Original Article

Positive Surgical Margins after Radical Prostatectomy: Associated Risk Factors in Thai Prostate Cancer Patients

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Objective: To explore and identify the associated risk factors contributing to positive surgical margins after open radical prostatectomy (ORP), laparoscopic radical prostatectomy (LRP), and robotic-assisted radical prostatectomy (RARP) in a high-volume tertiary center of Thailand.

Materials and Methods: From January 2013 to September 2019, the data of 1,070 prostate cancer patients treated with ORP, LRP, and RARP were retrospectively studied. After excluding cases with pathologically positive lymph nodes, the remaining 995 patients were categorized into 2 groups: one with PSMs and one without PSM. The data of both groups were evaluated using independent t-test, Mann–Whitney U-test, Pearson's Chi-squared test, and univariate and multivariate analyses.

Results: Of the 995 patients, 575 patients (57.8%) had PSMs. Oncologic factors (prostate specific antigen [PSA], prostate weight, percentage of tumor volume, pathologic T stage [pT], and ISUP Gleason Grade Group) were significantly different between the two groups. Meanwhile, patient factors (age and body mass index) and surgical factors (ORP, LRP, RARP, surgeon experience, and nerve sparing) were not significantly different. By multivariate logistic regression analysis, the independent factors associated with the occurrence of PSM were PSA >10 (odds ratio [OR]: 1.65; 95% confidence interval [CI]: 1.16 to 2.34; $p = 0.005$), prostate weight (OR: 0.99; 95% CI: 0.98 to 0.99; $p = 0.003$), tumor volume ≥50% (OR: 3.43; 95% CI: 1.48 to 7.95; $p = 0.004$), pT3 (OR: 2.34; 95% CI: 1.68 to 3.25; $p<0.001$), and ISUP Gleason Grade Group >1 ($p<0.05$).

Conclusion: The independent factors associated with PSM after radical prostatectomy were the oncologic factors, which were PSA, prostate weight (small prostate), percentage of tumor volume, pT, and ISUP Gleason Grade Group. On the contrary, patient factors (age and BMI) and surgical factors (surgical procedure, surgeon experience, and nerve sparing) were found to be unassociated with PSM.

Keywords: Prostate cancer, Radical prostatectomy, Positive surgical margins, Associated factors, Risk factors, Predictive factors

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Prostate cancer is a very common malignancy in men after the age of 50[1]. Among the male population, it is the 2nd most common cancer worldwide[2] and the 4th most common cancer in Thailand[3]. For localized prostate cancer, there are many curative treatment options. Radical prostatectomy is widely accepted as an effective standard management[4,5]. Various oncologic outcomes are used to assess the primary success of radical prostatectomy, with surgical margin status being one of those[6]. Positive surgical margin (PSM) after radical prostatectomy is, by definition, the histological presence of cancer cells at the ink-stained margin of an excised specimen[7], implying that incomplete surgical resection of the cancer has occurred. Many results from contemporary studies indicate that PSM can lead to poorer oncologic outcomes, such as a higher risk of biochemical recurrence (BCR)[8-16], as the earliest sign of cancer relapse resulting in clinical progression and death from cancer[17]. PSM is also associated with worse cancer-specific survival, overall survival, cancer-specific mortality, and overall mortality in prostate cancer patients[9,18]. In addition, extensive or multifocal PSMs can result in an even higher risk of biochemical recurrence[10,11,19]. The occurrence rate of PSM in the literature widely ranges from 5 to 30% in organ-confined disease to 17 to 65% in locally-advanced disease[20-22]. Several recent studies have been conducted to figure out the associated risk factors contributing to PSM[23-29]. Nevertheless, most research has been performed on American and European populations, thus this study purposefully aimed to investigate the associated risk factors leading to PSM from a contemporary cohort of radical prostatectomy cases in a Thai population. The large volume of data of this study was collected in a tertiary referral center with a high volume of the prostatectomy patients in Thailand.

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Materials and Methods

Study setting and population

The study protocol was approved by the Ethics Committee of Siriraj Institutional Review Board (419/2562(EC2)), Faculty of Medicine, Siriraj Hospital, Mahidol University.

A total of 1,070 prostate cancer patients who underwent open radical prostatectomy (ORP), laparoscopic radical prostatectomy (LRP), or robotic-assisted radical prostatectomy (RARP) using Intuitive da Vinci robotic surgical system (model S, Si, and Xi) from January 2013 to September 2019 in Siriraj Hospital, a tertiary care university center, were retrospectively investigated in the study. After excluding pathologically positive lymph node (pN+) cases and cases with incomplete information, 995 patients remained in the study for data analysis.

Data collection procedures

Data from operative and histopathologic records were thoroughly evaluated in terms of patient factors, surgical factors, and oncologic factors. Patient factors were the patient's age and body mass index (BMI). Surgical factors consisted of the surgical procedures (ORP, LRP, and RARP), nerve sparing status, and surgeon experience, which were categorized into <10 years' (5 surgeons) and ≥10 years' experience (5 surgeons) in prostatectomy. Meanwhile, serum prostate specific antigen (PSA) level, prostate weight, percentage of tumor volume within the prostate, pathological T status (pT; based on the 2016 TNM system[30]), and ISUP Gleason Grade Groups (1 to 5; according to the 2014 International Society of Urologic Pathology (ISUP) system[31]) were considered as oncologic factors. Patients with metastatic disease and a pathologically positive lymph node from nodal specimens were excluded from the study. The patients who had received neoadjuvant hormonal therapy were also excluded from the study.

Outcome measures and statistical analysis

The purpose of the study was to search for the associated factors contributing to PSM from the contemporary data from the radical prostatectomy of Thai patients. The authors categorized patients into two groups: one group with PSMs and one without PSM. A positive surgical margin (PSM) was defined as the presence of cancer cells at the inked margin of an excised prostate specimen. All variables (patient, surgical, and oncologic factors) were analyzed in both groups. For continuous data, they were reported as the means and medians, whereas the numbers of patients and their percentages were presented for the categorical data. Data of both groups were analyzed using an independent t-test or Mann-Whitney U-test for continuous variables, and Pearson's Chi-squared test for the categorical ones. Univariate logistic regression analysis was conducted for all variables. Then, we used a multivariate logistic regression model by a backward selection method to discover the truly independent factors associated with PSM and their degrees of correlation from the adjusted odds ratio (OR).

PASW (SPSS) Statistics version 18.0 software was used for the statistical calculations. Statistical significance was confirmed when the *p*-value was <0.05.

Results

In total, 995 patients remained after exclusion of the nodal metastatic cases. The mean age was 67.87 years old and mean BMI was 24.69 kg/m^2. These 995 patients comprised 575 (57.8%) cases with PSMs and 420 (42.2%) without PSM. Factors of interest and their distribution in both groups are summarized in Table 1. Along with the patient factors (age and BMI), the surgical factors (ORP, LRP, RARP, surgeon experience of 10 years, and nerve sparing) were not significantly different between the two groups. Meanwhile, the oncologic factors (PSA, prostate weight, % tumor volume, pT, and ISUP Gleason Grade Group) were evidently different. The patients with PSM had a higher PSA and % tumor volume, but lower prostate weight. As well as pT and ISUP Gleason Grade Group, there were more patients in the PSM group than the other one for the higher pT (pT3) and Gleason Groups (2 to 5).

As per the above results, similar results were found from our univariate and multivariate logistic regression models for PSM prediction (Table 2). In the univariate analysis, the factors significantly related to PSM were PSA, prostate weight, percentage of tumor volume, pathological T, and ISUP Gleason Grade Group. Similarly, these five variables were all significant as independent factors associated with PSM in the multivariate logistic regression analysis (*p*-value <0.05). On the other hand, the variables in the patient and surgical factors (age, BMI, surgical procedure, surgeon experience, and nerve sparing) were not significantly correlated with PSM in both logistic regression models.

Discussion

PSM leads to an increased risk of many adverse oncologic outcomes after radical prostatectomy, namely, BCR[8-16], prostate cancer-specific mortality, and overall mortality[9,18]. PSM may also predict metastatic progression of the disease[32]. Thus, it is essential to identify the risk factors associated with PSM when treating prostate cancer by surgical means.

Recently, a series of contemporary studies have pointed out identifiable risk factors related to PSM. Nevertheless, most of those studies included only robotic-assisted or laparoscopic procedures (LRP or RARP)[23-25,27,28]. According to a recently published systematic review and meta-analysis of all prospective comparative studies[33], and also another meta-analysis comparing RARP with ORP[34], it has been demonstrated that there are no significant differences between RARP/LRP and open surgery (ORP) in terms of the overall PSM rate and overall complication rate. Therefore, we included ORP, LRP, and RARP all together in this study and we found out in the same way that all three surgical procedures were not different in terms of the PSM rate (Table 1), with a similar result in the univariate analytic model (Table 2).

Table 1. Demographic data and factors of interest in the study

Factors	Overall (n = 995)	Patients with PSM (n = 575)	Patients without PSM (n = 420)	*p*-value
Patient factors				
Age (years old)	67.87±6.43	67.73±6.55	68.06±6.62	0.417
BMI (kg/m^2)	24.69±3.33	24.75±3.39	24.59±3.24	0.453
Surgical factors				
Surgical procedure				
RARP	611 (61.4)	351 (61.0)	260 (61.9)	0.896
LRP	272 (27.3)	157 (27.3)	115 (27.4)	
ORP	112 (11.3)	67 (11.7)	45 (10.7)	
Surgeon experience				
<10 years	291 (29.2)	162 (28.2)	129 (30.7)	0.384
≥10 years	704 (70.8)	413 (71.8)	291 (69.3)	
Nerve sparing				
None	648 (65.3)	376 (65.6)	272 (64.9)	0.770
Unilateral	69 (7.0)	37 (6.5)	32 (7.6)	
Bilateral	275 (27.7)	160 (27.9)	115 (27.4)	
Oncologic factors				
PSA (ng/ml)	9.98 (0.30, 191.70)	11.00 (1.00, 191.70)	8.49 (0.30, 160.00)	<0.001
Prostate weight (grams)	38.35 (7.0, 243.0)	37.15 (7.0, 243.0)	40.00 (10.0, 151.0)	0.023
Tumor volume (%)	12.00 (0.50, 95.00)	17.00 (0.50, 95.00)	8.00 (1.00, 90.00)	<0.001
Pathological T				
pT2	531 (54.1)	237 (41.3)	294 (72.2)	<0.001
pT3	450 (45.9)	337 (58.7)	113 (27.8)	
ISUP Gleason Grade Group				
1	104 (11.8)	30 (5.8)	74 (20.1)	<0.001
2	356 (40.3)	199 (38.7)	157 (42.5)	
3	196 (22.2)	117 (22.8)	79 (21.4)	
4	91 (10.3)	67 (13.0)	24 (6.5)	
5	136 (15.4)	101 (19.6)	35 (9.5)	

The data are presented as n (%) or mean ± SD or median (minimum, maximum).
PSM = Positive surgical margin, BMI = Body mass index, ORP = Open radical prostatectomy, LRP = Laparoscopic radical prostatectomy, RARP = Robotic-assisted radical prostatectomy

Unlike several studies[23-27], the authors excluded pathologic nodal metastatic (pN+) cases from the study after reviewing the histopathologic results of pelvic lymph node specimens dissected during prostatectomy. This is because we mainly aimed to conduct the study in localized prostate cancer patients where the nodal positive ones were excluded.

In the previous literature, the reported rate of PSM widely ranged from 5 to 30% in organ-confined disease to 17 to 65% in locally-advanced disease[20-22]. In our report, the overall PSM rate was 57.7% (575/995), which was quite a bit higher than in the other studies. The possible reason for this might be that the authors conducted our research in a tertiary care referral center in Thailand, therefore a large volume of patients with locally-advanced cancer that was considered to be difficult to operate on in surgery at other hospitals were referred to our center. Consequently, as high as 45.0% and 47.9% of the cases in our cohort of patients were high stage (pT3) and high grade (ISUP Gleason Grade Group 3 to 5), respectively. Both these factors are accepted as contributors to PSM in most studies, as well as in our results. Moreover, the different ethnicity may involve a distinct pelvic anatomy or gene, leading to an alteration in surgical outcomes between our Thai cohort and Western populations[35]. The PSM rate for the pT3 subgroup in the present study was 58.7%, which was comparable to those of Porcaro et al[24] (71.2% in pT3 treated with RARP) and Ceylan et al[36] (71.5% in pT3 treated with ORP).

Similar to most reports[24-28,37], after controlling for the confounding factors, the multivariate analysis of our study (Table 2) demonstrated that the independent factors associated with PSM were the oncologic factors, namely, PSA, prostate weight, tumor volume, pathological T, and Gleason Group. All these variables were risk factors increasing the chance of producing PSM (adjusted OR >1.0), except for prostate weight. The adjusted OR for prostate weight was 0.99, 95% CI (0.98, 0.99; $p = 0.003$), indicating that a higher volume of prostate decreased the risk for PSM. This was consistent with some other studies[38,39]. It was possible that a lower prostate weight (or volume) might lead to a higher proportion of tumor-to-prostate, and thus more chance of PSM being obtained. This was also the explanation for the percentage of tumor volume, as in our findings, being a contributing factor to PSM.

On the other hand, the patient factors (age and

Table 2. Univariate and multivariate analyses of the risk factors for PSM

Variables	Univariate analysis		Multivariate analysis	
	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age (years old)				
>65	1 (ref)			
≤65	1.10 (0.85, 1.43)	0.465		
BMI (kg/m^2)				
Underweight (<18.5)	1 (ref)			
Normal (18.5 to 24.9)	0.73 (0.27, 1.99)	0.536		
Overweight (25.0 to 29.9)	0.75 (0.27, 2.07)	0.574		
Obese (≥30.0)	0.86 (0.28, 2.64)	0.797		
Surgical procedure				
RARP	1 (ref)			
LRP	1.01 (0.76, 1.35)	0.939		
ORP	1.10 (0.73, 1.66)	0.640		
Surgeon experience				
<10 years	1 (ref)			
≥10 years	1.13 (0.86, 1.49)	0.384		
Nerve sparing				
None	1 (ref)			
Unilateral	0.84 (0.51, 1.38)	0.482		
Bilateral	1.01 (0.76, 1.34)	0.965		
PSA (ng/ml)				
<10	1 (ref)		1 (ref)	
10 to 20	1.79 (1.14, 2.39)	<0.001	1.65 (1.16, 2.34)	0.005
>20	2.44 (1.69, 3.53)	<0.001	1.51 (0.95, 2.41)	0.082
Prostate weight (grams)	0.99 (0.98, 0.99)	0.003	0.99 (0.98, 0.99)	0.003
Tumor volume (%)				
<50	1 (ref)		1 (ref)	
≥50	5.73 (2.70, 12.15)	<0.001	3.43 (1.48, 7.95)	0.004
Pathological T				
pT2	1 (ref)		1 (ref)	
pT3	3.70 (2.82, 4.86)	<0.001	2.34 (1.68, 3.25)	<0.001
ISUP Gleason grade group				
1	1 (ref)		1 (ref)	
2	3.13 (1.95, 5.02)	<0.001	2.59 (1.55, 4.32)	<0.001
3	3.65 (2.19, 6.09)	<0.001	2.07 (1.18, 3.63)	0.011
4	6.89 (3.67, 12.93)	<0.001	3.69 (1.85, 7.35)	<0.001
5	7.12 (4.02, 12.62)	<0.001	2.75 (1.42, 5.33)	0.003

PSM = Positive surgical margin, CI = Confidence interval, OR = Odds ratio, BMI = Body mass index, ORP = Open radical prostatectomy, LRP = Laparoscopic radical prostatectomy, RARP = Robotic-assisted radical prostatectomy, PSA = Prostate specific antigen, ref = reference

BMI) and surgical factors (surgical procedure, surgeon experience, and nerve sparing) were unassociated with PSM in our research. For BMI, the association with PSM is still controversial. Some studies found that BMI was related to PSM[23,24,26,28], while other studies[27,40,41], including ours, did not. For surgeon experience, our result seemed different from most of the previous studies demonstrating that high-volume or high-experience surgeons were associated with lower PSM[23,24,26,42,43]. However, those studies reported the surgeon experience in terms of the numbers of cases they operated on, whereas the present study analyzed surgeons by experience duration of <10 years and ≥10 years of performing prostatectomy (each group consisted of 5 surgeons) and we did not find a significant difference in the PSM rate. The authors used a 10-year duration because almost every surgeon in our center had operated on a nearly-equal frequency of cases in the same period of time. Nonetheless, the authors hypothesized that some degree of association might be discovered if the authors analyzed in detail regarding the location of PSM within the prostate of PSM cases between these two groups of surgeons. A study by Tian and associates[27] did not find an association of PSM with differences in the experiences of the surgeons either. The nerve sparing procedure was found to be unassociated with PSM in our research, which confirmed literature findings[24,28].

There were some limitations in the present study. First, the study was retrospective in nature, and thus bias was unavoidable. Second, some pre-operative data, such as core needle biopsy or magnetic resonance imaging (MRI) findings, were not included in the present study. It was quite difficult to collect all these data since some of them had been performed elsewhere in other hospitals. Third, further oncologic outcomes, such as BCR rate, salvage therapy rate, cancer-specific mortality, or overall mortality, were not yet obtainable. Therefore, our further study aims to evaluate more data, such as preoperative MRI, positions of PSM, and more suitable oncologic outcomes.

Conclusion

According to the present study, conducted in a high-volume center, the independent factors associated with PSM after radical prostatectomy were oncologic factors, namely, PSA, prostate weight, percentage of tumor volume, pathological T, and ISUP Gleason Grade Group. On the contrary, patient factors (age and BMI) and surgical factors (surgical procedure, surgeon experience, and nerve sparing) were found to be unassociated with PSM.

What is already known on this topic?

There have been several studies about predictive factors associated with PSM after prostatectomy. However, most of those contemporary studies primarily focused only on robotic-assisted or laparoscopic procedures (LRP or RARP) and were conducted mainly in Caucasian (American and European) patients. Therefore we decided to create this study.

What this study adds?

The present study provides information about the associated risk factors leading to PSM from the latest contemporary data of radical prostatectomy cases, mainly focused on Thai patients. The large volume of data in this study was collected in a tertiary referral center with a high volume of prostatectomy cases in Thailand. Moreover, the study included all surgical procedures, namely, ORP, LRP, and RARP.

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Potential conflicts of interest

The authors declare no conflict of interest.

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ผลบวกมะเร็งที่ขอบชิ้นเนื้อหลังการผ่าตัดต่อมลูกหมากออกทั้งหมด: ปัจจัยเสี่ยงที่เกี่ยวข้องในผู้ป่วยมะเร็งต่อมลูกหมากชาวไทย

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วัตถุประสงค์: เพื่อสำรวจและระบุปัจจัยเสี่ยงที่เกี่ยวข้องที่มีส่วนทำให้เกิดผลบวกมะเร็งที่ขอบชิ้นเนื้อหลังการผ่าตัดต่อมลูกหมากออกทั้งหมดแบบผ่าตัดเปิด ผ่าตัดผ่านกล้อง และผ่าตัดโดยใช้หุ่นยนต์ช่วย ในศูนย์ระดับตติยภูมิที่มีผู้ป่วยจำนวนมากของประเทศไทย

วัสดุและวิธีการ: จากเดือนมกราคม พ.ศ. 2556 ถึง เดือนกันยายน พ.ศ. 2562 ข้อมูลผู้ป่วยมะเร็งต่อมลูกหมากจำนวน 1,070 รายที่รักษาด้วยการผ่าตัดต่อมลูกหมากออกทั้งหมดแบบผ่าตัดเปิด ผ่าตัดผ่านกล้อง และผ่าตัดโดยใช้หุ่นยนต์ช่วย ได้ถูกนำมาศึกษาย้อนหลัง ภายหลังการคัดออกผู้ป่วยที่มีผลต่อมน้ำเหลืองทางพยาธิวิทยาเป็นบวก ผู้ป่วยที่เหลืออยู่ 995 รายได้ถูกจำแนกออกเป็น 2 กลุ่ม คือกลุ่มที่มีผลบวกมะเร็งที่ขอบชิ้นเนื้อจากการผ่าตัด และไม่มีผลบวกมะเร็งที่ขอบชิ้นเนื้อจากการผ่าตัด ข้อมูลผู้ป่วยทั้งสองกลุ่มได้ถูกประเมินโดยใช้ independent t-test, Mann-Whitney U-test, Pearson's Chi-squared test, univariate และ multivariate analyses

ผลการศึกษา: จากผู้ป่วย 995 ราย พบผู้ป่วย 575 ราย (ร้อยละ 57.8) มีผลบวกมะเร็งที่ขอบชิ้นเนื้อจากการผ่าตัด ปัจจัยด้านมะเร็ง (prostate specific antigen [PSA], น้ำหนักต่อมลูกหมาก, ร้อยละของปริมาณมะเร็ง, ระยะโรคทางพยาธิวิทยา [pT] และ ISUP Gleason Grade Group) มีความแตกต่างอย่างมีนัยสำคัญระหว่างทั้งสองกลุ่ม ในขณะที่ปัจจัยด้านผู้ป่วย (อายุและดัชนีมวลกาย) และปัจจัยด้านการผ่าตัด (การผ่าตัดต่อมลูกหมากออกทั้งหมดแบบผ่าตัดเปิด, ผ่าตัดผ่านกล้อง, ผ่าตัดโดยใช้หุ่นยนต์ช่วย, ประสบการณ์ของศัลยแพทย์ และการเก็บเส้นประสาท) ไม่มีความแตกต่างอย่างมีนัยสำคัญ จากการวิเคราะห์ multivariate logistic regression ปัจจัยอิสระที่เกี่ยวข้องกับการเกิดผลบวกมะเร็งที่ขอบชิ้นเนื้อจากการผ่าตัดคือ PSA >10 (odds ratio [OR]: 1.65; 95% confidence interval [CI]: 1.16 ถึง 2.34; $p = 0.005$), น้ำหนักต่อมลูกหมาก (OR: 0.99; 95% CI: 0.98 ถึง 0.99; $p = 0.003$), ปริมาณมะเร็ง ≥50% (OR: 3.43; 95% CI: 1.48 ถึง 7.95; $p = 0.004$), pT3 (OR: 2.34; 95% CI: 1.68 ถึง 3.25; $p<0.001$) และ ISUP Gleason Grade Group >1 ($p<0.05$)

สรุป: ปัจจัยอิสระที่เกี่ยวข้องกับการเกิดผลบวกมะเร็งที่ขอบชิ้นเนื้อหลังการผ่าตัดต่อมลูกหมากออกทั้งหมดคือ ปัจจัยด้านมะเร็ง ซึ่งได้แก่ PSA, น้ำหนักต่อมลูกหมาก (ต่อมลูกหมากเล็ก), ร้อยละของปริมาณมะเร็ง, pT และ ISUP Gleason Grade Group ในทางตรงกันข้ามปัจจัยด้านผู้ป่วย (อายุและดัชนีมวลกาย) และปัจจัยด้านการผ่าตัด (การผ่าตัดต่อมลูกหมากออกทั้งหมดแบบผ่าตัดเปิด, ผ่าตัดผ่านกล้อง, ผ่าตัดโดยใช้หุ่นยนต์ช่วย, ประสบการณ์ของศัลยแพทย์ และการเก็บเส้นประสาท) ถูกพบว่าไม่เกี่ยวข้องกับการเกิดผลบวกมะเร็งที่ขอบชิ้นเนื้อจากการผ่าตัด