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# Gleason score at the margin can predict biochemical recurrence after radical prostatectomy, in addition to preoperative PSA and surgical margin status

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**Background/aim:** To evaluate the relation between biochemical recurrence (BCR) of prostate cancer and the extent of positive surgical margins (PSMs), Gleason score (GS) of the tumor at the margins, and preoperative prostate-specific antigen (PSA) levels.

**Materials and methods:** A total of 94 patients who underwent radical prostatectomy were recruited for this study and received postoperative follow-up care for 2 years. All specimens were evaluated for surgical margin status, PSM length, GS at positive margin, size of tumor, multifocality, invasion of seminal vesicle, lymphovascular invasion, and perineural invasion. PSM was defined as a prostate tumor.

**Results:** Out of 94 patients, 34 patients (36.2%) had PSMs and 46 patients (48.9%) had BCR. A statistically significant relation between having a high risk of BCR of prostate cancer and having high preoperative PSA levels ($P < 0.001$), PSMs ($P < 0.001$), or a high GS at the surgical margin ($P = 0.024$) was found.

**Conclusion:** High preoperative PSA levels, PSMs, and tumors with high GS at the margins have a poor prognostic impact, and they correlate with a higher rate of BCR. Close follow-up of patients with PSMs with high GS and high levels of preoperative PSA is recommended.

**Key words:** Prostate cancer, surgical margin, biochemical recurrence

## 1. Introduction

A positive surgical margin (PSM) in a radical prostatectomy specimen means that the tumor has not completely been excised and that the cancer has extended outside the prostate into the resection margins (1–4). On pathologic examination of prostate specimens, a PSM is the presence of tumor cells at the inked margin. If there is a fibrin layer between the tumor cells and the ink, it is considered as negative (3). In addition, if the ink is on tumor cells in which the glandular structure is not disrupted, it is again considered as negative (3). Surgical margins are considered as positive when tumor cells with disrupted glandular structure are identified on the inked surface (3). However, PSM may occur artificially when neoplastic glands are exposed to disruption of the prostatic capsule during surgery, tissue trauma during the intraoperative retraction of the prostate gland, or disruption of the capsule during pathological processing of the specimen (4).

Disease recurrence in organ-confined prostate cancer is reported to occur in up to 27% of the patients after radical prostatectomy (RP) (5–7). The prognostic impact of PSM on the outcomes after RP is controversial (7). The association of biochemical recurrence (BCR) with PSM has been studied and was found to be highly variable due to the multiple causes underlying PSM (1–4).

Previous studies have found that margin status is not an independent predictor of BCR when adjusted for other factors, such as Gleason score (GS) and preoperative serum prostate-specific antigen (PSA) levels (6,8). Nevertheless, several studies have demonstrated that a higher rate of BCR, local recurrence, and development of distant metastasis are associated with PSM (9–11). Moreover,

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some reports have shown that PSM is an independent predictor of BCR following RP (9,12,13). Although the current TNM staging system does not reflect the impact of PSM, recent reports have shown that patients with a PSM but no extracapsular extension had PSA recurrence rates similar to or worse than patients with extracapsular extension with or without positive margins (14–16).

Recently, a PSM of greater than 3 mm was identified as an independent predictor of BCR (17). Most of the data evaluating these margin-based parameters originate from large open prostatectomy series with intermediate to long follow-up periods (18).

In the literature, there are many published studies that evaluated the relationship between BCR and tumor GS. However, there was only one study that looked into the relationship among PSM, GS, and BCR. Song et al. (7) showed that GS and BCR are 2 independent prognostic factors for biochemical recurrence in patients with PSM. In addition to the study by Song et al., our study is another one that evaluates the GS at the PSM. We have investigated the correlation of BCR with the length of PSM, GS at the surgical margin, and preoperative PSA in patients who underwent RP for the treatment of prostatic cancer.

## 2. Materials and methods

### 2.1. Patient population

We reviewed the data of patients who underwent RP for the treatment of prostate cancer and received postoperative follow-up care for more than 2 years at our institution between September 2001 and March 2010. Clinical (age and PSA level) and pathological data were collected prospectively into an institutional review board-approved database. Follow-up data were gathered from chart reviews so that only patients followed at our institution were represented. Among these patients, those with pathologic stage T2 and T3 were identified, while the patients with node-positive disease and neoadjuvant or adjuvant therapy were excluded from the study. As a result, 94 patients were included in our study group.

The patients underwent routine evaluation and PSA testing every 3–6 months in the first 2 years and annually thereafter in the postoperative period. BCR was defined as a serum PSA level of ≥0.2 ng/mL after RP.

### 2.2. Pathologic evaluation

Using a standard protocol, we systematically sampled and evaluated all RP specimens (19). The prostatic apex was also evaluated in the same fashion in each protocol, and the entire external surface of the prostate was inked. The distal 5 to 8 mm (apex) was amputated and sectioned parallel to the urethra. PSM was defined as prostate tumor in contact with ink. The length of PSM was categorized as either being <10 mm or ≥10 mm. In addition to the surgical margin status, the PSM length, GS at the margin, largest diameter of the tumor, multifocality, presence of seminal vesicle (SVI), lymphovascular invasions (LVIs), and perineural invasions (PNIs) were also evaluated.

### 2.3. Statistical analysis

For statistical analysis of the data, SPSS 15.0 for Windows was used. The chi-square test and Fisher's exact chi-square test were used for the evaluation of quantitative parameters. Logistic regression analysis was used for multivariate analysis and for statistical significance, and a P-value of less than 0.05 was considered to show statistically significant results.

## 3. Results

We have included 94 patients that underwent RP between 2001 and 2010 at our institution. The age of the patients ranged between 42 and 73 years old with a mean of 62.81 ± 6.87. The demographics of the study are given in Table 1.

**Table 1.** Demographics and histological findings of patients.

| | | n | % |
|---|---|---|---|
| Age | <65 | 51 | 54.3 |
| | ≥65 | 43 | 45.7 |
| Preop. PSA (ng/mL) | <4 ng/mL | 4 | 4.3 |
| | 4–10 ng/mL | 44 | 46.8 |
| | >10 ng/mL | 46 | 48.9 |
| Surgical margins | Positive | 34 | 36.2 |
| | Negative | 60 | 63.8 |
| Length of tumor at the margin (n = 34) | <10 mm | 18 | 52.9 |
| | ≥10 mm | 16 | 47.1 |
| GS at the margin | <7 | 52 | 55.3 |
| | ≥7 | 42 | 44.7 |
| Largest tumor diameter | <25 mm | 60 | 63.8 |
| | ≥25 mm | 34 | 36.2 |
| SVI | Positive | 21 | 22.3 |
| | Negative | 73 | 77.7 |
| LVI | Positive | 30 | 31.9 |
| | Negative | 64 | 68.1 |
| BCR | Yes | 46 | 48.9 |
| | No | 48 | 51.1 |
| PNI | Positive | 64 | 68.1 |
| | Negative | 30 | 31.9 |

PSA, prostate-specific antigen; GS, Gleason score; SVI, seminal vesicle invasion; LVI, lymphovascular invasion; BCR, biochemical recurrence; PNI, perineural invasion.

We have analyzed the patients according to the presence of BCR in the follow-up examinations. A statistically significant relation was detected between BCR and the preoperative PSA levels (P = 0.01). Patients with a preoperative PSA level of >10 ng/mL had a statistically significant higher BCR rate compared to those with preoperative PSA levels of <10 ng/mL. In addition, a statistically significant relation was found between higher BCR rate (P = 0.01) and PSM; however, the relation between BCR rate and the length of tumor at the PSM was not statistically significant (P = 1). BCR rate and GS at the surgical margin were found to be significantly related (P = 0.024). Patients with BCR had a significantly higher GS (GS ≥ 7) at the margin. Additionally, patients with BCR had a significantly higher rate of SVI and LVI. The correlation of BCR with the other clinical and histopathological parameters is summarized in Table 2.

Table 3 summarizes the logistic regression analysis of BCR. Parameters, from the most significant downwards, were as follows: SVI (OR: 13.122), LVI (OR: 6.443), preoperative PSA (OR: 4.229), and PSM length of >10 mm (OR: 3.931). There was no relation between BCR and GS of ≥7 at the PSM.

When patients were analyzed according to the surgical margin status, it was seen that patients with PSMs had higher preoperative PSA levels (>10 ng/mL) compared to the patients with negative surgical margins. A statistically significant relation was detected between PSM and GS at the margin (P = 0.003); patients with a PSM had a higher rate of having GS of ≥7 compared to negative surgical margins. We found a significant relation between PSM and SVI (P = 0.023), LVI (P = 0.001), and PNI (P = 0.007). In addition to all these findings summarized in Table 4, no significant relation was detected between PSM and age or tumor size.

Table 5 summarizes the logistic regression analysis of PSM with other parameters, which are listed from the most significant downwards: LVI (OR: 3.761) and preoperative PSA (OR: 3.251). There was no relation between PSM and GS of ≥7 at the PSM, SVI, or PNI.

**Table 2.** Relation between biochemical recurrence of prostate cancer (BCR) and clinicopathologic factors.

| | | BCR | | P |
|---|---|---|---|---|
| | | Yes | No | |
| | | n (%) | n (%) | |
| Age | <65 | 26 (56.5%) | 25 (52.1%) | 0.666 |
| | ≥65 | 20 (43.5%) | 23 (47.9%) | |
| Preop. PSA | <4 ng/mL | 1 (2.2%) | 3 (6.3%) | 0.001** |
| | 4–10 ng/mL | 12 (26.1%) | 32 (66.7%) | |
| | >10 ng/mL | 33 (71.7%) | 13 (27.1%) | |
| Surgical margins | Positive | 26 (56.5%) | 8 (16.7%) | 0.001** |
| | Negative | 20 (43.5%) | 40 (83.3%) | |
| Length of tumor at the margin | <10 mm | 14 (53.8%) | 4 (50.0%) | 1 |
| | ≥10 mm | 12 (46.2%) | 4 (50.0%) | |
| GS at the margin | <7 | 20 (43.5%) | 32 (66.7%) | 0.024* |
| | ≥7 | 26 (56.5%) | 16 (33.3%) | |
| Tumor size | <25 mm | 27 (58.7%) | 33 (68.8%) | 0.391 |
| | ≥25 mm | 19 (41.3%) | 15 (31.2%) | |
| SVI | Positive | 20 (43.5%) | 1 (2.1%) | 0.001** |
| | Negative | 26 (56.5%) | 47 (97.9%) | |
| LVI | Positive | 26 (56.5%) | 4 (8.3%) | 0.001** |
| | Negative | 20 (43.5%) | 44 (91.7%) | |
| PNI | Positive | 34 (73.9%) | 30 (62.5%) | 0.235 |
| | Negative | 12 (26.1%) | 18 (37.5%) | |

PSA, prostate-specific antigen; GS, Gleason score; SVI, seminal vesicle invasion; LVI, lymphovascular invasion; BCR, biochemical recurrence; PNI, perineural invasion. Chi-square test: * P < 0.05, ** P < 0.001.

**Table 3.** Logistic regression analysis of biochemical recurrence (BCR) of prostate cancer and clinicopathologic factors.

| | B | SE | P | OR | 95% CI |
|---|---|---|---|---|---|
| Preop. PSA (>10 ng/mL) | 1.442 | 0.587 | 0.014* | 4.229 | 1.338–13.363 |
| Tumor length at margin | 1.369 | 0.626 | 0.029* | 3.931 | 1.152–13.416 |
| GS (≥7) at the margin | –0.762 | 0.670 | 0.256 | 0.467 | 0.126–1.736 |
| SVI (positive) | 2.574 | 1.152 | 0.025* | 13.122 | 1.372–125.532 |
| LVI (positive) | 1.863 | 0.780 | 0.017* | 6.443 | 1.396–29.746 |

PSA, prostate-specific antigen; GS, Gleason score; SVI, seminal vesicle invasion; LVI, lymphovascular invasion; BCR, Biochemical Recurrence; B, beta coefficient; SE, standard error; OR, odds ratio; CI, correlation index.

**Table 4.** Relation between surgical margin status and clinicopathologic features.

| | | Surgical margin | | P |
|---|---|---|---|---|
| | | Positive | Negative | |
| | | n (%) | n (%) | |
| Age | <65 | 17 (50.0%) | 34 (56.7%) | 0.533 |
| | >65 | 17 (50.0%) | 26 (43.3%) | |
| Preop. PSA | <4 ng/mL | 1 (2.9%) | 3 (5.0%) | 0.007** |
| | 4–10 ng/mL | 9 (26.5%) | 35 (58.3%) | |
| | >10 ng/mL | 24 (70.6%) | 22 (36.7%) | |
| GS at the margin | <7 | 12 (35.3%) | 40 (66.7%) | 0.003** |
| | ≥7 | 22 (64.7%) | 20 (33.3%) | |
| Tumor size | <25 mm | 19 (55.9%) | 41 (68.3%) | 0.227 |
| | ≥25 mm | 15 (44.1%) | 19 (31.7%) | |
| SVI | Positive | 12 (35.3%) | 9 (15.0%) | 0.023* |
| | Negative | 22 (64.7%) | 51 (85.0%) | |
| LVI | Positive | 19 (55.9%) | 11 (18.3%) | 0.001** |
| | Negative | 15 (44.1%) | 49 (81.7%) | |
| PNI | Positive | 29 (85.3%) | 35 (58.3%) | 0.007** |
| | Negative | 5 (14.7%) | 25 (41.7%) | |

PSA, prostate-specific antigen; GS, Gleason score; SVI, seminal vesicle invasion; LVI, lymphovascular invasion; BCR, biochemical recurrence; PNI, perineural invasion. Chi-square test: * $P < 0.05$, ** $P < 0.001$.

Finally, patients with PSMs were analyzed and a statistically significant relation was detected between BCR and high preoperative PSA (P = 0.029). Patients with preoperative PSA of >10 ng/mL had a higher rate of BCR. Additionally, in these patients, a significant relation was detected between BCR and GS at the margin (P = 0.024). Patients with BCR had significantly higher GS results (GS ≥ 7) at the margin. BCR also had a significant relation with SVI (P = 0.017) and LVI (P = 0.01). These findings are summarized in Table 6.

Table 7 shows the logistic regression analysis of PSM with other parameters, which are listed from the most significant to less significant: LVI (OR: 6.074) and preoperative PSA (OR: 4.721). There was no relationship between PSM and GS of ≥7 at the PSM, SVI, or PNI.

**Table 5.** Logistic regression analysis of positive surgical margin (PSM) and clinicopathologic factors.

| | B | SE | P | OR | 95% CI |
|---|---|---|---|---|---|
| Preop. PSA (>10 ng/mL) | 1.179 | 0.525 | 0.025* | 3.251 | 1.162–9.093 |
| GS (≥7) at the margin | 0.439 | 0.544 | 0.419 | 1.552 | 0.534–4.506 |
| SVI (positive) | –0.512 | 0.723 | 0.478 | 0.599 | 0.145–2.471 |
| LVI (positive) | 1.325 | 0.626 | 0.034* | 3.761 | 1.104–12.820 |
| PNI (positive) | 0.967 | 0.634 | 0.127 | 2.630 | 0.759–9.107 |

PSA, prostate-specific antigen; GS, Gleason score; SVI, seminal vesicle invasion; LVI, lymphovascular invasion; PNI, perineural invasion; B, beta coefficient; SE, standard error; OR, odds ratio; CI, correlation index.

**Table 6.** Relation between biochemical recurrence of prostate cancer (BCR) and clinicopathologic factors in patients with positive surgical margin (PSM).

| | | BCR | | P |
|---|---|---|---|---|
| | | Present | Absent | |
| | | n (%) | n (%) | |
| Age | <65 | 13 (50.0%) | 4 (50.0%) | 1 |
| | >65 | 13 (50.0%) | 4 (50.0%) | |
| Preop. PSA | <4 ng/mL | 0 (0.0%) | 1 (12.5%) | 0.029* |
| | 4–10 ng/mL | 5 (19.2%) | 4 (50.0%) | |
| | >10 ng/mL | 21 (80.8%) | 3 (37.5%) | |
| GS at the margin | <7 | 8 (30.8%) | 4 (50.0%) | 0.320 |
| | ≥7 | 18 (69.2%) | 4 (50.0%) | |
| Tumor size | <25 mm | 14 (53.8%) | 5 (62.5%) | 1 |
| | ≥25 mm | 12 (46.2%) | 3 (37.5%) | |
| SVI | Positive | 12 (46.2%) | 0 (0.0%) | 0.017* |
| | Negative | 14 (53.8%) | 8 (100.0%) | |
| LVI | Positive | 19 (73.1%) | 0 (0.0%) | 0.001** |
| | Negative | 7 (26.9%) | 8 (100.0%) | |
| PNI | Positive | 22 (84.6%) | 7 (87.5%) | 1 |
| | Negative | 4 (15.4%) | 1 (12.5%) | |

PSA, prostate-specific antigen; GS, Gleason score; SVI, seminal vesicle invasion; LVI, lymphovascular invasion; BCR, biochemical recurrence; PNI, perineural invasion. Chi-square test and Fisher's exact test: * $P < 0.05$, ** $P < 0.01$

**Table 7.** Logistic regression analysis of prostate-specific antigen (PSA) recurrence and other parameters in positive surgical margin (PSM) cases.

| | B | SE | P | OR | 95% CI |
|---|---|---|---|---|---|
| Preop. PSA (>10 ng/mL) | 1.552 | 0.535 | 0.004** | 4.721 | 1.654–13.481 |
| GS (≥7) at the margin | –0.389 | 0.594 | 0.512 | 0.677 | 0.212–2.169 |
| SVI (positive) | 1.674 | 0.882 | 0.058 | 5.333 | 0.947–30.027 |
| LVI (positive) | 1.804 | 0.693 | 0.009** | 6.074 | 1.563–23.606 |

PSA, prostate-specific antigen; GS, Gleason score; SVI, seminal vesicle invasion; LVI, lymphovascular invasion; PNI, perineural invasion; B, beta coefficient; SE, standard error; OR, odds ratio; CI, correlation index.

## 4. Discussion

While many studies have reported that patients with positive margin prostate cancer are more likely to progress biochemically, locally, and systemically (20–24), the prognostic significance of a PSM in the case of organ-confined cancer remains debatable (7).

Traditionally, the extent of a PSM in RP specimens was categorized as focal or extensive (3,4,10,18). The major issue with this method is the lack of a standard to define how much of a tumor at the margin should be considered a focal or extensive positivity. This makes it difficult to compare the results among studies. As a result, the International Society of Urological Pathology has recently recommended reporting the length of PSMs as the extent of a positive margin (25). Only a few studies have been published on this subject (4,10,18,26,27). Shikanov et al. found that the length of a PSM was an independent prognostic factor for BCR, both as a continuous variable and as a categorical variable (≤1 mm, 1–3 mm, or >3 mm) (18). Ochiai et al. found that the prognosis of patients with a length of tumor at the surgical margin of ≤3.0 mm and those with a length of PSM of >3.0 mm were statistically different ($P < 0.01$) (17). Other groups also made similar observations (10,27) In contrast, Emerson et al. and Marks et al. found that the length of PSM was not an independent prognostic factor (26,28).

While evaluating the tumor length at the surgical margin, we subgrouped the patients as having PSMs of less than 10 mm and having PSMs of greater than or equal to 10 mm in our study. We confirmed that BCR is much higher in cases with PSMs (36.2%). However, the tumor length at the surgical margin was independent from BCR. It is clear that the number of cases in our study is not enough to reach a statistically significant conclusion.

Shikanov et al. prospectively studied 1398 patients. According to them, in patients with a PSM, the margin length was associated with BCR. They found total PSM length to be independently associated with BCR. Longer positive margins are associated with higher risk of BCR. This emphasizes the importance of minimizing not only the incidence but also the extent of PSM surgically. Interestingly, in our study, the risk of BCR did not differ between patients with a negative surgical margin and those with a PSM of less than 1 mm. This finding suggests that patients with a small positive margin have a false-positive margin or that, given our relatively short follow-up, persistent microscopic disease following surgery has yet to be translated into BCR (18).

Stephenson et al. analyzed follow-up data from 7160 patients treated with RP. They found that an increased risk of biochemical recurrence was associated with multiple versus solitary PSMs (adjusted HR: 1.4, $P = 0.002$) and extensive versus focal PSMs (adjusted HR: 1.3, $P = 0.004$) in multivariable analysis. Consequently, they reported that the number and extent of PSMs significantly influence the risk of biochemical recurrence after RP (4).

In the studies done to date, specimen GS has been taken into consideration. However, as seen in a few other studies, we assessed the GS at the surgical margin in order to ascertain whether GS at the surgical margin has any implication on the recurrence (7).

Song et al. evaluated the surgical margin GS, similar to our study. On multivariate analysis, surgical GS was independently prognostic of BCR. Song et al. found that the surgical GS ($P = 0.021$) was the independent predictor of BCR (7).

In our study, we also found that BCR is higher in PSM cases with a GS of ≥7 at the margin. Our findings support that having a tumor with GS of ≥7 at the margin increases the PSA recurrence by at least 2.6 times.

In conclusion, certain factors can predict biochemical recurrence after RP, including preoperative PSA levels, surgical margin positivity, and GS of ≥7 at the PSM, in patients with localized prostate cancer. There was no relation between the length of the PSM and BCR when cut-off was taken as 10 mm for the length. With the use of several different cut-offs for the length of invasion, more detailed analysis can be performed in a larger series.

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