)	0.426
Percentage of tumor in positive core		40.7 ± 26.2 (5–100)	49.5 ± 28 (10–90)	0.313
Prostate biopsy ISUP grade, n (%)	1	29 (44.6)	3 (17.6)	**0.005**
	2	16 (24.6)	3 (17.6)	
	3	7 (10.8)	5 (29.4)	
	4	8 (12.3)	5 (29.4)	
	5	1 (1.5)	1 (5.9)	
RP GS		7.3 ± 1 (6–9)	7.7 ± 1 (6–9)	0.082
RP ISUP grade, n (%)	1	15 (23.1)	2 (11.1)	**0.031**
	2	19 (29.2)	1 (5.6)	
	3	10 (15.41)	5 (27.8)	
	4	10 (15.4)	5 (27.8)	
	5	11 (16.9)	5 (27.8)	
EPE, n (%)		42 (64.6)	12 (66.7)	0.553
SVI, n (%)		21 (32.3)	7 (38.9)	0.415
PNI, n (%)		9 (13.8)	5 (27.8)	0.172
LVI, n (%)		4 (6.2)	1 (5.6)	0.693
Tumor volume (cc)		6.3 ± 6.4 (0.7–24)	7.5 ± 7 (0.1–23)	0.635
Tumor density		17.7 ± 18 (0.4–90)	20.2 ± 13.2 (1.3–47)	0.237
LN positivity, n (%)		5 (7.7)	4 (22.2)	0.127
Adjuvant RT, n (%)		31 (47.7)	9 (50)	0.450

BCR = biochemical recurrence, PSA = prostate-specific antigen, GS = Gleason score, ISUP = International Society of Urological Pathology, RP = radical prostatectomy, EPE = extraprostatic extension, SVI = seminal vesicle invasion, PNI = perineural invasion, LVI = lymphovascular invasion, LN = lymphnode, RT = radiotherapy.
Mann–Whitney U test and Pearson χ^2 test were used.
Significant p values were given as bold.

BCR, although biopsy GS, percentage of tumor in positive cores, and prostate biopsy ISUP grade were statistically significant in univariate analysis, none of them were significant predictors after multivariate regression analysis (p values were 0.920, 0.655, and 0.125 in logistic regression analysis; respectively). In postoperative data, only SM positivity was an independent risk factor for BCR after multivariate analysis among the data detected as significant with univariate analysis (Logistic regression analysis results: RP GS (p = 0.364), RP ISUP grade (p = 0.373), EPE (p = 0.190), SVI (p = 0.657), SM positivity (p = 0.013, OR: 0.267 CI: 0.094–0.755) and LN positivity (p = 0.133)). Patients were divided into subgroups as SM positive and SM negative based on the SM status in the RP specimen. Comparison results of the data between the subgroups are given in Table 2. In accordance with this, biopsy GS, ISUP grade, positive core number, and percentage of tumor were found to be associated with SM positivity after RP. In addition, all postoperative prognostic factors were associated with SM status. In addition, in the Kaplan–Maier analysis, mean BCR-free survivals were found to be 86.8 ± 3.7 (79.5–94.1) months and 72.8 ± 4.7 (63.6–82.1) months for the SM-negative and SM-positive patients, respectively, (p = 0.031) (Fig. 1). Then, subgroups of the SM-positive and SM-negative patients were separately evaluated for BCR status.

In the evaluation of SM-positive patients, there were 83 patients in the SM-positive subgroup. Based on BCR status, 65 of 83 patients were evaluated in Group 1 (BCR negative) and 18 of 83 patients were evaluated in the Group 2 (BCR positive). Univariate analysis results of demographic, clinical, and pathological findings between Group 1 and Group 2 for SM-positive patients are given in Table 3. Prostate biopsy GS (p = 0.014, OR: 2.404, CI: 1.194–4.840) and prostate biopsy ISUP grade (p = 0.007, OR: 1.881, CI: 1.185–2.984) were found to be independent predictive factors for BCR among preoperative factors (Table 4). However, all of the postoperative factors were seen to be not a risk factor for BCR (logistic regression analysis for RP ISUP grade p = 0.063, OR: 0.116, CI: 0.012–1.123).

In the evaluation of SM-negative patients, there were 171 patients in the SM-negative subgroup. Among these, 158 were in Group 1 and 13 were in Group 2. Analysis results of demographic, clinical, and pathological findings between Group 1 and Group 2 for SM-negative patients are given in Table 5. Of all data, only TSMD was found to be an independent risk factor for BCR (for Group 1 and 2: the TSMD were 331.3 ± 483.4 vs 36 ± 19.5 [p = 0.024], respectively). There were only 77 of 171 patients who had known TSMD data. In ROC curve analysis of TSMD, the predictive cutoff value was found to be 75 μm for BCR (AUC = 0.803, p = 0.024) (Fig. 2). The sensitivity and specificity levels of the cutoff value were 100% and 63.9%, respectively. In the 77 patients with TSMD data, 46 had >75 μm distance and 31 had <75 μm distance. In 46 patients with >75 μm distance, all of them were recurrence free. However, in 31 patients with <75 μm distance, BCR was observed in 5 patients (p = 0.009; OR: 0.839 CI: 0.719–0.979).

4. Discussion

In summary of our results, SM positivity was found to be an independent predictive factor for BCR after RP in all patients. In SM-positive patients, GS and ISUP grade of prostate biopsy were found to be associated with BCR. In SM-negative patients, only TSMD was an independent predictive factor for BCR. The predictive threshold of TSMD was detected as 75 μm (100% sensitivity and 63.9% specificity). Although BCR was observed in 16.1% of patients with <75 μm distance, there is no BCR in patients with >75 μm distance.

RP is the standard first-line treatment modality in eligible patients with localized PCa (especially in intermediate and high risk patients).[6] However, BCR was reported in approximately 25–35%

Table 4
Multivariate analysis results of the factors on BCR in SM-positive patients.

Factors	p value	Odds Ratio (OR)	95% Confidence Interval (CI)
Prostate biopsy GS	**0.014**	**2.404**	**1.194–4.840**
Prostate biopsy ISUP grade	**0.007**	**1.881**	**1.185–2.984**
RP ISUP grade	0.063	0.116	0.012–1.123

GS = Gleason score, ISUP = International Society of Urological Pathology, RP = radical prostatectomy.
Logistic regression analysis was used.
Significant p values were given as bold.

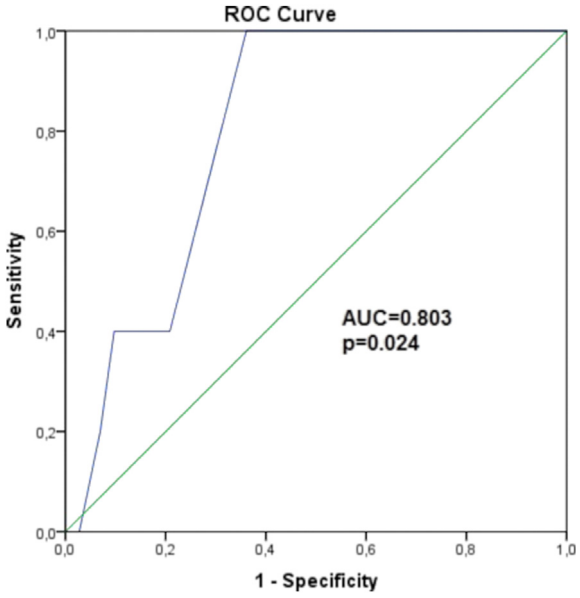

Fig. 2. Receiver operating characteristic (ROC) curve analysis of TSMD.

patients after RP.[7] For these patients the necessity for adjuvant treatment is raised because of metastasis.[8,9] Previously, many nomograms were created for prediction of BCR after RP and prognostic factors were defined in these predictive nomograms. The most commonly used factors in the nomograms are preoperative PSA level, pathological T stage, and pathological GS.[10-12] Based on these factors, D'Amico risk stratification and Cancer of the Prostate Risk Assessment scores were adopted to predict BCR.[9,13] In addition, six predictive pathological features for BCR were determined by Liu et al.[14] after their meta-analysis report. They stated that SVI, SM positivity, EPE, lymphovascular invasion, LN positivity, and perineural invasion were statistically significant factors for recurrence-free survival after RP (all significant at the level of $p < 0.001$). At this point, several reports show positive SM is an important prognostic factor that can affect BCR, recurrence-free survival, and related adjuvant therapy after RP.[8,15-18] SM positivity is also related to unfavorable pathological characteristics (including EPE, SVI, high pathological T stage, and postoperative detectable PSA level). In addition, high GS on RP is a more important predictive factor compared to pathological T stage after RP in patients with positive SM.[5] In the present study, we evaluated the effect of SM status on BCR after RP and the additional predictive factors in both SM-negative and SM-positive patients. We detected that there is a high

Table 5
Analysis results of demographic, clinical, and pathological findings between Group 1 (BCR negative) and Group 2 (BCR positive) in SM-negative patients.

SM-negative patients		Group 1 (BCR negative) (n = 158)	Group 1 (BCR positive) (n = 13)	p
Age (year)		62.9 ± 6 (45–75)	62.5 ± 6.7 (48–74)	0.856
PSA (ng/ml)		9.5 ± 8.2 (1.4–60)	12.1 ± 10.3 (3.43–34)	0.948
Clinical T stage, n (%)	T1c	101 (63.9)	5 (38.5)	0.074
	T2a	37 (23.4)	7 (53.8)	
	T2b	13 (8.2)	0 (0)	
	T2c–T3	7 (4.4)	1 (7.7)	
Prostate biopsy GS		6.3 ± 0.6 (6–8)	6.4 ± 0.5 (6–7)	0.498
Number of positive core		1.6 ± 1.6 (1–14)	1.5 ± 0.5 (1–2)	0.326
Percentage of tumor in positive core		23.3 ± 22.9 (5–90)	30.8 ± 31.5 (5–80)	0.652
Biopsy ISUP grade, n (%)	1	113 (71.5)	8 (61.5)	0.389
	2	23 (14.6)	4 (30.8)	
	3	9 (5.7)	1 (7.7)	
	4	10 (6.3)	0 (0)	
	5	0 (0)	0 (0)	
RP GS		6.7 ± 0.8 (6–9)	6.8 ± 0.8 (6–8)	0.496
RP ISUP grade, n (%)	1	72 (45.6)	5 (38.5)	0.446
	2	47 (29.7)	3 (23.1)	
	3	17 (10.8)	1 (7.7)	
	4	13 (8.2)	3 (23.1)	
	5	5 (3.2)	0 (0)	
EPE, n (%)		12 (7.6)	1 (7.7)	0.687
SVI, n (%)		2 (1.3)	1 (7.7)	0.185
PNI, n (%)		22 (13.9)	1 (7.7)	0.497
LVI, n (%)		0 (0)	0 (0)	–
TSMD (μm)		331.3 ± 483.4 (1–2500)	36 ± 19.5 (10–50)	**0.024**
Tumor volume (cc)		3 ± 3.3 (0.04–17.5)	2.6 ± 2.8 (0.1–8.5)	0.777
Tumor density		7.8 ± 9.2 (0.02–60)	10.5 ± 14.9 (0.3–51.8)	0.799
LN positivity, n (%)		0 (0)	0 (0)	–
Adjuvant RT, n (%)		4 (2.5)	1 (7.7)	0.511

BCR = biochemical recurrence, PSA = prostate-specific antigen, GS = Gleason score, ISUP = International Society of Urological Pathology, RP = radical prostatectomy, EPE = extraprostatic extension, SVI = seminal vesicle invasion, PNI = perineural invasion, LVI = lymphovascular invasion, TSMD = tumor to SM distance, LN = lymphnode, RT = radiotherapy.
Significant p values were given as bold.
*Mann–Whitney U test and Pearson χ^2 test were used.

relationship between positive SM and BCR after RP. BCR-free survival was significantly lower in patients with positive SM compared with those with negative SM ($p = 0.031$). In addition, positive SM was found to be associated with unfavorable pathological outcomes in both biopsy and RP specimens, similar to the literature.

Positive SM occurs in the range of 6–45.7% and is associated with a >70% risk of BCR after RP in a lot of series.[18–24] However, our BCR rate for SM-positive patients was 21.7%. Although this rate was lower than the previous studies, adjuvant RT rate was found to be 48.2% in this group. When we look at the facts aforementioned, while the effect of positive SM on BCR is clearly defined, definitive prognostic factors related to positive SM are not clear because of detection of several factors associated with BCR in previous studies. Therefore, we additionally evaluated the factors affecting BCR in the subgroup of SM-positive patients. High prostate biopsy GS and high ISUP grade were found to be independently associated with BCR after RP similar to the previous study reported by Roux et al.[5] In addition, based on the recent reports, detected high GS/ISUP grade at the positive SM has been stated as another important predictive factor for BCR after RP.[25] We did not evaluate the GS at the positive margin. However, high tumor grade has been a possible predictive factor in univariate analysis regardless the evaluation of tumor grade at SM in our cohort.

When we evaluated the prognostic value of TSMD for BCR, distance of tumor from the SM was defined as close to SM in the studies, while we refer to it as TSMD.[26] In different studies, the various thresholds for TSMD were previously defined as <0.1 mm and <1 mm. In one of those, Izard et al.[27] reported that TSMD of <0.1 mm was an independent predictive and prognostic factor for BCR during 25 months follow-up and that patients with <0.1 mm distance were not statistically different from patients with positive SM. In another study, Lu et al.[17] concluded that BCR was significantly higher in patients with <0.1 mm TSMD than in patients with negative SM (39% vs 21%). In two recently published studies, the distance of <1 mm was defined and evaluated as close to SM.[15,26] Despite the threshold of TSMD increasing to 1 mm from 0.1 mm, the significant correlation between BCR and close SM was still found to be present. Herforth et al.[26] reported that close SM can be a prognostic factor for choosing adjuvant therapy in patients with negative SM. In their study, patients with close SM and positive SM had higher rates of BCR than patients with negative SM (hazard ratio (HR): 1.51, $p < 0.001$ for close SM and HR: 2.09, $p < 0.001$ for positive SM), respectively.[26] In the study, patients with close SM and negative SM were evaluated in separate groups. However, close SM status was previously described as pathologically SM 'negative'.[28–30] Therefore, TSMD was evaluated only in the SM negative group in our study. In accordance with our results, TSMD was an independent prognostic factor for BCR in the subgroup analysis of SM-negative patients. In this analysis, the predictive threshold of the TSMD was found to be 75 μm with high rates of sensitivity and specificity (100% and 63.9%). In accordance with the threshold of 75 μm, there were 16.1% and 0% BCR in patients with <75 μm and >75 μm distance, respectively, ($p = 0.009$; OR: 0.839 CI: 0.719–0.979). Therefore, SM-negative patients with TSMD <75 μm may have a higher risk of BCR than others. However, large series are required to clarify our results.

The major limitation of the current study is that was retrospectively reviewed. The other limitation is the small sample size of the BCR group in the analysis of the whole group and subgroups. However, we think that the present study provides important results to understand the relationship between BCR and SM status.

In conclusion, high GS and ISUP grade in prostate biopsy specimen were found to be associated with BCR in SM-positive patients. For SM-negative patients, only TSMD was found to be associated with BCR after RP. In accordance with our findings, if high ISUP grade (or high GS) accompanies positive SM, adjuvant treatment can be discussed due to the high risk of BCR in patients with positive SM after RP. In addition, in patients with negative SM especially patients with <75 μm TSMD should be closely followed-up for BCR risk after RP.

Conflict of interest

All authors have no conflict of interest to declare.

Acknowledgments

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