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

Serdar Celik a, b, *, Anıl Eker a, İbrahim Halil Bozkurt a, Deniz Bolat a, İsmail Basmacı a, Ertuğrul Şefik a, Tansu Değirmenci a, Bülent Günlüsoy a

a Health Science University, Izmir Bozyaka Training and Research Hospital, Urology Clinic, Izmir, Turkey
b Dokuz Eylül University, Institute of Oncology, Department of Basic Oncology, Izmir, Turkey

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): 2.67, 95% Confidence Interval (CI): 0.92-7.55). 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 SM distance 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.

© 2020 Asian Pacific Prostate Society. Publishing by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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.
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 subgroups as SM negative and SM positive. Data from the 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 $\chi^2$ 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 $\chi^2$ 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 (+) (Group 2). Significant p values were given as bold.

Mann–Whitney U test and Pearson $\chi^2$ test were used.

### Table 1

Analysis results of demographic, clinical, and pathological findings between Group 1 (BCR negative) and Group 2 (BCR positive) in 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 ± 6.3 (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 ± 2.65 (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 (28.6)                        | 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)             | 0.233 |
| 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)                       | 0.412 |

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 $\chi^2$ test were used.
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 SM-positive and SM-negative patients.

### Table 2

Analysis of demographic, clinical, and pathological findings between negative and positive SM 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 (7.5)              | 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) | 121 (70.8) | 32 (38.6) | <0.001 |
| 1                        | 82 (47.9)             | 17 (20.5)            |     |
| 2                        | 50 (29.2)             | 20 (24.1)            |     |
| 3                        | 18 (10.5)             | 15 (18.1)            |     |
| 4                        | 16 (9.4)              | 15 (18.1)            |     |
| 5                        | 10 (5.8)              | 12 (14.5)            |     |
| EPE, n (%)               | 5.6 ± 2.9 (1—7)       | 5.4 ± 4.2 (1—9)      | <0.001 |
| SVI, n (%)               | 3 (1.8)               | 28 (33.7)            | <0.001 |
| Tumor volume (cc)        | 5 ± 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 χ² test were used.

Fig. 1. Kaplan–Meier survival plots for recurrence-free survivals of SM-positive and SM-negative patients.
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 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 PCs (especially in intermediate and high risk patients). However, BCR was reported in approximately 25–35%
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 4

| 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.

### 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 χ² test were used.

Fig. 2. Receiver operating characteristic (ROC) curve analysis of TSMD.
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 = 0.0031). 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 effects 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.25 In addition, based on the recent reports, detected high GS/ISUP grade at the positive SM has been stated as another important 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.28 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.29 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.29 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 specificity 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 it 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 specimens 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

None.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69(1):7–34.
2. Mottet N, Cornford P, van den Bergh RCN, Briers E, De Santis M, Fanti S, et al. EFU Guideline on Prostate Cancer, 2019. available at: https://uroweb.org/guideline/prostate-cancer/.
3. Fujimura T, Fukuhara H, Taguchi S, Yamada Y, Sugihara T, Nakagawa T, et al. Robot-assisted radical prostatectomy significantly reduced biochemical recurrence compared to retroperitoneal radical prostatectomy. BMC Canc 2017;17:454.
4. Isbarn H, Wanner M, Salomon G, Steuber T, Schlomm T, Kollermann J, et al. Long-term data on the survival of patients with prostate cancer treated with radical prostatectomy in the prostate-specific antigen era. BJU Int 2010;106:37–43.
5. Roux V, Eyraud R, Brureau L, Gourtaud G, Senechal C, Fofana M, et al. Impact of Gleason score on biochemical recurrence free survival after radical prostatectomy with positive surgical margins. Prog Urol 2017;27(8–9):467–73.
6. Minciovic R, Berglund RK, Stephenson AJ, Jones JS, Fergany A, Kasuk J, et al. Avoiding androgen deprivation therapy in men with high-risk prostate cancer: the role of radical prostatectomy as initial treatment. Urology 2011;77:946–50.
7. Kumar A, Samavedi S, Mouravev V, Bates AS, Coelho RF, Rocco B, et al. Predictive factors and oncological outcomes of persistently elevated prostate-specific antigen in patients following robot-assisted radical prostatectomy. J Robot Surg 2017;11:37–45.
8. Sooriakumaran P, Haendler L, Nyberg T, Gronberg H, Nilsson A, Carlsson S, et al. Biochemical recurrence after robot-assisted radical prostatectomy in a European single-centre cohort with a minimum follow-up time of 5 years. Eur Urol 2012;62:768–74.
9. Pagano MJ, Whalen MJ, Pauluzzi DJ, Reddy BN, Matulaj JT, Rothberg M, et al. Predictors of biochemical recurrence in pT3b prostate cancer after radical prostatectomy without adjuvant radiotherapy. Prostate 2016;76:226–34.
10. Ku JH, Moon KC, Cho SY, Kwak C, Kim HH, Serum prostate-specific antigen value adjusted for non-cancerous prostate tissue volume in patients undergoing radical prostatectomy: a new predictor of biochemical recurrence in localized or locally advanced prostate cancer. Asian J Androl 2011;13:248–53.
11. Hashimoto T, Yushoika K, Horiguchi Y, Ioune R, Yoshio O, Nakashima J, et al. Clinical effect of a positive surgical margin without extraprostatic extension after robot-assisted radical prostatectomy. Urol Oncol 2015;33(503):501–6.
12. Adella O, Ploussard G, Mouracade P, Xylinaеe, de la Taille A, Allyor Y, et al. Impact of the primary Gleason pattern on biochemical recurrence-free survival after radical prostatectomy: a single-center cohort of 1,248 patients with Gleason 7 tumors. World J Urol 2011;29:671–6.
13. Cooperberg MR, Pasta DJ, Elkin EP, Litwin MS, Latini DM, Du Chane J, et al. The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straight forward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol 2005;173:1938–42.
14. Liu H, Zhou H, Yan L, Ye T, Lu H, Sun X, et al. Prognostic significance of six clinicopathological features for biochemical recurrence after radical prostatectomy: a systematic review and meta-analysis. Oncotarget 2017;9(63):32238–49.
15. Whalen MJ, Shapiro EY, Rotheberg MB, Turk AT, Woldui SL, Roy Choudhury J, et al. Close surgical margins after radical prostatectomy mimic biochemical recurrence rates of positive margins. Urol Oncol 2015;33(494):499–514.
16. Chen MK, Luo Y, Zhang H, Qiu JG, Wen XQ, Pang J, et al. Laparoscopic radical prostatectomy plus extended lymph nodes dissection for cases with non-extendable metastatic prostate cancer: 5-year experience in a single Chinese institution. J Canc Res Clin Oncol 2013;139:871–8.
17. Lu J, Wirth GJ, Wu S, Chen J, Dahl DM, Olumí AF, et al. A close surgical margin after radical prostatectomy is an independent predictor of recurrence. J Urol 2012;188:91–7.
18. Zhang L, Wu B, Zha Z, Zhao H, Jiang Y, Yuan J. Positive surgical margin is associated with biochemical recurrence risk following radical prostatectomy: a meta-analysis from high-quality retrospective cohort studies. World J Surg Oncol 2018;16(1):124.
19. Hsu M, Chang SL, Ferrari M, Nolley R, Presti Jr JC, Brooks JD. Length of site specific positive surgical margins as a risk factor for biochemical recurrence following radical prostatectomy. Int J Urol 2011;18:272–9.
20. Alkhatteeb S, Alibhai S, Fleshner N, Finelli A, Jewett M, Zlotta A, et al. Impact of positive surgical margins after radical prostatectomy differs by disease risk group. J Urol 2010;183:145–50.
21. Pettenati C, Neuzillet Y, Radulescu C, Herve JM, Molinie V, Lebret T. Positive surgical margins after radical prostatectomy: what should we care about? World J Urol 2015;33:1973–8.
22. Swanson GP, Lerner SP. Positive margins after radical prostatectomy: implications for failure and role of adjuvant treatment. Urol Oncol 2013;31:531–41.
23. Cimitan M, Evangelista L, Hodolic M, Mariani G, Baseric T, Bodanza V, et al. Gleason score at diagnosis predicts the rate of detection of 18F-choline PET/CT performed when biochemical evidence indicates recurrence of prostate cancer: experience with 1,000 patients. J Nucl Med 2015;56:209–15.
24. Jastaniyah N, Sloboda R, Kamal W, Moore H, Ghosh S, Pervez N, et al. Regional treatment margins for prostate brachytherapy. Brachytherapy 2013;12:596–602.
25. Lysenko I, Mori K, Mostafaei H, Enikeev DV, Karakiewicz PI, Briganti A, et al. Prognostic Value of Gleason Score at Positive Surgical Margin in Prostate Cancer: A Systematic Review and Meta-analysis. Clin Genitourin Canc 2020. S1558-7673(20)30045-30048.
26. Herforth C, Stroup SP, Chen Z, Howard LE, Freedland SJ, Moreira DM, et al. Radical prostatectomy and the effect of close surgical margins: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. BJU Int 2018;122(4):592–8.
27. Izard JP, True LD, May P, Ellis WJ, Lange PH, Dalkin B, et al. Prostate cancer that is within 0.1 mm of the surgical margin of a radical prostatectomy predicts greater likelihood of recurrence. Am J Surg Pathol 2014;38:333–8.
28. Epstein JI, Sauvageot J. Do close but negative margins in radical prostatectomy specimens increase the risk of postoperative progression? J Urol 1997;157:241–3.
29. Gupta R, O’Connell R, Haynes AM, Stricker PD, Barrett W, Turner JJ, et al. Extraprostatic extension (EPE) of prostatic carcinoma: is its proximity to the surgical margin or Gleason score important? BJU Int 2015;116:343–50.
30. Tan PH, Cheng L, Srigley JR, Griffiths D, Humphrey PA, van der Kwast TH, et al. International Society of Urological Pathology (ISUP) Consensus Conference on handling and staging of radical prostatectomy specimens. Working group 5: surgical margins. Mod Pathol 2011;24:48–57.