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ORIGINAL ARTICLE – UROLOGIC ONCOLOGY

# Impact of Nerve-Sparing Status on Positive Surgical Margin Location and Biochemical Recurrence in Patients with Prostate Cancer Post Radical Prostatectomy

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## ABSTRACT

**Purpose.** This study was designed to assess the relationship between nerve-sparing (NS) status, positive surgical margin (PSM) location, and biochemical recurrence (BCR) based on a multicenter, radical prostatectomy (RP) database.

**Methods.** We retrospectively reviewed data from 726 patients who underwent RP without any neoadjuvant or adjuvant treatment between 2010 and 2014. We statistically assessed the impact of NS sides on PSM location and BCR.

**Results.** PSM rates were 21.9% in the 726 patients studied, 13.2% in patients with ≤pT2, and 46.8% in patients with ≥pT3. Regarding PSM locations, the anterior-apex (AA) was the most common site for PSM (43.3%). After adjusting for confounding factors, bilateral nerve sparing (BNS) had a significantly higher odds ratio of PSM than the absence of NS did (odds ratio [OR] 3.04, 95% confidence interval [CI] 1.85–4.99). In the UNS RP in patients with ≤pT2, non-AA PSM on the non-NS side was significantly higher than that on the NS side (92.9% vs. 45.5%, $p = 0.009$). In all patients, 5.8% experienced BCR during a median follow-up of 43.5 months. PSM was significantly associated with BCR-free survival in patients with ≤pT2 ($p = 0.013$), but not in patients with ≥pT3 ($p = 0.185$). Non-AA PSM at the non-NS side was an independent risk factor for BCR (hazard ratio [HR] 2.56, 95% confidence interval [CI] 1.12–5.85), whereas AA PSMs, including NS/non-NS sides and non-AA PSM at the NS side, were not associated with BCR-free survival.

**Conclusions.** Avoidance of non-AA PSM on the non-NS side may be rather important for maintaining BCR-free survival after RP.

Prostate cancer (PCa) is the second most frequent tumor and the fifth leading cause of mortality in men.[1] Radical prostatectomy (RP) is one of the most established therapies with a longer life expectancy compared with watchful waiting in patients with localized PCa.[2]

Because a positive surgical margin (PSM) after RP reflects incomplete cancer excision and has been associated with worse prognosis, negative surgical margins should be achieved as one of the trifecta after RP.[3,4] Nerve-sparing (NS) is a technique that includes periprostatic capsular dissection. It has been widely applied to avoid

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complications, such as erectile dysfunction and possible urinary incontinence, and maintain quality of life after RP.[5,6] Therefore, it is important to maintain a balance between preservation of the neurovascular bundle during NS and securing negative surgical margins in patients with PCa after RP.

Previous studies have investigated the impact of margin status on clinical outcomes in patients with PCa post RP. They showed differential impacts of margin status according to the location, length, and detailed microscopic findings on clinical outcomes.[7] Several of them have reported that location of margin status influenced clinical outcomes in patients with PCa after RP.[8–10] Although NS was reported to be associated with a higher rate of PSM, the impact of NS on clinical outcomes is controversial.[11] In particular, the influence of PSMs after NS or non-NS sides on clinical outcomes in patients with PCa undergoing RP remains unknown.

We have previously developed a multicenter, retrospective database of patients with PCa who received RP at four institutions located in the Tohoku district of Japan. This database reported trends in RP in Japan and influential factors for clinical outcomes of patients with localized PCa after RP.[12–15] Herein, we evaluated the relationship between PSM location, NS status, and BCR in patients with localized PCa who underwent RP using this multicenter database after adjusting for confounding factors, such as patients' backgrounds and clinicopathological factors.

## METHODS

### *Study Population*

A total of 1,135 consecutive patients with clinically localized PCa who underwent RP between January 2010 and December 2014 at Akita University Hospital, Tohoku University Hospital, Hirosaki University Hospital, and Miyagi Cancer Center were enrolled in the present study. No patients had a history of prostate surgery or radiation therapy. Patients who underwent surgery with any neoadjuvant and adjuvant treatment or without information on positive margins were excluded from further analyses. The study was approved by each Institutional Review Board, and all participating centers provided the necessary institutional data-sharing agreements before study initiation.

### *Treatment and Evaluation*

Radical prostatectomy was performed using one of three procedures: open (ORP), pure laparoscopic (LRP), or robot-assisted laparoscopic approach (RARP). NS surgery was performed at each surgeon's discretion. Biopsy and surgical specimens were evaluated pathologically at each institution according to the Gleason grading system and the 2002 tumor-node-metastasis (TNM) classification. Positive surgical margin status was evaluated by pathologists at each institute according to the International Society of Urological Pathology (ISUP) consensus conference, and location of PSM was classified by laterality, axiality, and horizontality, as shown in Supplementary Fig. 1.[16]

The level of PSA measured immediately before biopsy was defined as a preoperative PSA level. The follow-up schedule after RP consisted of a PSA test every 3 months for the first 2 years, every 6 months for the following 3 years, and annually thereafter.

### *End-Points*

The date of BCR was defined as a serum PSA level exceeding 0.2 ng/mL. The day of surgery was considered to be the date of BCR when postoperative PSA level did not decrease below 0.2 ng/mL. The time to events was calculated from the day of surgery.

### *Statistical Analysis*

We assessed differences in PSM status using the chi-squared test for categorical variables. To identify PSM and BCR risk factors, univariate analysis was performed on the following variables: patient age, patient body mass index (BMI), preoperative PSA level, surgical procedure, prostate volume, primary Gleason score, clinical T stage, Damico's risk classification, extended lymph node dissection, NS status, pathological Gleason score, pathological T stage, pathological N stage, and PSM. Odds ratios for PSM were estimated using multiple logistic regression analysis after adjusting for confounding factors that were significantly associated with PSM in our univariate analysis of risk factors for PSM. BCR-free survival was calculated using the Kaplan-Meier method, and comparisons among the groups were performed using log-rank tests. Multivariable analysis was carried out using a Cox proportional hazards regression model. Hazard ratios for BCR-free survival were estimated using multiple Cox regression analysis after adjusting for confounding factors that were significantly associated with BCR-free survival in our univariate analysis. All statistical analyses were carried out using the SPSS software package version 24.0 (SPSS, Chicago, IL). All reported *P*-values were two-sided, with statistical significance considered at $P < 0.05$.

**TABLE 1** Patient characteristics

| | | All patients | | Non-NS | | Unilateral NS | | Bilateral NS | |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | % | *n* | % | *n* | % | *n* | % |
| Number of patients | | 726 | | 287 | | 225 | | 214 | |
| Age (median, IQR) | Median | 66 | 62–70 | 67.0 | 63–71 | 65.0 | 61–689 | 65.0 | 59–69 |
| BMI (kg/m$^2$) (median, IQR) | Median | 23.9 | 22.3–25.7 | 23.8 | 22.1–25.7 | 24.0 | 22.4–25.5 | 23.9 | 22.4–25.6 |
| Preoperative PSA (ng/mL) (median, IQR) | Median | 6.14 | 4.98–8.83 | 6.5 | 5.1–9.4 | 6.1 | 5.0–8.9 | 5.6 | 4.7–7.7 |
| Prostate volume (g) (median, IQR) | Median | 25.4 | 20.0–35.0 | 26.0 | 20.0–36.0 | 25.5 | 19.0–33.5 | 25.0 | 19.1–34.2 |
| | Unknown | 34 | 4.7 | 14 | 4.9 | 13 | 5.8 | 7 | 3.3 |
| Biopsy GS | 3+3 | 204 | 28.1 | 54 | 18.8 | 60 | 26.7 | 90 | 42.1 |
| | 3+4 | 306 | 42.1 | 130 | 45.3 | 88 | 39.1 | 88 | 41.1 |
| | 4+3 | 150 | 20.7 | 66 | 23.0 | 57 | 25.3 | 27 | 12.6 |
| | 4+4 | 55 | 7.6 | 30 | 10.5 | 17 | 7.6 | 8 | 3.7 |
| | 4+5/5+4/5+5 | 11 | 1.5 | 7 | 2.4 | 3 | 1.3 | 1 | 0.5 |
| Clinical *T* stage | 1c | 505 | 69.6 | 186 | 64.8 | 139 | 61.8 | 180 | 84.1 |
| | 2 | 197 | 27.1 | 88 | 30.7 | 77 | 34.2 | 32 | 15.0 |
| | 3 | 23 | 3.2 | 13 | 4.5 | 8 | 3.6 | 2 | 0.9 |
| | 4 | 1 | 0.1 | 0 | 0.0 | 1 | 0.4 | 0 | 0.0 |
| D'Amico classification | Low | 160 | 22.0 | 35 | 12.2 | 45 | 20.0 | 80 | 37.4 |
| | Intermediate | 460 | 63.4 | 191 | 66.6 | 145 | 64.4 | 124 | 57.9 |
| | High | 106 | 14.6 | 61 | 21.3 | 35 | 15.6 | 10 | 4.7 |
| Surgical procedure | RALP | 324 | 44.6 | 120 | 41.8 | 90 | 40.0 | 114 | 53.3 |
| | LRP | 56 | 7.7 | 28 | 9.8 | 23 | 10.2 | 5 | 2.3 |
| | ORP | 346 | 47.7 | 139 | 48.4 | 112 | 49.8 | 95 | 44.4 |
| Pelvic lymph node dissection | No | 328 | 45.2 | 101 | 35.2 | 91 | 40.4 | 136 | 63.6 |
| | Limited | 179 | 24.7 | 94 | 32.8 | 46 | 20.4 | 39 | 18.2 |
| | Extended | 219 | 30.2 | 92 | 32.1 | 88 | 39.1 | 39 | 18.2 |
| Nerve sparing | No | 287 | 39.5 | 287 | 100.0 | 0 | 0.0 | 0 | 0.0 |
| | Unilateral (right) | 102 | 14.0 | 0 | 0.0 | 102 | 45.3 | 0 | 0.0 |
| | Unilateral (left) | 115 | 15.8 | 0 | 0.0 | 115 | 51.1 | 0 | 0.0 |
| | Bilateral | 214 | 29.5 | 0 | 0.0 | 0 | 0.0 | 214 | 100.0 |
| | Unknown | 8 | 1.1 | 0 | 0.0 | 8 | 3.6 | 0 | 0.0 |
| Pathological GS | 0 | 4 | 0.6 | 1 | 0.3 | 0 | 0.0 | 3 | 1.4 |
| | 3+3 | 81 | 11.2 | 18 | 6.3 | 20 | 8.9 | 43 | 20.1 |
| | 3+4 | 311 | 42.8 | 108 | 37.6 | 101 | 44.9 | 102 | 47.7 |
| | 4+3 | 201 | 27.7 | 90 | 31.4 | 71 | 31.6 | 40 | 18.7 |
| | 4+4 | 76 | 10.5 | 40 | 13.9 | 23 | 10.2 | 13 | 6.1 |
| | 4+5/5+4/5+5 | 53 | 7.3 | 30 | 10.5 | 10 | 4.4 | 13 | 6.1 |
| Pathological T stage | 0 | 4 | 0.6 | 1 | 0.3 | 0 | 0.0 | 3 | 1.4 |
| | $\leqq 2$ | 534 | 73.6 | 199 | 69.3 | 171 | 76.0 | 164 | 76.6 |
| | $\geq 3$ | 188 | 25.9 | 87 | 30.3 | 54 | 24.0 | 47 | 22.0 |
| Pathological *N* stage | 0+*x* | 713 | 98.2 | 279 | 97.2 | 220 | 97.8 | 214 | 100.0 |
| | 1 | 13 | 1.8 | 8 | 2.8 | 5 | 2.2 | 0 | 0.0 |
| Resection margin | 0 | 567 | 78.1 | 237 | 82.6 | 177 | 78.7 | 153 | 71.5 |
| | 1 | 159 | 21.9 | 50 | 17.4 | 48 | 21.3 | 61 | 28.5 |
| Median follow up (months) (median, IQR) | | 43.5 | 28.0–60.0 | 42.0 | 25.0–59.0 | 39.0 | 28.0–59.0 | 44.0 | 32.0–60.8 |

*NS* nerve sparing, *IQR* interquartile range, *BMI* body mass index, *PSA* prostate specific antigen, *GS* Gleason Score, *RALP* robot assisted laparoscopic radical prostatectomy, *LRP* laparoscopic radical prostatectomy, *ORP* open radical prostatectomy

## RESULTS

Table 1 shows the patients' baseline characteristics. In total, 726 patients with PCa (median age at diagnosis: 66 years (interquartile range [IQR], 62–70) were enrolled in this study. The median preoperative serum PSA level and prostate volume were 6.14 ng/mL (range, 4.98–8.83) and 25.4 g (range, 20.0–35.0), respectively. The proportions of patients with low, intermediate, and high D'Amico risk criteria were 22.0%, 63.4%, and 14.6%, respectively. Prostatectomy was performed using ORP in 346 (47.7%), LRP in 56 (7.7%), and RARP in 324 (44.6%) patients. Bilateral NS (BNS) was performed in 214 patients (29.5%), whereas 217 patients (29.8%) underwent unilateral NS (UNS), including 102 right, 115 left, and 8 unknown sides of NS. Totally, NS surgery on any side was performed in 431 patients (59.3%).

The patients' pathological characteristics are shown in Table 1. The patients were categorized as patients with ≤pT2: 538 (74.1%) and ≥pT3: 188 (25.9%). Among all patients, 159 (21.9%) had a PSM. Among the patients with ≤pT2, 71 (13.2%) had PSM, whereas 88 (46.8%) had PSM in patients with ≥pT3. Supplementary Table 1 shows the location of the PSM sides based on the lateral, axial, and horizontal sides in all patients. The apex (59.1%) was the most frequent axial side of PSM, whereas the anterior (54.1%) was the most frequent horizontal side of PSM in all patients. Among the patients with any PSM, 69 (43.3%) had anterior-apex (AA) PSM. There was no difference in laterality of the PSM side (right 40.9% vs. left 50.9%, bilateral 8.2%, $p = 0.181$). In the ≥pT3 stage group, the rate of base PSM was significantly higher than that in the ≤pT2 stage group (26.1% vs. 11.3%, $p = 0.025$).

Next, we statistically assessed the risk factors of PSM. Among the perioperative variables, preoperative PSA level, surgical procedure, NS, and pathological T stage were significantly associated with PSM (Supplementary Table 2). To assess the impact of NS on PSM, we performed a logistic regression analysis by adjusting for other influential factors of PSM (Table 2; Supplementary Table 3). NS was associated with a significantly higher risk of PSM than did the non-NS group (odds ratio [OR] 2.29, 95% confidence interval [CI] 1.49.3.52, $p < 0.001$). The UNS was not associated with a higher risk of ipsilateral and contralateral PSMs (OR 0.56, 95% CI 0.31–0.99, $p = 0.049$; OR 1.00, 95% CI 0.58–1.73, $p = 0.990$), and BNS was associated with a significantly higher odds ratio of PSM than the absence of NS (OR 3.04, 95% CI 1.85–4.99, $p < 0.001$). We also assessed the location of PSMs in relation to pathological stages and NS technique (Table 3). In patients who underwent UNS, the rate of non-AA PSM was significantly higher on the non-NS side than on the NS side (78.1% vs. 52.4%, $p = 0.049$; Table 3). The tendency of the higher rate of non-AA PSM in patients with UNS on the non-NS side rather than that on the NS side was more evident in patients with ≤pT2 (92.9% vs. 45.5%, $p = 0.009$; Table 3).

In all patients, 42 (5.8%) patients experienced BCR during a median follow-up period of 43.5 months. In all patients, there was no difference in the BCR rates between the patients in the margin positive and margin negative groups ($p = 0.169$, Supplementary Fig. 2). In the ≤pT2 stage group, the PSM was significantly associated with a higher BCR rate ($p = 0.013$; Fig. 1a). However, the PSM was not associated with BCR rates in the ≥pT3 stage group ($p = 0.185$; Fig. 1b). As shown in Supplementary Table 4, among the preoperative variables, preoperative PSA, biopsy Gleason score, and Damico risk classification were significant risk factors for BCR using the univariate analyses. In terms of postoperative pathological variables, pathological Gleason score, pathological T stage (≥T3), and pathological lymph node involvement were significant risk factors for BCR. There was no significant difference in BCR-free survival between the patients with NS and non-NS (HR 0.75, 95% CI 0.41.1.38, $p = 0.351$). After adjusting for other influential factors of BCR-free survival (Table 4), PSMs at the AA and non-AA were not independent risk factors for BCR (HR 0.15, 95% CI 0.02–1.11, $p = 0.063$; HR 1.97, 95% CI 0.42–9.25, $p = 0.388$).

**TABLE 2** Impact of nerve sparing on PSMs

| | | Any location | | | Anterior-apex | | | Non-anterior+apex | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | OR | 95%CI | *p* value | OR | 95%CI | *p* value | OR | 95%CI | *p* value |
| Non NS | | 1.00 | | | 1.00 | | | 1.00 | | |
| NS | Yes versus no | 2.29 | 1.49–3.52 | <0.001 | 1.35 | 0.79–2.31 | 0.279 | 1.79 | 0.63–5.06 | 0.275 |
| Unilateral NS* | Yes versus no | 0.56 | 0.31–0.99 | 0.049 | 0.53 | 0.25–1.15 | 0.107 | 0.81 | 0.20–3.50 | 0.810 |
| Bilateral NS | Yes versus no | 3.04 | 1.85–4.99 | <0.001 | 2.04 | 1.11–3.76 | 0.021 | 2.67 | 0.84–8.49 | 0.097 |

Adjusting by preoperative PSA, surgical procedure, pT stage

*OR* odds ratio, *CI* confidence interval, *NS* nerve sparing

*The risk of ipsilateral PSMs was evaluated

**TABLE 3** Location of PSMs in relation to pathological stage and nerve sparing status

| | ALL | | | | ≤pT2 | | | | ≥pT3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NNS ($n$ = 50) | UNS (NS side, $n$ = 21) | UNS (non-NS dside, $n$ = 32) | BNS ($n$ = 61) | NNS ($n$ = 11) | UNS (NS side, $n$ = 11) | UNS (non-NS dside, $n$ = 14) | BNS ($n$ = 36) | NNS ($n$ = 39) | UNS (NS side, $n$ = 10) | UNS (non-NS dside, $n$ = 18) | BNS ($n$ = 25) |
| Anterior-apex | 26 (52) | 10 (47.6) | 7 (21.9) | 28 (45.9) | 6 (54.5) | 6 (54.5) | 1 (7.1) | 15 (41.7) | 20 (51.3) | 4 (40.0) | 6 (33.3) | 13 (52.0) |
| Non-anterior-apex | 24 (48) | 11 (52.4) | 25 (78.1) | 33 (54.1) | 5 (45.5) | 5 (45.5) | 13 (92.9) | 21 (58.3) | 19 (48.7) | 6 (60.0) | 12 (66.7) | 12 (48.0) |

*NNS* non nerve sparing, *UNS* unilateral nerve sparing, *BNS* bilateralnerve sparing

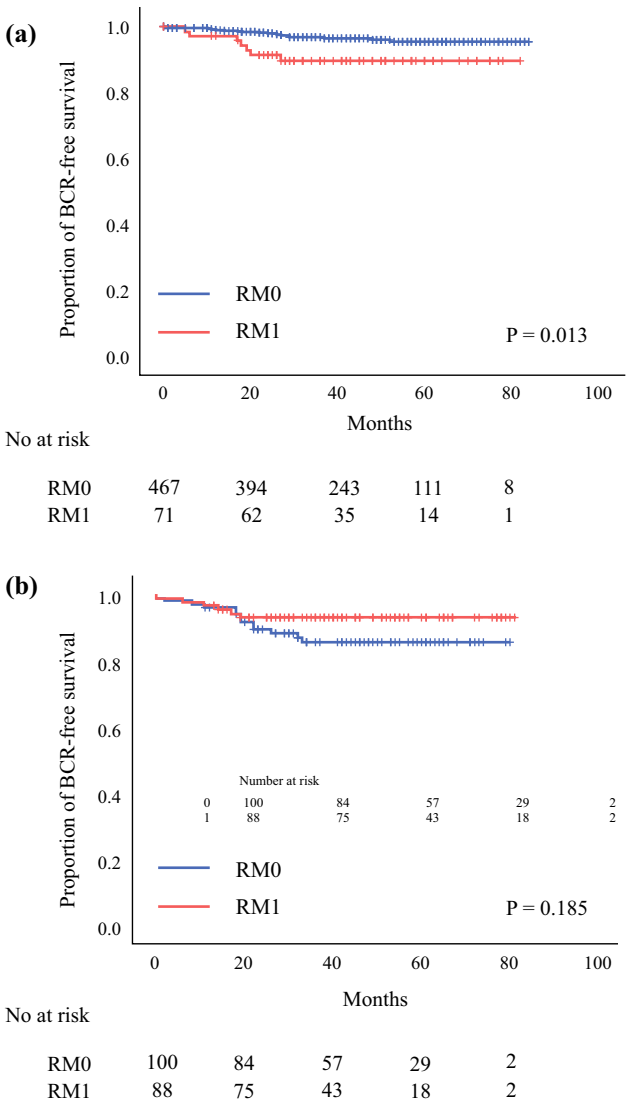


**FIG. 1** Biochemical recurrence curve based on margin status in patient who underwent radical prostatectomy. **a** Patients with ≤pT2. **b** Patients with ≥pT3

Finally, we investigated the impact of PSM location considering the NS status on BCR. The BCR was observed in 2 (4.9%) patients with PSM in the non-AA of NS side, one (3.2%) with PSM in the AA of non-NS side, and 10 (21.7%) with PSM in the non-AA of non-NS side, whereas 29 (5.1%) in patients with negative surgical margin had BCR. We excluded the patients with PSM on both NS and non-NS sides from further analyses (n = 5). The patients with PSM in the non-AA of non-NS side had significantly lower BCR-free survival than those with negative surgical margins ($p < 0.001$; Fig. 2). There was no significant difference in BCR-free survival between the patients with negative margins and any other PSMs. Adjusted for other influential factors of BCR, PSM at the non-AA of the non-NS side was an independent risk factor for BCR (HR 2.56,

**TABLE 4** Impact of PSM location and nerve sparing status on BCR

| | HR | 95%CI | *p* value |
|---|---|---|---|
| Negative surgical margin | 1.00 | | |
| PSM | 1.11 | 0.53–2.34 | 0.777 |
| PSM at anterior-apex | 0.15 | 0.02–1.11 | 0.063 |
| PSM at non-anterior apex | 1.97 | 0.42–9.25 | 0.388 |
| PSM at anterior+apex of nerve sparing side | 0.97 | NA | NA |
| PSM at non-anterior+apex of nerve sparing side | 1.06 | 0.24–4.64 | 0.940 |
| PSM at anterior+apex of non-nerve sparing side | 0.37 | 0.05–2.85 | 0.339 |
| PSM at non-anterior+apexof non-nerve sparing side | 2.56 | 1.12–5.85 | 0.026 |

*HR* hazard ratio, *CI* confidence interval, *PSM* positive surgical margin

Adjusted for preoperative PSA, biopsy Gleason score, pathological T, pathological N

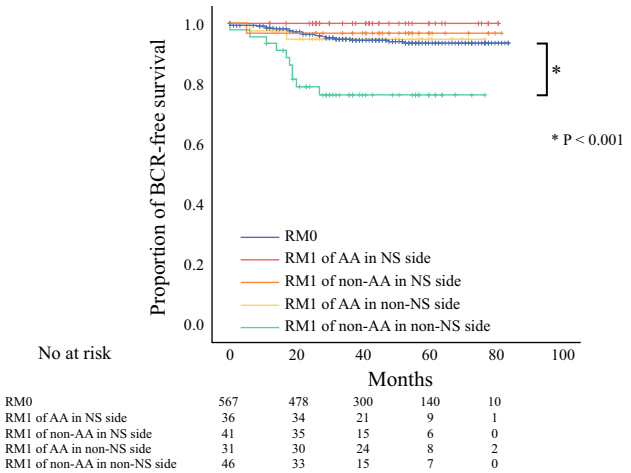


**FIG. 2** Biochemical recurrence curve based on PMS location and NS status

95% CI 1.12–-5.85, $p = 0.026$; Table 4). However, PSM at the AA of non-NS was not statistically associated with BCR-free survival (HR 0.37, 95% CI 0.05-2.85, $p = 0.339$). Additionally, neither AA nor non-AA PSMs of the NS side were significantly associated with BCR-free survival (not assessed due to no event in one group and $p = 0.940$, respectively; Table 4).

## DISCUSSION

In this study, we evaluated the impact of NS on specific locations of PSM and BCR-free survival in patients with localized PCa who underwent RP without any neoadjuvant or adjuvant treatment. When we subcategorized PSM locations into the axial and horizontal planes, the apex and anterior were the most frequent PSM locations. However, the PSM rate at the base increased in the advanced-stage PCa. Regarding the impact of NS on PSM, any NS and BNS were significantly associated with a higher PSM rate after adjusting for confounding factors. In addition, the non-AA PSM rate on the non-NS side in the UNS was significantly higher than that on the NS side in the UNS. In the BCR-free survival analyses, the rate of BCR was significantly higher in patients with PSM than in those without PSM just in case of organ-confined disease. Regarding PSM location and NS status, PSM at non-AA of the non-NS side was a significant risk factor for BCR. However, the AA PSM did not affect BCR regardless of NS status. Generally, NS status differentially affected PSM location and BCR-free survival in patients with PCa after RP.

In a systematic review and meta-analysis of the relationship between NS and PSM, Nguyen et al. showed that NS did not increase the risk of PSM in patients with pT2 or pT3.[17] To reduce the impact of selection bias, Soeterik et al. evaluated the association between NS and the risk of ipsilateral PSM after RALP using multivariate regression analysis.[18] The analysis showed that NS was an independent predictor of ipsilateral PSM (OR 1.42, 95% CI 1.14-1.82). The present study showed that NS was significantly associated with a higher risk of PSM compared with non-NS after adjusting for other influential factors derived from our database (OR 2.29, 95% CI 1.49–3.52). These results, including the present study, suggest that NS affects PSM after adjusting for confounding factors. Therefore, more careful dissection may be required to avoid PSM at the NS side during prostatectomy.

Regarding the impact of UNS or BNS on PSM, a large historical cohort of 9915 patients who underwent RP at a single center between 2000 and 2010 was conducted. It showed that patients with pT2-category disease who underwent the BNS procedure were more likely to have a PSM than those who underwent nerve resection using multivariate analysis.[19] In accordance with the study, we showed that BNS was significantly associated with any PSM after adjusting for confounders. Coelho et al. reported the risk factors of PSM in patients after RALP using 876 consecutive surgical series. In that multivariate analysis including pre-, intra-, and postoperative variables, pathological stage and percentage of the tumor were the only independent risk factors of PSM.[9] They also revealed that NS status, including UNS and BNS, was not statistically

associated with PSM, which is inconsistent with the present study. The surgeries reported by Coelho et al. were performed by a single surgeon with a previous experience of >1500 cases. Although it remains elusive why the difference in the impact of UNS or BNS on PSM occurred, surgeon's experience, including the technique of surgery and judgment of indication for NS, may have had a potential impact on the results. Regarding the technique of NS, a recent meta-analysis has shown that patients undergoing intrafascial NS had a significantly lower PSM rate compared with those experiencing interfascial NS (relative risk [RR] = 0.64, 95% CI 0.48–0.86, $p = 0.003$). Because the present study was a multicenter, retrospective analysis, the indications and techniques of NS varied according to the surgeon's and institutional discretion. Moreover, there might have been several unknown confounding factors due to the substantial number of surgeons involved. Further validation studies are needed to assess the impact of NS on PSM using a unified indication strategy and surgical technique. On the other hand, a deeper understanding of tumor location using preoperative MRI and other potential radiographic imaging was considered to reduce the risk of PSM during RP. However, a randomized study to assess the utility of preoperative 1.5-T MRI revealed that there was no statistically significant difference in the rates of PSM between the MRI and no-MRI groups when looking at all-comers who underwent RP.[20] There is a lack of evidence for the effect of 3T MRI and novel PET imaging modalities on PSM. Therefore, validating these effects of imaging modalities o PSM is imperative in future trials.

There is less evidence regarding the impact of NS status on PSM location. A previous study using data on 945 consecutive patients post RP by a single surgeon between 2002 and 2007 showed that patients with BNS were at higher risk of a posterolateral PSM.[21] In a series of patients who underwent RARP with interfascial NS between 2003 and 2005 in a single-institution study, Zorn et al. evaluated the relationship between NS status and PSM location.[21] They found a significant difference in pT3 posterolateral PSM between men undergoing NS compared with non-NS (73% vs. 33%, $p = 0.05$). Notably, the present study revealed that non-AA PSM at the non-NS side markedly increased in patients with UNS. In addition, the tendency is evident in patients with ≤pT2 disease. Several reasons may explain this result. First, UNS was selected in patients with relatively advanced PCa compared with BNS RP. Second, incremental tissue preservation around the prostate capsule tended to be applied even at the non-NS side during UNS RP. This yielded incomplete resection of NVBs on the non-NS side. Although the reason for this phenomenon is still unclear, we should pay a specific caution of wide resection at the non-AA, including the posterolateral of the non-NS side as well as the NS side during UNS RP.

The systematic review and meta-analysis described above also showed that none of 11 studies demonstrated an increased risk of BCR with any type of NS after adjusting for known prognostic factors.[17] Consistent with this result, our study showed that NS was not a risk factor for BCR after adjusting for confounding factors. In this study, we also assessed the impact of NS on each location of the PSMs with and without considering the NS sides. Accumulating evidence suggested that apical PSM was associated with an equal risk with a negative surgical margin and lower BCR compared with other PSM locations.[10,22] On the other hand, nonapical PSM had the highest risk of BCR.[8] Two important findings of the present study can be observed from the perspective of the impact of NS on BCR while considering PSM location and NS status. First, the AA PSM was not associated with BCR-free survival regardless of the presence or absence of NS. The prostatic apex, which lacks a well-defined capsule and has fewer periprostatic tissues, undergoes stronger retraction during RP than other regions and tends to have pathological artifacts.[22] A retrospective study with a large cohort of the SEARCH database and a long median follow-up (76.8 months) revealed that PSMs at the prostatic apex had lower BCR, metastasis, and PCa death compared with PSMs at other locations.[22] The present results confirm that the PSM at the AA had no impact on BCR regardless of NS status, at least in the short median follow-up period (43.5 m). Second, the risk of BCR in patients with non-AA PSM was different between the NS and non-NS groups. Røder et al. reviewed 1,133 consecutive RP series between 1995 and 2011 in a single-institution study without any adjuvant therapy. They demonstrated that pT2 apical and nonapical PSMs were individually associated with a 2.2- and 3.8-fold increased risk of BCR compared with negative surgical margins.[8] In the study, although the NS-side specific impact of PSM on BCR was not assessed, NS was not statistically associated with BCR (HR 1.2, 95% CI 0.5–1.6). Zorn et al. reported that patients with pT3 tumors who underwent intrafascial NS had a significantly higher posterolateral PSM compared with patients with pT3 tumors undergoing non-NS RALP.[21] To the best of our knowledge, this is the first report to evaluate the impact of PSM location of the non-NS side on clinical outcomes after RP, promoting awareness of PSMs at the non-NS side in the NS RP as well as those at the NS side.

The short duration of follow-up and lack of central pathologists were limitations to the present study. Furthermore, because of the nature of the multicenter retrospective study, the study included different techniques of RP (ORP, LRP, and RARP) and NS techniques (interfascial and intrafascial). In fact, our study has previously demonstrated that the location of PSMs differed according to the type of RP.[23] Unknown confounding factors caused

by the substantial number of surgeons involved in the study cannot be ignored. In addition, the current database was developed in the era of the introduction of RARP in Japan. Therefore, validation studies should be conducted using the pure RARP cohort with unified NS techniques in a recent mature phase of RARP.[24]

## CONCLUSIONS

NS status differentially affects PSM location and BCR-free survival in patients with PCa who underwent RP. UNS increased the risk of non-AA PSM on the non-NS side, which has the potential to be a higher risk of BCR. Avoidance of non-AA PSM on the non-NS side may be rather important than the PSMs on the NS side during RP.

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