Prediction of A Positive Surgical Margin and Biochemical Recurrence After Robot-Assisted Radical Prostatectomy

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Abstract

A positive surgical margin (PSM) detected in a prostatectomy specimen is associated with poor oncotherapeutic outcomes. Certain aspects regarding the determination of surgical margins and their effects on biochemical recurrence (BCR) remain unclear. This study investigated the predictive factors for PSM and BCR. We prospectively included 419 robot-assisted radical prostatectomy cases. The number of PSM cases was 126 (30.1%), stratified as 22 (12.2%) in stage T2 and 103 (43.6%) in stage T3. Preoperative prostate-specific antigen (PSA) > 10 ng/mL (p = 0.047; odds ratio [OR] 1.712), intraoperative blood loss > 200 mL (p = 0.006; OR 4.01), and postoperative pT3 stage (p < .001; OR 6.901) were three independent predictors for PSM in multivariate analysis. PSA > 10 ng/mL (p < 0.015; hazard ratio [HR] 1.8), pT3 stage (p = 0.012; HR 2.264), ISUP grade > 3 (p = 0.02; HR 1.964), and PSM (p = 0.027; HR 1.725) were four significant predictors for BCR in multivariate analysis. Among PSM cases, ISUP grade > 3 (p = 0.002; HR 2.689) was a significant BCR predictor. These results indicate that PSA level and pathological stage markedly influence the PSM and BCR.

Introduction

Up to 2019, an estimated 4986 robotic systems have been installed in medical centers worldwide, of which 561 are located in Asian countries [1]. Robot-assisted radical prostatectomy (RARP) has become a standard approach for localized prostate cancer (PCa) treatment [2]. This method yields comparable oncological outcomes as previous open and laparoscopic methods, primarily with respect to positive surgical margin (PSM) and biochemical recurrence (BCR), along with enhancements in functional outcomes, including urinary continence and recovery of erectile potency [3–5].

PSM detected in radical prostatectomy (RP) specimens is considered a poor oncological outcome [6]; however, its long-term effect on mortality remains uncertain [7]. Previous studies have reported several predictors for PSM, including prostate-specific antigen (PSA) concentration, prostate weight [8], obesity [9], the histopathological findings from biopsy and RP specimens [10], surgeon experience [11], pathologist interpretation [12], surgical approach [13], and surgical method [14–17], may potentially influence postoperative PSM. However, data from Asian countries regarding the prediction of PSM and BCR are still lacking owing to differences in PCa phenotypes between individuals in Asian and Western countries [18]. It remains difficult for surgeons to determine the risk of PSM before surgery and the effect of PSM on the BCR rate after surgery. In this study, we used case-cohort data from an Asian medical center to further the current understanding of PSM and BCR after RARP.

Results

PSM predictors

In total, 419 patients who underwent RARP were assessed herein (Table 1). Overall, 181 (43.4%) patients were pT2 stage and 236 (56.6%) were pT3 stage. The upgrading rate of the International Society of Urological Pathology (ISUP) grade between biopsy and final RP was significantly higher at the stage T3 (49.6%) than at stage T2 (34.8%; $p = 0.003$).

Table 1
Baseline characteristics of 419 patients treated with robotic prostatectomy. RARP: robot-assisted radical prostatectomy, BMI: body mass index, PSA: prostate-specific antigen, ISUP: International Society of Urological Pathology, RP: radical prostatectomy.

Characteristics	Median (IQR)
Age, year, median (IQR)	66 (62 – 60)
BMI, kg/m^2, median (IQR)	25.2 (23.3–27.2)
Preoperative PSA level, ng/ml, median (IQR)	8.7 (6.2–13.0)
Prostate weight after RARP, g, median (IQR)	30.5 (22.1–43.3)
Follow up, months, median (IQR)	28.2(14.1–51.8)
ISUP grade at biopsy, %	
1	44.0
2	17.5
3	16.6
4	13.2
5	8.7
Pathological T stage, %	
T2	43.4
T3	44.8
T3b	11.8
ISUP grade at RP, %	
1	15.0
2	33.7
3	32.0
4	5.3
5	14.0

Preoperative predictors

Preoperative PSA levels were 8.2 ng/mL among patients with a negative surgical margin (NSM) and 10.6 ng/mL for those with a PSM. Two preoperative factors, namely PSA level ($p < 0.001$) and ISUP grade at biopsy ($p = 0.025$) were significant predictors of PSM in RP specimens. Furthermore, 39% of patients with PSA > 10 ng/mL and 43.2% of those with ISUP grade > 3 had PSM after RARP. Age ($p = 0.84$), body mass index (BMI; $p = 0.158$), and clinical stage determined through magnetic resonance imaging (MRI; $p = 0.827$) exhibited no significant difference between groups displaying positive and negative margins (Table 2).

Table 2

Comparison of predictive characteristics between positive and negative surgical margins for 419 patients having undergone robotic prostatectomy. BMI: body mass index, PSA: prostate-specific antigen, MRI: magnetic resonance imaging, ISUP: International Society of Urological Pathology, RP: radical prostatectomy, TURP: transurethral resection of the prostate, *p-value for difference between margins status < 0.05; statistical analysis, continuous data: t-test, categorical data: chi-square test.

Variable predictors	Negative Margin	Positive Margin	p value
	N = 293	N = 126	
Preoperative			
Age			0.840
Median (range)	66(43–85)	66(48–84)	
BMI			0.158
Median (range)	25.0(15.2–35.5)	25.5(17.8–33.8)	
PSA			< 0.001*
Median (range)	8.2(1.0-52.5)	10.6(4.3–89.9)	
MRI clinical-stage, n(%)			0.827
≤ T2	165(71.1)	67(28.9)	
> T2	84 (70)	36(30)	
ISUP grade at biopsy, n(%)			0.025*
1	137(74.9)	46(25.1)	
2	52(70.3)	22(29.7)	
3	48(70.6)	20(29.4)	
4	37(67.3)	18(32.7)	
5	17(47.2)	19(52.8)	
Intraoperative			
Operative time (mins)			0.625
Median (range)	230(154–480)	233(160–480)	
Estimated blood loss (ml)			0.015*
Median (range)	27(3-800)	30(3-1350)	
Surgical cases, n(%)			0.881
001-100	71(71)	29(29)	

Variable predictors	Negative Margin	Positive Margin	*p* value
	N = 293	N = 126	
101–200	72(72)	28(28)	
201–300	67(67)	33(33)	
301–420	83(70)	36(30)	
Median lobe, n(%)			0.837
Yes	256(69.8)	111(30.2)	
No	37(71.2)	15(28.8)	
History of TURP, n(%)			0.936
Yes	275(70)	112(30)	
No	18(69.2)	14(30.8)	
History of abdominal surgery, n(%)			0.408
Yes	186(69.7))	81(30.3)	
No	20(62.5)	12(37.5)	
Nerve-sparing, n(%)			0.047*
Yes	10(50)	10(50)	
No	282(70.9)	116(29.1)	
Postoperative			
Clavien complication, n(%)			0.248
Grade 0	241(68.7)	110(31.3)	
Grade ≥ 1	52(76.5)	16(23.5)	
ISUP grade at RP, n(%)			< 0.001*
1	54(85.7)	9(14.3)	
2	104(73.8)	37(26.2)	
3	89(66.4)	45(33.6)	
4	18(81.8)	4(18.2)	
5	28(47.5)	31(52.5)	
Pathological T stage, n(%)			< 0.001*
T2	159(87.8)	22(12.2)	

Variable predictors	Negative Margin	Positive Margin	*p* value
	N = 293	N = 126	
T3a	107(57.2)	80(42.8)	
T3b	26(53.1)	23(46.9)	
Prostate weight			
Median (range)	30.9(6-124.4)	29.3(8.4-170.4)	0.141

Intraoperative predictors

The surgical duration of RARP did not affect the PSM rate. The estimated blood loss increased slightly but significantly (30 mL vs. 27 mL; $p = 0.015$) in the PSM group over the NSM group. The PSM rate was steady, with approximately 30% per 100 cases ($p = 0.881$) in a single surgeon's experience. The intraoperative factors associated with surgical complexity, including having had previous abdominal surgery, previous transurethral resection of the prostate (TURP), and a prominent median lobe, displayed a similar one-third of patients PSM and NSM groups.

Postoperative predictors

Overall, 125 (30.1%) patients presented PSM, and they were classified as follows in accordance with their pT stage: 22 (12.2%) at stage T2, 80 (44.8%) at stage T3a, and 23 (46.9%) at stage T3b ($p < 0.001$). Furthermore, the PSM rate was significantly higher at a higher grade of ISUP in RP specimens ($p < 0.001$). The prostate weight in prostatectomy was similar between the two groups ($p = 0.141$). Overall, the postoperative findings indicated that the more advanced the disease's progression was, the higher the PSM rate was upon final pathological examination.

The location and number of PSMs

The percentage of PSMs (Table 3) in the apex, bladder neck, and posterolateral regions was 27.7%, 13.5%, and 73.8%. Ninety-four (74.6%) RP specimens presented unifocal, while 29 (23%) presented multifocal positive margins. The PSA level, pT stage, and ISUP grade at RP were significantly associated with PSMs in the bladder neck, posterolateral, and unifocal and multifocal regions, respectively. The amount of intraoperative estimated blood loss was significantly higher in the apex of the PSM ($p < 0.001$), whereas an enlarged prostate median lobe was significantly more common in the bladder neck of PSM (9.6% vs. 3.3%; $p = 0.047$). Moreover, the nerve-sparing (NS) procedure was significantly associated with PSM in the bladder neck ($p < 0.001$) and posterolateral ($p = 0.012$) regions. Regarding the number of PSMs, BMI, previous abdominal surgery, and NS procedures were predictive factors for PSMs in multifocal regions. Prostate weight, surgical cases, and previous TURP history were not significantly correlated with the foci between the positive and negative margins.

Table 3

Predictors based on the location and number of positive surgical margins. PSA: prostate-specific antigen, BMI: body mass index, ISUP: International Society of Urological Pathology, RP: radical prostatectomy, TURP: transurethral resection of the prostate, AP: apex, BN: bladder neck, PL: posterolateral, UF: unifocal, MF: multifocal, *p-value for difference between margins status < 0.05; statistical analysis, continuous data: t-test, categorical data: chi-square test.

Variable predictors	**AP**	**BN**	**PL**	**UF**	**MF**
	N = 35	**N = 17**	**N = 93**	**N = 94**	**N = 29**
Continuous data					
Age					
Median (range)	68(48–76)	65(50–70)	66(43–85)	66(43–85)	67(55–78)
BMI					*p = 0.025
Median (range)	25.6(20–31)	26.3(21–33)	25.8(18–34)	25.0(18–34)	26.8(22–33)
PSA		*p = 0.001	*p < 0.001	*p = 0.023	*p < 0.001
Median (range)	11.6(4–78)	11(5–90)	10.4(4–90)	9.7(4–87)	12.2(5–90)
Prostate weight					
Median (range)	28.1(14–90)	29.3(16–87)	29(8-170)	29.6(8-170)	28.1(15–77)
Operative time (mins)					
Median (range)	230(165–480)	215(180–345)	235(160–480)	234(165–440)	230(160–480)
Estimated blood loss (ml)	*p < 0.001				
Median (range)	30(5-1350)	30(3-550)	30(3-1350)	32(3-750)	30(5-1350)
Categorical data					
Biopsy ISUP score, n(%)			*p = 0.019	*p = 0.017	
1	14(7.7)	5(2.7)	35(19.1)	32(17.5)	12(6.6)
2	10(13.5)	3(4.1)	16(21.6)	13(17.6)	8(10.8)
3	4(5.9)	4(5.9)	13(19.1)	18(26.5)	2(2.9)
4	4(7.3)	1(1.8)	12(21.8)	17(30.9)	1(1.8)
5	3(8.3)	4(11.1)	16(44.4)	14(38.9)	5(13.9)
RP ISUP score, n(%)		*p = 0.005	*p = 0.001	*p = 0.005	*p = 0.032
1	4(6.3)	0(0)	6(9.5)	10(15.9)	0(0)

Variable predictors	AP	BN	PL	UF	MF
	N = 35	N = 17	N = 93	N = 94	N = 29
2	12(8.5)	3(2.1)	27(19.1)	23(16.5)	11(7.8)
3	14(10.4)	7(5.2)	32(23.9)	34(25.4)	10(7.5)
4	0(0)	0(0)	4(18.2)	4(18.2)	0(0)
5	5(8.5)	7(11.9)	24(40.7)	23(39.0)	8(13.6)
MRI clinical Stage, n(%)					
≤ T2	20(8.6)	6(2.6)	48(20.7)	50(21.6)	15(6.5)
> T2	7(5.8)	8(6.7)	27(22.5))	30(25)	6(5)
Pathological T stage, n(%)		*$p < 0.001$	*$p < 0.001$	*$p < 0.001$	*$p < 0.001$
T2	17(9.4)	0(0)	10(5.5)	20(11.0)	3(1.7)
T3	18(7.6)	16(6.8)	82(34.7)	74(31.4)	25(10.6)
Clavien complication, n(%)					
Grade 0	31(8.8)	15(4.3)	81(23.1)	81(23.1)	25(7.1)
Grade ≥ 1	4(5.9)	2(2.9)	12(17.6)	13(19.1)	4(5.9)
Median lobe, n(%)		*$p = 0.047$			
Yes	3(5.8)	5(9.6)	9(17.3)	13(25.0)	2(3.8)
No	32(8.7)	12(3.3)	84(22.9)	81(22.1)	27(7.4)
History of TURP, n(%)					
Yes	0(0)	1(3.8)	7(26.9)	4(15.4)	3(11.5)
No	35(8.9)	16(4.1)	86(21.9)	90(22.9)	26(6.6)
History of abdominal surgery, n(%)					*$p = 0.018$
Yes	3(9.4)	2(4.1)	11(34.4)	6(18.8)	6(18.8)
No	19(7.1)	11(6.2)	62(23.2)	59(22.1)	18(6.7)
Nerve-sparing, n(%)		*$p < 0.001$	*$p = 0.012$		*$p = 0.018$
Yes	34(8.5)	13(3.3)	84(21.1)	88(22.1)	25(6.3)
No	1(5)	4(20)	9(45)	6(30)	4(20)
Surgical cases, n(%)					

Variable predictors	AP	BN	PL	UF	MF
	N = 35	N = 17	N = 93	N = 94	N = 29
001-100	11(11)	4(4)	18(18)	25(25)	5(5)
101–200	9(9)	2(2)	19(19)	20(20)	4(4)
201–300	6(6)	7(7)	27(27)	24(24)	9(9)
301–420	9(7.6)	4(3.4)	29(24.4)	25(21)	11(9.2)

Multivariate analysis of PSMs

In multivariate analysis (Table 4), the pT3 stage, PSA > 10 ng/mL, and estimated blood loss > 200 mL were significant predictors for PSM rates ($p < 0.001$, odds ratio [OR] 6.901; $p = 0.047$, OR 1.712; and $p = 0.001$, OR 4.010, respectively). Conversely, a higher clinical T (cT) stage was significantly associated with a lower PSM rate ($p = 0.040$, OR 0.058), which was in contrast with the effect of the pT stage on the margin status. The ISUP grade at biopsy ($p = 0.130$) or RP specimens ($p = 0.787$) displayed a similar ratio between PSM and NSM groups. On comparing the NS and non-NS methods, no significant changes in the PSM rate were observed ($p = 0.742$).

Table 4
Analysis of the primary parameters to predict positive surgical margins after robotic prostatectomy by multivariate logistic regression analysis. PSA: prostate-specific antigen, EBL: estimated blood loss, cT: clinical T stage by MRI, pT: pathological stage by RP specimens, ISUP: International Society of Urological Pathology, RP: radical prostatectomy, NS: nerve-sparing, *p-value for difference between margins status in multivariate analysis < 0.05.

Predictive parameters	*p* value	Odds Ratio (95% CI)
PSA > 10 ng/ml	0.047*	1.712 (1.008–2.907)
EBL > 200 ml	0.006*	4.010 (1.496–10.752)
cT3 stage	0.040*	0.548 (0.308–0.974)
pT3 stage	< 0.001*	6.901 (3.624–13.142)
ISUP at biopsy > 3	0.130	1.656 (0.862–3.180)
ISUP at RP > 3	0.787	0.908 (0.449–1.833)
NS procedure	0.742	0.825 (0.261–2.602)

Effect of PSMs on biochemical recurrence

In total, 395 (94.3%) patients were available for follow-up evaluation, and 97 (24.6%) patients developed recurrent PSA. The overall 5-year biochemical recurrence (BCR)-free survival rate was 66.7%. Figure 1 indicates that PSM's presence significantly decreased the 5-year BCR-free survival rate in the log-rank test

($p < 0.001$). Among patients with a PSM, the 1-, 3-, and 5-year BCR-free survival rates were 79.7%, 61.1%, and 41.9%; by comparison, those with an NSM were 88.9%, 80.9%, and 71.4%, respectively. Regarding the number of PSMs, the 5-year BCR-free survival curve was similar in the multifocal and unifocal groups ($p = 0.172$).

In univariate analysis (Table 5), the initial predictors of PSA, BMI, cT stage, pT stage, PSM, NS procedures, ISUP grade at biopsy, and RP were significantly correlated with the 5-year BCR-free survival rate. In multivariate analysis, only four independent predictors, namely PSA > 10 ng/mL ($p = 0.015$, hazard ratio [HR] 1.801), pT3 stage ($p = 0.012$, HR 2.264), ISUP grade > 3 at RP ($p = 0.020$, HR 1.964), and PSM ($p = 0.027$, HR 1.725), were positively correlated with PSA recurrence. When pooling four independent predictors during multivariate analysis, the PSM parameter became less significant in predicting the 5-year BCR-free survival rate (Table 6). In pT2 stage disease, the PSA level, ISUP at RP, and PSM were not significant predictors of BCR-free survival. For pT3 stage disease, the predictors of both PSA > 10 ng/mL ($p = 0.025$, HR 1.710) and ISUP grade at RP > 3 ($p = 0.002$, HR 2.851) were significantly associated with BCR-free survival. Among patients with an NSM, the predictors of PSA > 10 ng/mL ($p = 0.006$, HR 2.218), ISUP grade at RP > 3 ($p = 0.001$, HR 2.774), and pT3 stage ($p = 0.003$, HR 2.615) significantly influenced the BCR-free survival. However, an ISUP grade > 3 detected in RP specimens was the only significant predictor of BCR-free survival ($p = 0.002$, HR 2.689).

Table 5
Analysis of the primary predictors of 5-year biochemical recurrence-free survival by the log-rank test and univariate analysis and multivariate Cox regression models. PSA: prostate-specific antigen, pT: pathological T, PSM: positive surgical margin, ISUP: International Society of Urological Pathology, RP: radical prostatectomy, cT: clinical T, NS: nerve-sparing, BMI: body mass index. *p-value for difference between biochemical recurrence in multivariate analysis < 0.05.

Predictive parameters	Univariate	Multivariate	
	p value	Hazard ratio (95% CI)	p value
PSA > 10 ng/ml	< 0.001	1.801(1.123–2.888)	0.015*
pT3 stage	< 0.001	2.264(1.199–4.275)	0.012*
PSM	< 0.001	1.725(1.065–2.792)	0.027*
ISUP at RP > 3	< 0.001	1.964(1.111–3.472)	0.020*
ISUP at biopsy > 3	< 0.001	0.809(0.463–1.413)	0.809
cT3 stage	< 0.001	1.548(0.944–2.536)	0.083
NS procedure	0.001	0.518(0.240–1.118)	0.094
BMI > 25 kg/m2	0.012	1.176(0.744–1.859)	0.487

Table 6
Analysis of the primary parameters classified based on pathological stage and margin status to predict the 5-year biochemical recurrence-free survival through multivariate Cox regression analysis. pT: pathological T, PSA: prostate-specific antigen, ISUP: International Society of Urological Pathology, RP: radical prostatectomy, NSM: negative surgical margin, PSM: positive surgical margin, *p-value for difference between biochemical recurrence in multivariate analysis < 0.05.

Predictive parameters	Hazard Ratio (95% CI)	p value
Overall (n = 417)		
ISUP at RP > 3	2.727(1.776–4.185)	< 0.001*
pT3 stage	2.510(1.441–4.370)	0.001*
PSA > 10 ng/ml	1.660(1.092–2.523)	.018*
PSM	1.365(0.895–2.081)	.149
pT2 stage (n = 181)		
ISUP at RP > 3	1.384(0.180-10.618)	.775
PSA > 10 ng/ml	2.393(0.784–7.305)	.126
PSM	1.504(0.566–3.994)	.413
pT3 stage (n = 236)		
ISUP at RP > 3	2.851(1.816–4.476)	.002*
PSA > 10 ng/ml	1.710(1.069–2.737)	.025*
PSM	1.251(0.802–1.952)	.323
NSM (n = 293)		
ISUP at RP > 3	2.744(1.523–4.944)	.001*
pT3 stage	2.615(1.379–4.956)	.003*
PSA > 10 ng/ml	2.218(1.379–4.956)	.006*
PSM (n = 126)		
ISUP at RP > 3	2.689(1.428–5.067)	.002*
pT3 stage	1.655(0.564–4.856)	.359
PSA > 10 ng/ml	1.158(0.630–2.130)	.636

Discussion

RARP offers potential benefits such as a low PSM rate compared with open RP owing to better visibility and less blood loss [19,20]. In our series, the overall PSM rate was 30.1%, which is a higher rate than that reported in high-volume RARP studies, in which the range typically was 10.8–22% [21]. This may be attributable to a much higher percentage (56.6%) of patients in the pT3 stage in our study than in other studies, where the percentage of pT3 stage patients ranged from 9.3 to 37.5% [21].

We determined the major preoperative predictor for the PSM rate to be PSA > 10 ng/mL. The predictors of the ISUP score upon biopsy and the cT stage defined through MRI did not exhibit a positive correlation in multivariate analysis. Liss et al. assessed 216 cases of RARPs and concluded, similar to us, that the preoperative predictive factor of PSM was PSA level instead of cT stage and ISUP score [22]. The author explained this phenomenon because a portion of patients was transferred from other hospitals; thus, biopsy methods and MRI outcomes were not standardized, potentially yielding different results. Another reason we proposed may be the high pathological ISUP (43%) and T stage (30.2%) upgrading rate from biopsy to prostatectomy in our database. These factors may limit the precise prediction of the postoperative PSM rate through the use of the preoperative cT stage and ISUP grade.

Estimated blood loss > 200 mL is a significant intraoperative predictor of the PSM rate, and we speculated that intraoperative bleeding would hinder clear visualization from identifying prostate margins and prolonging the surgical time. In our study, further analysis found the operative time was longer among patients with an estimated blood loss of > 200 mL than in those with an estimated blood loss of ≤ 200 mL (mean: 303 min vs. 235 min, respectively). Kim et al. determined that higher blood loss was associated with larger prostate size in a series of 1168 RARPs. Nevertheless, the final PSM rate did not significantly differ among divided-size subgroups [23]. Tamhankar et al. reviewed 1406 RARPs to determine the steepness of the surgical learning curve reflected by the extent of blood loss and reported a 70% reduction in blood loss from the start to the end of the training period. However, the surgical time and the number of cases were not associated with the risk of PSM [24].

Individualized surgical experiences may influence RARP performance. Several studies have reported that the PSM rate is inversely proportional to the number of surgical cases [25–28]. In our study, a single surgeon with extensive prior experience in laparoscopic surgery performed the surgeries; consequently, the PSM rate was almost the same at approximately 30% per 100 cases. This finding suggests that the surgeon's previous experience in minimally invasive surgery can minimize the risk of PSMs when using a robotic surgical approach. White et al. reported a single-urologist case series and revealed that extensive previous experience in ORP might potentially prevent an increase in the PSM rate during the initial learning curve in RARP [29].

The pT3 stage predictor was significantly correlated with a high PSM rate according to previous reports [21,22,30–33]. Ficarra et al. studied 322 RARPs and reported that the pathological findings of extraprostatic extension (EPE) were the only relevant PSM predictor [34]. Previous studies have reported that T upstaging rates varied widely from 4.5–68% of cases [35,36]. In this study, T upstaging occurred in one-third of cases,

suggesting that preoperative understaging data may result in underresection of prostate tumors. In particular, the ISUP grade at RP is not considered an independent predictor, implying that total resection of high-grade tumors can be accomplished without leaving positive margins. A Partin table is a useful tool developed at John Hopkins Hospital for evaluating the risk of EPE before prostatectomy on the basis of preoperative PSA, ISUP, and clinical stage [37]. However, in our data, only preoperative PSA level was significantly associated with EPE in multivariate analysis. The discrepancy of preoperative ISUP and clinical stage in pathological reports of RP specimens may reduce the utility of preoperative parameters for predicting postoperative PSM.

Kang et al. reported the distribution of surgical margins in high-risk PCa, with positive rates of 16.2% in the apex, 14.7% in the bladder neck, 38.2% in posterolateral regions, and 26.5% in multifocal regions [30]. For our study, the majority of PSM is 73.8% in the posterolateral, 27.7% in apical and 13.5% in bladder neck regions. Previous studies have reported that the high PSM rate occurs in the posterolateral area, especially for high-risk pT3 diseases [30,38]. Eastham et al. reported large amounts of neurovascular tissue over the posterolateral region, potentially enhancing tumor cell migration and promoting local invasion [39]; furthermore, the BCR rate was higher among individuals with posterolateral PSM than in those with NSM (HR: 2.80). The NS procedure is associated with the PSM in the posterolateral region [22,40], potentially explaining the high technical skill needed for successful dissection of the correct planes of fascia. However, the current results demonstrated that the NS group had a lower risk of PSM in the posterolateral region than the non-NS group did (3% vs. 20%). This is probably because of the higher percentage of patients in the pT3 stage than in the pT2 stage in the non-NS group (79% vs. 21%), which may be more influential than NS techniques.

Previous studies have been reported the apex is the most frequent region of PSM in RP specimens [31,41]. This is attributable to the unclear prostate capsular margins, which are difficult to identify in pT2 and pT3 stages [38]. More other studies have reported that apical PSM is correlated with the surgeon's approach and skills rather than the tumor stage [21,26,41]. The surgeon in this study has extensive laparoscopic experience, explaining the relatively low rate of PSM in the apex. The estimated blood loss was significantly higher among patients with apical PSM, which implies potential bleeding from the dorsal vein complex upon dissection of the apical prostate [42]. Coelho et al. reported that high BMI was a predictor for apical PSM in a cohort study involving 876 RARPs [31], and our study determined that high BMI was significantly associated with higher odds of PSMs at multifocal regions ($p = 0.025$) but not apical regions.

Koizumi et al. reported that employing the RARP approach has a higher likelihood of leading to PSM at the bladder neck than either ORP or LARP do [29]. This is possible because of the excessive preservation of bladder neck tissue to secure postoperative urinary continence [15]. Furthermore, the presence of a prominent median lobe during surgery might increase the risk of PSM over the bladder neck ($p = 0.047$), indicating the challenging task of identifying surgical margins between the protruding prostatic lobe and bladder neck.

Several studies have reported patients who underwent prostatectomy with a 5-year BCR-free survival rate ranging from 74–87% and a median PSA recurrence time of 2.6 years [43–45]. In this study, the 5-year BCR-free survival rate was 66.7%, which was lower than that reported in other studies; this is probably owing to the higher ratio (53%) of aggressive pT3 disease at the outset of the accumulation of RARP cases. Evidence supports the characterization of PSM as a strong predictor of disease progression [46–48]. Our data indicate that the hazard ratio for PSM with BCR is 1.725 ($p = 0.027$). Recently, Zhang et al. performed a systematic review and meta-analysis, wherein they included 38000 patients and determined PSM to be an independent factor with higher BCR in multivariate analysis ($p < 0.001$, pooled HR 1.35) [6]. Ploussard et al. analyzed a prospective study including 1943 RPs with a mean follow-up of 68 months and suggested that PSM was a significant predictor of BCR, the need for salvage therapy, and even cancer-related death. However, PSM was significantly correlated with BCR at stage pT2 and pT3a disease but not pT3b stage disease [48]. PSM's effect on BCR in stage pT3b disease was reportedly weak owing to a markedly higher risk of micrometastatic lesions, which are more influential than PSM is. Similarly, our study's PSM effect was nonsignificant in the pT3 stage compared with the other two predictors, PSA and ISUP grade.

In particular, among men who underwent RARP with postoperative PSM, an ISUP grade > 3 at RP ($p = 0.002$, HR 2.689) was the sole predictor of BCR-free survival regardless of pT stage and PSA concentration. Karakiewicz et al. reported similar results among 5831 RPs, indicating that the PSM group had a 3.7-fold higher risk of progression, particularly in the group with tumors at an ISUP grade > 2 in PSM [47]. Furthermore, Kang et al. reported that pathological ISUP grade > 3 was a predictor for BCR ($p = 0.047$, HR 4.180). These results suggest that disease progression depends on the PCa tumor grade in surgical margins [49]. Moreover, Stephensen et al. reported the effect of the number and extent of PSM on BCR, indicating that a mildly increased risk of BCR is significantly correlated with multifocal and extensive PSM [50]. However, we did not analyze the effect of PSM's extent; the current evidence is inadequate to differentiate the effect of unifocal and multifocal PSM on BCR-free survival. The residual low-grade tumors on PSM may not increase the BCR rate. Our study’s surgeon used electrocautery methods when dissecting the prostate fascia, thus indirectly decreasing the residual tumors on margins and reducing PSA recurrence risk. Furthermore, in Asian countries, the incidence of PCa is relatively low; however, the type of PCa typical to Asia is more aggressive than that in Western countries [18,51]. A high percentage of PCa patients have pT3 stage disease in prostatectomy, which may reduce the influence of PSM in terms of PCa progression.

Limitations

First, since we retrospectively obtained clinical data, there may have been an inherent selection bias in the analysis. Second, the lack of standardized MRI and pathological interpretations from other hospitals may affect the results in prostatectomy. Third, the results were obtained from a single experienced surgeon; thus, the technical details regarding NS methods and the determination of prominent prostate median lobes may have led to subjective bias. Fourth, we determined prostate size by using the data from RP

specimens instead of presurgical imaging, which may have restricted the clinical application of this method for preoperative assessment. Finally, some cases were lost to follow-up early during the study, and some clinically significant diseases recurred after five years. The current follow-up duration was limited for the prediction of the final endpoint of BCR.

Conclusion

This study is the most up-to-date study in an Asian population to assess the predictors of PSM and BCR on RARP. Our results indicated that PSA level, pT stage, and estimated blood loss were the significant predictors of the PSM rate. Regarding the 5-year BCR-free survival, PSA, pT stage, ISUP grade, and PSM were identified as clinically significant predictors in multivariate analysis. In pT3 stage disease, PSM was less significant than PSA and ISUP grade for predicting PSA recurrence. Nevertheless, in cases of PSM observed after prostatectomy, ISUP grade > 3 was the sole predictor of PSA recurrence.

Material And Methods

Patients and study design

A medical record of 419 patients who underwent RARP from December 2010 to January 2018 at Taipei Veterans General Hospital, Taiwan, were analyzed retrospectively in this study. The research protocol was approved, and the need for informed consent was agreed to be waived by the Institutional Review Board and Human Research Protection Center of Taipei Veterans General Hospital (No.: 2020-05-001BC). The patient records were anonymized and de-identified before analysis. All study procedures involving data collection and management were in accordance with relevant guidelines and regulations. The indication for prostatectomy was clinically localized prostate cancer revealed through prostate biopsy. Most patients had undergone MRI for presurgical clinical-stage evaluation. We preoperatively collected the following clinical data: age, BMI, PSA, ISUP grade, and cT stage (defined through MRI). The following intraoperative parameters were noted: surgical time, estimated blood loss, previous TURP, previous abdominal surgery, prominent prostate median lobe (observed by the surgeon), number of surgical cases, and the use or nonuse of NS methods. The following postoperative parameters were recorded: margin status, ISUP at RP specimens, pT stage, prostate weight, Clavien complication grades, and the point of PSA recurrence within five years (defined as PSA level ≥ 0.2 ng/mL in two separate measurements). The locations of PSM were classified as apical, bladder neck, posterolateral, unifocal, and multifocal areas to evaluate the predictive risks. At least two qualified pathologists interpreted the final RP pathological reports.

Exclusion criteria: patients with a history of neoadjuvant hormone therapy or any focal treatment, including radiotherapy, cryotherapy, high-intensity focused ultrasound therapy, and salvage prostatectomy, were excluded. Furthermore, patients lost to follow-up within two months of RARP, and those who received adjuvant therapy owing to adverse pathological outcomes before PSA relapse were excluded.

Preoperative PSA levels were determined immediately before the prostate biopsy, and postoperative PSA levels were determined within 1-month post-biopsy and then at 3-month intervals until PSA recurrence was confirmed. Time zero marked the date of RARP, and patients without BCR did not present PSA recurrence on the most recent follow-up evaluation before the end of 2019. An increase in serum PSA levels was identified twice, and other factors potentially elevating PSA levels were excluded.

RARP

All RARPs were performed by a single urologist (H.J.C) who had > 15 years' experience in laparoscopic urological surgery. For RARP, the transperitoneal approach was adopted, employing the Intuitive Surgical da Vinci® Surgical System Si or Xi with six ports. The prostatic anterior fat pad was removed to visualize the prostatic boundaries. The bladder neck was opened and separated from the prostate. By dividing the vesicoprostatic muscle, the vas deferens and seminal vesicles were exposed. Bilateral vas deferens were transected and then pulled anteriorly to facilitate the dissection of seminal vesicles. The Denonvilliers' fascia was identified, and the posterior plane was carefully dissected from the base to the prostate apex to preserve neurovascular bundles. The prostatic apex was dissected, thus maximally preserving the urethral stump. The apex was laterally dissected from the anteromedial components of the levator ani. The urethra was posteriorly incised, and the prostate was removed. The vesicourethral anastomosis was conducted using a continuous suture. Finally, the incised detrusor apron was reapproximated.

Statistical analysis

The IBM SPSS® Statistics 20 United States was used for statistical analysis. Pearson's chi-square and independent samples *t*-test were used for assessing categorical and continuous data, respectively. The predictive factors of the PSM rate were compared through multivariable logistic regression analysis. The Kaplan–Meier method was used to estimate the 5-year BCR-free survival rate, and the log-rank test was performed to compare the correlations between each factor and BCR-free survival determined through univariate analysis. The factors influencing BCR-free survival were analyzed using multivariate Cox proportional hazards regression analysis in stratified pathological stage and surgical margin status, separately.

Declarations

Author contributions

Ching-Wei Yang is the first author. He is responsible for patient data collection, statistical analysis, and manuscript writing. Hsiao-Hsien Wang, Mohamed Fayez Hassouna, and Manish Chand are co-authors. They review the manuscript and provide academic reinforces. Hsiao-Jen Chung is the corresponding author. He is responsible for manuscript proofreading.

Competing interests

To the best of our knowledge, the named authors have no conflict of interest, financial or otherwise.

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Figures

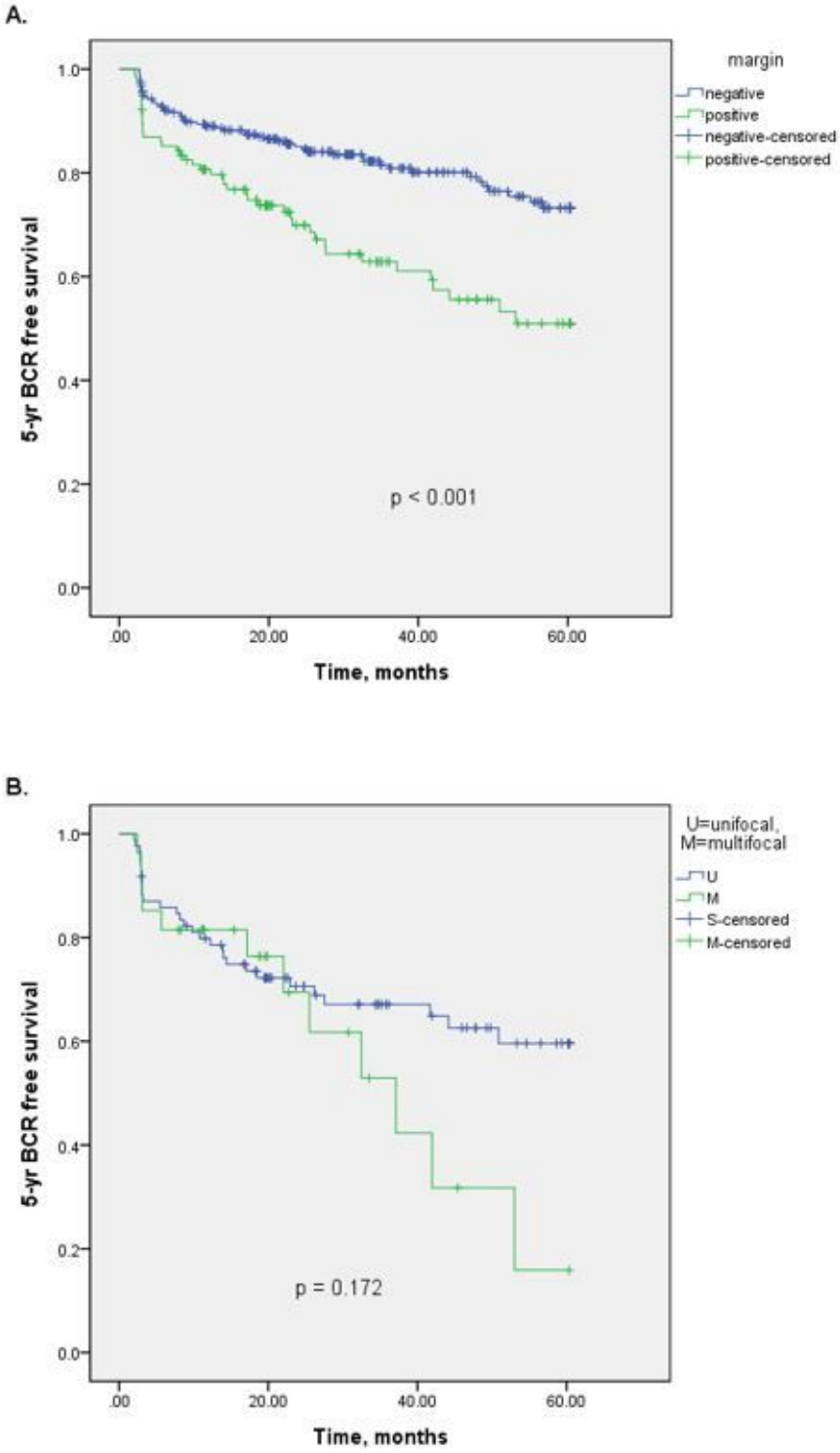

Figure 1

Kaplan–Meier curve for 5-year biochemical recurrence (BCR)-free survival stratified by margin status. (A) Stratified by positive and negative surgical margins ($p < 0.001$); (B) stratified by unifocal and multifocal positive surgical margins ($p = 0.172$).