# *Favorable risk factors in patients with positive surgical margin after robot-assisted radical prostatectomy*

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***Introduction:*** *Positive surgical margin (PSM) has classically been associated with biochemical recurrence (BCR) following radical prostatectomy (RP) and immediate adjuvant radiotherapy has been advocated based on two large randomized prospective clinical studies. However, a significant percentage of patients with PSM never experience BCR. This study evaluated factors potentially affecting risk of BCR among the patients with PSM after robot-assisted radical prostatectomy (RARP).*
***Materials and methods:*** *From a prospectively maintained database, 699 patients with localized prostate cancer who underwent a RARP without any adjuvant therapy were identified. Median follow up was 46.0 months. To determine the pathologic and clinical factors that influenced BCR, univariate and multivariate analyses using the Cox proportional hazards model were performed. BCR-free survival curves were estimated with Kaplan-Meier method.*
***Results:*** *Surgical margins were positive in 115 patients (16.5%), of whom 23 (20%) had BCR. In the univariate analyses, serum PSA level, surgical Gleason score (GS), and non-organ confined disease were significantly associated with BCR in men with PSM. Multivariate Cox analysis showed that BCR was significantly associated with PSA ($p = 0.011$), and the surgical GS ($p = 0.008$). In patients with lower PSA cutoff (5.3 ng/mL), GS ≤ 7, and organ-confined disease, there were no BCR.*
***Conclusions:*** *In this study, we identified favorable risk factors in patients with PSM following RARP. The results suggest that immediate adjuvant therapy for PSM may not be necessary in men with Gleason score 7 or less, organ-confined disease, and low preoperative PSA.*

**Key Words:** positive surgical margin, biochemical recurrence, RARP

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## Introduction

Although the early detection of prostate cancer with PSA testing has allowed many patients the option of radical treatment with curative intent, prostate cancer is still the second-leading cause of cancer death in men claiming an estimated 28,170 lives in 2012.[1] Radical prostatectomy (RP) has long been recognized as the most definitive treatment for localized prostate cancer while radiotherapy has shown acceptable efficacy. Despite the effectiveness of the therapies for localized disease, approximately 25%-35% of patients eventually develop biochemical recurrence (BCR) within 10 years after RP.[2-4] The ability to predict

BCR after a RP is critical for identifying appropriate patients for adjuvant therapy. In this regard, positive surgical margin (PSM) has been associated with BCR and local disease recurrence as well as the need for secondary treatment after RP.[5,6] More importantly, two large randomized prospective clinical trials have demonstrated that immediate adjuvant radiotherapy in patients with PSM following RP results in decreased BCR rates.[7-9] Notwithstanding, no consensus has yet been reached regarding the optimal treatment of patients with PSM because adjuvant radiation therapy causes complications in a small but significant proportion of patients.[10-12] As a majority of patients with PSM will never experience BCR, a widespread of use of adjuvant radiotherapy results in a considerable overtreatment.

Initially robot-assisted radical prostatectomy (RARP) has been associated with high PSM rates. However, more recent studies have demonstrated that the minimally-invasive surgical approach has equivalent PSM rates when compared to open radical prostatectomy.[13,14] For example, reported PSM rates ranged 11%-37% after open RP, 11%-30% after laparoscopic RP, and 9.6%-26% after RARP.[15-21] From the recent multi-institutional study involving high volume surgeons, overall PSM rate was 15.7%.[22] Accordingly, it is of great importance to establish a clear follow up strategies for patients with PSM.

In this study, we sought to identify factors affecting BCR in patients with PSM after RARP. The results of this study could help identify patients with PSM who may benefit most from adjuvant therapy.

## Materials and methods

### *Patient selection and clinical follow up*

To date, more than 1000 patients with clinically localized prostate cancer underwent RARP at The Cancer Institute of New Jersey (New Brunswick, NJ) by a single surgeon. After Institutional Review Board approval, we reviewed our prospectively maintained database and identified 699 patients with a minimum follow up of 18 months who had full clinical and pathologic information available. We excluded patients who had positive lymph nodes on pathologic evaluation. There were no patients who received neoadjuvant hormonal therapy or adjuvant treatment. All patients were evaluated postoperatively every 3 months for the first 1 year, every 6 months for the next 1 year, and yearly thereafter with serum PSA and physical examination. When BCR was detected, CT and bone scan were obtained. BCR was defined as two consecutive rises in PSA with the last PSA ≥ 0.2.

### *Surgical technique*

All procedures were performed using the da Vinci surgical robot system (Intuitive Surgical Inc., Sunnyvale, CA, USA) via the transperitoneal approach as described previously.[23] Procedure for the preservation of neurovascular bundle was performed using both interfascial and intrafascial nerve sparing techniques. Intrafascial nerve sparing was performed as previously described.[23]

### *Pathologic evaluation*

The prostatectomy specimens were processed by having the external surface inked and step sectioned every 4 mm transversely. The prostate apex was examined by sectioning the tissue sagitally. Following staining with hematoxylin and eosin, Gleason score (GS), pathologic stage, and margin status were assessed. Pathologic staging was done using the 2002 TNM classification. A PSM was defined as the unequivocal presence of tumor at the inked margin of the surgically removed prostate. "Quasi-contact" or "close-by" margins were regarded as negative.[24] Specimens with a single positive slide were considered unifocal PSM, and specimen with two or more positive sections were judged as multiple PSMs.[25]

### *Statistical analysis*

Independent sample Student t-test and the Pearson chi-square test were used to compare continuous and categorical variables, respectively. Kaplan-Meier survival curves were calculated, and the differences were assessed using the log-rank test. The area under the receiver operator characteristic curve (ROC) was used to measure predictive of PSA levels for BCR yielding the highest combined sensitivity and specificity. Univariate and multivariate Cox proportional hazard models were created to control for predictors of BCR. Hazard ratio (HR) and 95% confidence interval (CI) were computed. Statistical analysis was performed by using SPSS 12.0 software (SPSS Inc., Chicago, IL, USA), and a two-sided p value $< 0.05$ was considered to be statistically significant.

## Results

### *Baseline characteristics*

Overall, the PSM rate after RARP was 16.5% (115 of 699 patients). When stratified by surgical stage, PSM rates in organ-confined and non-organ confined disease were 10.2% and 38.0%, respectively. Median follow up was 46.0 months (range, 18-86 months), BCR was observed in 8.2% of enrolled patients during follow up periods. Clinical and pathologic

TABLE 1. **Characteristics of enrolled patients**

| Variables | Surgical margin status | | p value |
|---|---|---|---|
| | Negative (n = 584) | Positive (n = 115) | |
| Mean (range) age (yr) | 59.0 (36-77) | 59.5 (43-77) | 0.448 |
| Preoperative mean (range) PSA (ng/mL) | 6.0 (0.2-52.4) | 6.0 (0.3-21.7) | 0.986 |
| Prostate volume (range) (mL) | 48.1 (18-151) | 47.6 (19-153) | 0.799 |
| Biopsy Gleason score (%) | | | 0.065 |
| ≤ 7 | 540 (92.5) | 100 (81.0) | |
| ≥ 8 | 44 (7.5) | 15 (13.0) | |
| Postoperative Gleason score (%) | | | < 0.001 |
| ≤ 7 | 521 (89.2) | 85 (73.9) | |
| ≥ 8 | 63 (10.8) | 30 (26.1) | |
| Organ confinement (%) | | | < 0.001 |
| Organ-confined | 491 (84.1) | 56 (48.7) | |
| Extra-prostatic | 93 (15.9) | 59 (51.3) | |
| BCR (%) | | | < 0.001 |
| Did not occur | 550 (94.2) | 92 (80.0) | |
| Occurred | 34 (5.8) | 23 (20.0) | |

BCR = biochemical recurrence

characteristics of the patients are presented in Table 1. Margin-positive patients were more likely to bear tumors with high surgical GS and higher pathologic stage. Preoperative PSA and prostate volume were not different between patients with and without PSM. BCR was more frequently detected in PSM group than margin-negative patients (20.0% versus 5.8%).

## *BCR among the patients with PSM*

Initially, we compared the clinicopathological factors in patients with and without BCR in the subset of patients with PSM, Table 2. The preoperative serum PSA level in patients with BCR was significantly greater than that in patients without BCR. In contrast, age, BMI, prostate volume and PSA density were not significantly different between patients with BCR and those without BCR. The incidence of BCR in patients with postoperative GS ≥ 8 and extra-prostatic disease were significantly higher than that in patients with GS ≤ 7 and organ-confined disease. Furthermore, the incidence of BCR in patients with biopsy GS ≥ 8 and high clinical T stage (≥ cT2) were significantly higher than that in patients with biopsy GS ≤ 7 and clinical T1. The BCR rate among multiple PSMs patients was higher than that of unifocal PSM patients, however there was no statistically significant difference. Multiple PSM was significantly associated with GS and had marginal association with organ-confinement, Table 3. The BCR rate did not show any significant association with nerve sparing procedures. As demonstrated in Table 4, there was no difference in BCR according to the location of PSM in 97 patients with unifocal PSM.

Since preoperative PSA levels correlated with the rate of BCR, we next examined varying pre-operative PSA cutoffs on BCR. ROC analysis was carried out and AUC of PSA is shown in Figure 1a. PSA level > 5.3 ng/mL was shown to be a predictive parameter for BCR (sensitivity 78.3%, specificity 55.4%). Using these values patients were classified into high and low PSA groups. Kaplan-Meier estimates revealed significant differences in time to BCR between the low and high PSA groups (log rank test, p = 0.005; Figure 1b). Patients with GS ≥ 8 were significantly more likely to experience BCR than those with GS ≤ 7 (log rank test, p < 0.001; Figure 2a). Extra-prostatic disease was significantly associated with a greater risk of BCR than organ-confined disease (log rank test, p = 0.012; Figure 2b). By univariate Cox proportional hazards analysis, PSA, postoperative GS, and pathologic stage significantly influenced the time to BCR, Table 5. Multivariate Cox proportional hazard analysis revealed that BCR was significantly associated with postoperative GS (HR, 3.285; p = 0.008), and preoperative PSA (HR, 1.148 ; p = 0.011), Table 4.

TABLE 2. **Clinicopathological variables in positive surgical margin patients**

| Variables | BCR | | p value |
|---|---|---|---|
| | Did not occur (n = 92) | Occurred (n = 23) | |
| Mean (range) age (yr) | 59.1 (43-77) | 61.2 (52-69) | 0.179 |
| Mean (range) BMI (kg/m$^2$) | 28.1 (19.6-41.3) | 29.9 (23.5-37.7) | 0.072 |
| Mean (range) preoperative PSA (ng/mL) | 5.5 (0.3-12.1) | 8.2 (0.5-21.7) | 0.018 |
| Prostate volume (range) (mL) | 45.1 (19-101) | 57.6 (26-153) | 0.118 |
| PSA density (range) | 0.13 (0.01-0.34) | 0.17 (0.01-0.59) | 0.138 |
| Biopsy Gleason score (%) | | | 0.002 |
| ≤ 7 | 85 (92.4) | 15 (65.2) | |
| ≥ 8 | 7 (7.6) | 8 (34.8) | |
| Clinical stage (%) | | | 0.044 |
| cT1 | 76 (82.6) | 14 (60.9) | |
| ≥ cT2 | 16 (17.4) | 9 (39.1) | |
| Postoperative Gleason score (%) | | | < 0.001 |
| ≤ 7 | 76 (82.6) | 9 (39.1) | |
| ≥ 8 | 16 (17.4) | 14 (60.9) | |
| Organ confinement (%) | | | 0.02 |
| Organ-confined | 50 (54.3) | 6 (26.1) | |
| Extra-prostatic | 42 (45.7) | 1 7 (73.9) | |
| Number of PSMs (%) | | | 0.378 |
| Unifocal | 76 (82.6) | 17 (73.9) | |
| Multiple | 16 (17.4) | 6 (26.1) | |
| Nerve sparing (%) | | | 0.704 |
| No | 9 (9.8) | 3 (13.0) | |
| Yes* | 83 (90.2) | 20 (87.0) | |

BCR = biochemical recurrence; PSM = positive surgical margin
*all patients underwent bilateral nerve sparing procedures

### *Patient stratification*

Based on Cox proportional hazard analyses, we re-evaluated the patients according to the risk for BCR. At first we stratified the patients with PSM into favorable and unfavorable groups. Favorable group had GS ≤ 7 and preoperative PSA 5.3 ng/mL or less. Kaplan-Meir analysis revealed significant differences in the interval to BCR between the favorable unfavorable group

TABLE 3. **Clinicopathological characteristics according to the number of positive surgical margin**

| Variables | Multiplicity | | p value |
|---|---|---|---|
| | Unifocal (n = 93) | Multiple (n = 22) | |
| Mean preoperative PSA (ng/mL) | 5.88 | 6.95 | 0.265 |
| Postoperative Gleason score (%) | | | < 0.001 |
| ≤ 7 | 75 (88.2) | 10 (11.8) | |
| ≥ 8 | 18 (60.0) | 12 (40.0) | |
| Organ confinement (%) | | | 0.099 |
| Organ-confined | 49 (87.5) | 7 (12.5) | |
| Extra-prostatic | 44 (74.6) | 15 (25.4) | |

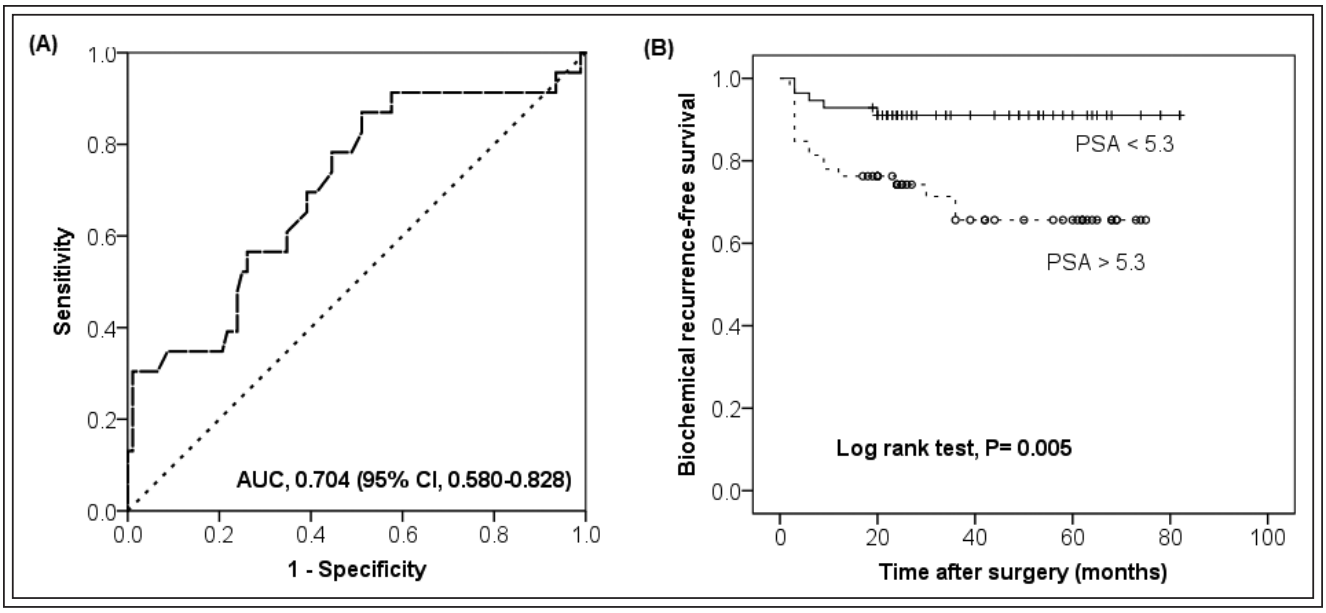


**Figure 1.** **(a)** ROC Receiver operator characteristic of optimal PSA values for biochemical recurrence **(b)** Time to biochemical recurrence for low versus high PSA.

(p = 0.001; Figure 3a). In patients who met all three criteria composed of lower PSA cutoff (5.3 ng/mL), GS ≤ 7, and organ-confined disease, there was no BCR (p = 0.001; Figure 3b). Our recommended algorithm for managing patients with PSM is shown in Figure 4.

## Discussion

In our current study, the overall PSM rate after RARP was 16.5%. This result is comparable to the recent multi-institutional report of 15.7% PSM rate by Patel et al.[22] The incidence of PSM is influenced by the presence of extra-prostatic extension and pathologic GS.[26,27] Likewise our result also has shown that PSM rate was significantly higher in men with extra-prostatic disease than those with organ-confined disease. Since the risk of BCR was significantly higher in patients with PSM (20.0% versus 5.8%, in PSM and negative surgical margin, respectively), results of the present study identify prognostic factors for BCR among patients PSM that may aid in selecting the optimal candidates for adjuvant radiotherapy following surgery.

When patients with PSM were analyzed, factors correlating with cancer aggressiveness such as surgical GS and preoperative PSA were the most important factors independently associated with an increased risk of BCR in our study. As organ-confined disease was associated with BCR only in the univariate analysis, pathologic stage is likely co-linear with surgical GS and/or preoperative PSA. Nevertheless, using these three parameters, we were able to stratify patients with PSM into favorable and unfavorable risk groups for BCR. In the favorable risk group (preoperative PSA < 5.3 ng/mL, surgical GS ≤ 7, and pathologic stage T2), there was no BCR. Therefore in these PSM patients with good prognosis, adjuvant radiotherapy is likely a profound overtreatment.

The number of PSM correlated with significantly increased risk of BCR after RP.[25] In the present study, BCR also occurred more frequently in multiple PSMs group than unifocal PSM group. However, the difference was not statistically significant. In addition, our study revealed that BCR was not associated with the location of PSM. Such finding is similar to the report that showed that the risk of BCR with apical PSM was

TABLE 4. **Margin mapping in unifocal positive surgical margin**

| Location | BCR rate (%) | p value |
|---|---|---|
| Anterior (n = 3) | 0 (0.0) | 0.680 |
| Apex (n = 44) | 8 (18.2) | |
| Bladder neck (n = 13) | 4 (30.8) | |
| Lateral & posterolateral (n =15) | 2 (13.2) | |
| Posterior (n = 18) | 3 (16.7) | |

BCR = biochemical recurrence

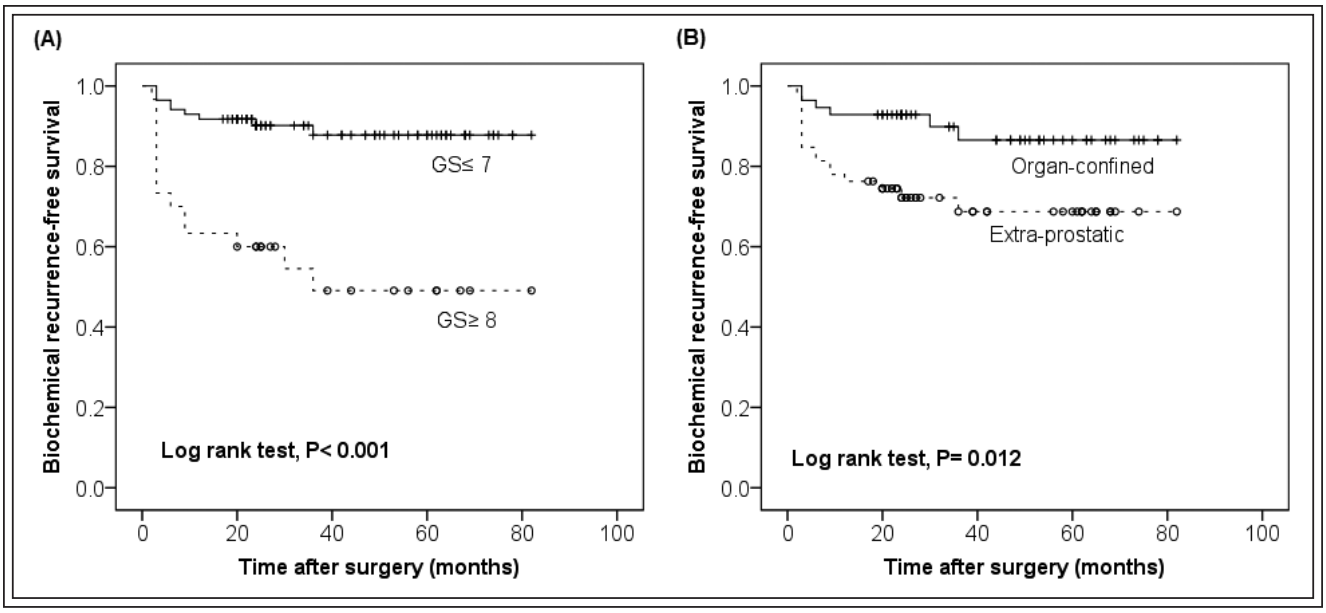


**Figure 2.** Biochemical recurrence-free survival curves according to Gleason score **(a)** and organ confinement **(B)**.

comparable to PSM at other locations.[25] Lastly, we also analyzed an association between nerve sparing procedures and BCR among patients who had PSM. Nerve sparing approach was not associated with BCR.

There have been intense efforts to find the prognostic sub-classification of PSM for BCR.[25,28] The former study by Stephenson et al showed that the number and extent of PSM are associated with a significantly increased of BCR compared to solitary and focal PSM.[25] The latter one found that the linear extent of margin positivity and highest Gleason grade at the PSM were associated with progression.[28] However, these new sub-categorization did not enhance the predictive value of prognosis, which was demonstrated by the concordance index in both study. In this study, we stratified the patients based on parameters easily obtained at most institutions: preoperative PSA, surgical GS, and pathologic stage. If these results are confirmed in a large-scale study, it will provide the clinical criteria for stratifying patients with PSM following RP.

The management of patients with PSM remains controversial. Even with the relatively short follow up period (median 46.0 months) in our study, 80% with PSM did not experience BCR. These results were

TABLE 5. **Cox analyses for biochemical recurrence**

| Variables | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | p value | HR (95% CI) | p value |
| Age | 1.039 (0.978-1.104) | 0.218 | | |
| Body mass index | 1.087 (0.997-1.186) | 0.060 | | |
| Prostate-specific antigen | 1.202 (1.102-1.311) | < 0.001 | 1.148 (1.033-1.277) | 0.011 |
| Postoperative ≤ 7 versus ≥ 8 | 5.210 (2.251-12.059) | < 0.001 | 3.285 (1.135-7.942) | 0.008 |
| Organ confinement (organ-confined versus extra-prostatic) | 3.036 (1.196-7.711) | 0.020 | 1.902 (0.737-4.911) | 0.184 |
| Number of PSMs (unifocal versus multiple) | 1.605 (0.632-4.074) | 0.319 | | |
| Nerve sparing procedure (non-sparing versus sparing) | 1.184 (0.350-4.005) | 0.786 | | |

HR = hazard ratio; CI = confidence interval; PSM = positive surgical margin

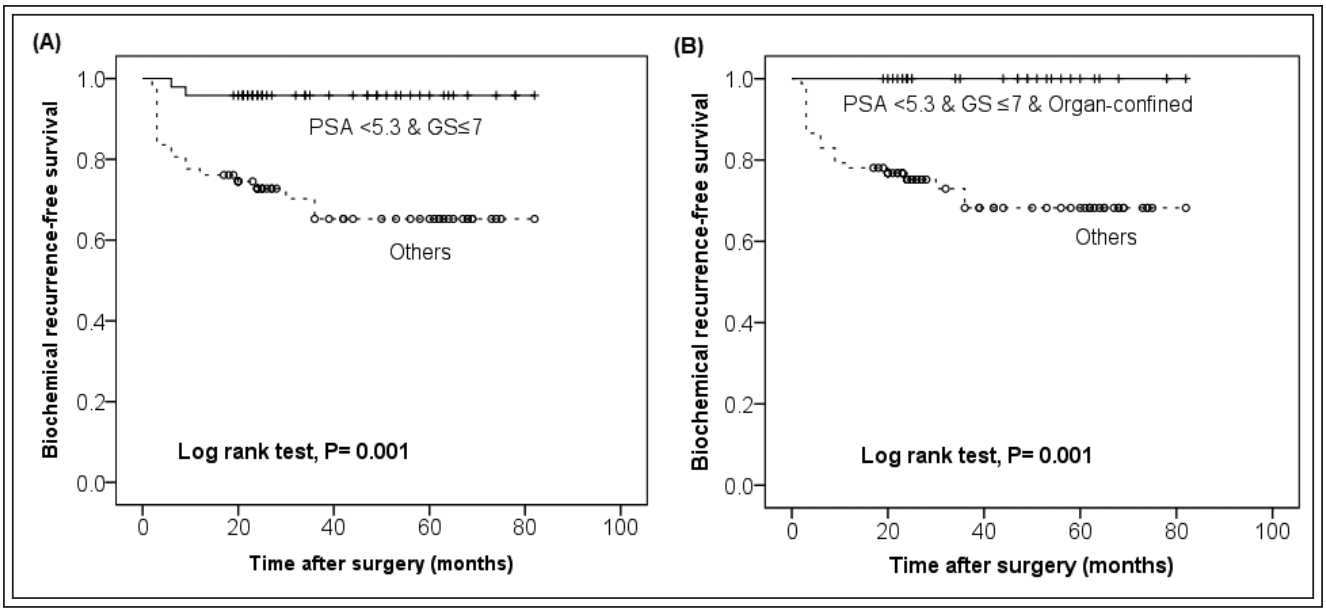


**Figure 3.** Biochemical recurrence after robot-assisted radical prostatectomy stratified by organ confinement, surgical Gleason score, and PSA. **(a)** GS ≤ 7 and less than PSA 5.3 ng/mL versus the others. **(b)** Lower PSA cutoff (5.3 ng/mL), GS ≤ 7, and organ-confined disease versus the others.

consistent with previous study from Simon et al.[29] In their study, only 19% patients with PSM experienced BCR. Several clinical trials have reported that adjuvant radiation was beneficial in patients with PSM.[7-9] However, Soloway et al demonstrated that PSM was associated with BCR but not overall mortality.[30]

That is, patients with PSM who underwent salvage RT after BCR had similar long term outcomes to those who had adjuvant radiotherapy and recurred. In this regard, adjuvant radiation in every man with PSM is clearly an overtreatment. Taken together, our current results suggest a reasonable follow up strategy for patients with PSM. Patients classified into favorable group should be observed. If BCR occurs in these patients, the salvage treatment is just as effective as adjuvant radiation.

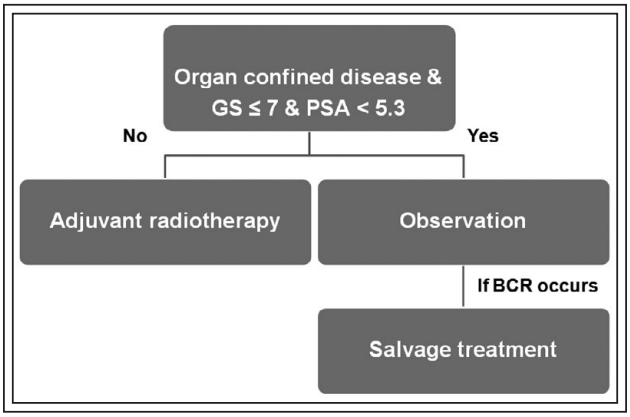


**Figure 4.** Algorithm for managing patients with positive surgical margin.

The drawbacks of the present study are the retrospective study design and relatively small number of events. Since this is a single center single surgeon series, the impact of individual surgeon technique cannot be assessed. However, surgeon volume was not associated with PSM from the first to the last 100 cases analyzed in this study (data now shown). In other aspects, follow up period was relatively short and long term outcomes could not be assessed. Despite these weaknesses, our study reported the predictive factors for the risk of BCR among patients with PSM for the first time in RARP series. With our risk stratification strategy, prospective randomized clinical trial will be initiated.

## Conclusion

In conclusion, in our RARP series of 699 men, PSM was observed in 115 patients (16.5%) and associated with BCR. Among patients with PSM, surgical GS and preoperative PSA were independent predictors of BCR. Based on these results, we have classified the patients into favorable group if the following criteria were met: GS 7 or less and preoperative PSA less than 5.3. These men should be observed after RARP, thereby avoiding overtreatment. □

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