Predictors of positive surgical margins after radical prostatectomy at a single institution: preoperative and pathologic factors, and the impact of surgeon variability and technique on incidence and location

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Introduction: *To identify and assess predictive factors for positive surgical margins (PSM) in patients undergoing radical prostatectomy (RP).*

Materials and methods: *An Institution Review Board (IRB) approved retrospective review of 1751 patients that underwent RP from March 2000 to June 2013 was performed. Identified were 1740 patients whom had not received neoadjuvant therapy; these were used for the purpose of this analysis. Univariate and multivariate analysis were performed to determine factors associated with and predictive of PSMs, divided into preoperative and pathological. Variables analyzed include age, body mass index (BMI), race, surgeon, surgical modality, pathologic T-stage and Gleason sum, extracapsular extension (ECE), seminal vesicle involvement (SVI), perineural invasion (PNI) and prostate weight. Finally, each surgical technique was analyzed to determine the most common site of PSM.*

Results: *Rate of PSM was 23.6%. Our analysis showed that preoperative prostate-specific antigen (PSA) level ≥ 10ng/mL, and pathologic T3/T4-stage and PNI significantly predicted PSM. Age > 60 years and prostate weight > 60 g were predictive against PSM. Gleason score ≥ 7 and PSM were significant risk factors for biochemical recurrence (BCR). Surgical approach did not affect the rate of PSM. Open RP was associated with a higher apical PSM rate (38.5%) and robotic RP with a higher posterolateral PSM rate (52.3%).*

Conclusions: *High preoperative PSA levels, and advanced TNM-staging predicted positive surgical margins in our cohort. Patients with PSM were subsequently found to have higher risk of BCR.*

Key Words: radical prostatectomy, positive surgical margins, prostate cancer, biochemical recurrence

Introduction

Positive surgical margins (PSM) after radical prostatectomy (RP) are an important adverse pathological feature, given their association with an increased risk of biochemical recurrence (BCR).[1,2] PSM are defined as presence of tumor at the inked margin of a resected surgical specimen. Despite the improvements in surgical techniques over the years, the occurrence of PSM is relatively common. Reported incidence of PSM in various contemporary studies ranges from less than 11% to as high as 38%.[3,4] Recent multivariate analyses have established that PSM are considered an independent predictor of prostate cancer specific mortality.[5-9] In an effort to provide patients with the best possible oncological outcome, it is universally accepted to minimize the incidence of PSM.

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Going back decades, advances in surgical technique (particularly a better understanding of the surgical anatomy) have helped to reduce the incidence of PSM while the impact of technology has not been agreed upon.[10] Additionally, patient stratification by perioperative and demographic risk factors has also aided in understanding the probability of PSM. Some of the risk factors that have been noted to correlate with PSM include: preoperative Gleason score, preoperative prostate-specific antigen (PSA) and tumor stage.[11] Adjuvant treatment strategies use these risk factors to determine patients at high risk for BCR and most appropriate for up-front additional treatment. Because RP has evolved toward a more minimally invasive procedure, we sought to identify additional risk factors for the development of PSM in RP by surgical approach.

Materials and methods

A single institution retrospective review of a RP database was performed, including procedures performed by several surgeons from March 2000 to June 2013. This is an Institution Review Board (IRB) approved database in which data has been collected prospectively. Patients were initially evaluated at the Multidisciplinary Genitourinary Cancer Center of the Kimmel Cancer Center at Thomas Jefferson University. A total of 1751 patients underwent RP over this time period. Patients that had received hormonal ablation therapy prior to undergoing surgical management were excluded from this analysis. In addition, patients that underwent a radical cystoprostatectomy for concurrent bladder carcinoma and/or who were incidentally found with prostate cancer at that time were also excluded. This provided a cohort of 1740 patients included in this analysis. This cohort comprised the transitional time period from open retropubic radical prostatectomy, [ORRP (505 patients)], to laparoscopic radical prostatectomy, [LRP (192 patients)], to robotic assisted radical prostatectomy, [RARP (1043 patients)]. Missing data were accounted for by using multiple imputations.

All prostate specimens were submitted in their entirety and underwent standard whole mount step sectioned pathologic analysis in order to determine surgical Gleason score, pathologic stage and margin status. The location of each positive margin on the prostatic specimen was examined. A confirmatory second level pathologic review with a genitourinary pathologist and the surgical team was performed weekly in a multidisciplinary genitourinary pathology conference.

TABLE 1. **Clinical and pathological characteristics of 1740 patients treated with radical prostatectomy between March 2000 and June 2013**

Predictors	n	Percentage (%)
Race		
White	1241	71.3
Non white	499	28.7
Body mass index (kg/m^2)		
≤ 24.9	309	17.8
> 24.9	1431	82.2
Age (years)		
< 60	903	51.9
≥ 60	837	48.1
Preoperative PSA		
< 10 ng/mL	1544	88.7
≥ 10 ng/mL	196	11.3
Pathologic Gleason score		
≤ 6	1209	69.4
7	405	23.4
≥ 8	126	7.2
T-stage		
T2	1340	77.0
T3/4	400	23.0
Prostate weight (g)		
≤ 30	412	23.9
31-60	1115	63.5
≥ 60	213	12.6
Extracapsular extension		
Unifocal	285	16.4
Multifocal	90	5.2
None	1365	78.4
Seminal vesicle involvement		
(+)	136	7.8
(-)	1604	92.2
Peripheral neural involvement		
(+)	1273	73.2
(-)	467	26.8
Surgical margins		
(+) margin	409	23.6
(-) margin	1331	76.4
Surgical modality		
ORRP	505	29.0
LRP	1192	11.0
RARP	1043	60.0

ORRP = open radical retropubic prostatectomy;
LRP = laparoscopic radical prostatectomy;
RARP = robotic assisted radical prostatectomy

Univariate analysis using Pearson's Chi-square and multivariate Logistic Regression analysis were performed to determine factors associated with and predictive of PSMs, respectively. Factors analyzed were age, body mass index (BMI) (normal was defined as ≤ 24.9), preoperative PSA (< 10 ng/mL versus ≥ 10 ng/mL), surgeon, surgical approach, postoperative stage (T2 versus T3/4), postoperative Gleason sum (≤ 6 versus 7 versus ≥ 8), extracapsular extension, ECE, (unifocal versus multifocal versus none), seminal vesicle involvement (SVI), perineural invasion (PNI), and prostate size as determined by weight in grams (≤ 30 versus 31-60 versus ≥ 61). A total of 13 possible surgeon scenarios were assessed (including individual versus a combination of attending physicians). For LRP and our first 2 years of RARP (150 cases), we performed a lymph node dissection (LND) only on patients who were considered intermediate or high risk by D'Amico classification. Starting in late 2007 until current, we have performed a LND on all patients undergoing RARP, regardless of risk stratification. We have always performed a LND on all patients undergoing ORRP. Our template for LND is standard with the exception of extended in a very select group of patients. The importance of PSM as a risk factor of BCR was demonstrated using data available on 424 follow up patients. A Cox regression model and Kaplan Meier method were used for this purpose. Finally, each surgical modality was analyzed for the most common sites of PSM using One-Way ANOVA analysis.

Results

The distribution of demographic and pathological characteristics of the cohort in this study is shown in Table 1. In total, there was PSM in 409 (23.6%) specimens. Table 2 shows univariate analysis comparing these characteristics in patients with PSM and those without PSM. Preoperative PSA ($p < 0.001$), pathologic T-stage ($p < 0.001$), Gleason sum ($p < 0.001$), ECE ($p < 0.001$), SVI ($p < 0.001$), PNI ($p < 0.001$) and prostate weight ($p = 0.002$) were associated with PSM. There was no significant association between age, BMI, race and the surgeons involved, with PSM.

In the multivariate analysis, Table 3, PSA level ≥ 10 ng/ml (OR: 1.99[1.35-2.95], $p = 0.001$), pathologic T3/T4-stage (OR: 2.83[1.38-5.83], $p = 0.005$), and PNI (OR: 2.89[1.98-4.23], $p < 0.001$) were associated with a significantly higher risk of PSM. Age > 60 years (OR: 0.73[0.56-0.95], $p = 0.018$) and prostate weight > 60 g (OR: 0.58[0.35-0.96], $p = 0.033$) were inversely correlated with PSM. Surgical approach (ORRP versus

TABLE 2. **Association of individual categorical and continuous variables with positive surgical margin**

	PSM (n = 409)	NSM (n = 1331)	p value
Preoperative factors			
Age			0.144
< 60 years	255	678	
≥ 60 years	184	653	
Body mass index (kg/m^2)			0.195
≤ 24.9	64	245	
> 24.9	345	1086	
Preoperative PSA			< 0.001*
< 10 ng/mL	323	1221	
≥ 10 ng/mL	86	110	
Race			0.515
White	297	944	
Others	112	387	
Pathologic factors			
T-stage			< 0.001*
T2	209	113	
T3/T4	200	200	
Gleason			< 0.001*
≤ 6	233	976	
7	114	291	
≥ 8	62	64	
Prostate weight			0.002*
≤ 30 g	110	302	
31 g-60 g	268	847	
≥ 61 g	31	18	
Extracapsular extension			< 0.001*
Unifocal	143	142	
Multifocal	44	46	
None	222	114	
SVI			< 0.001*
Yes	75	61	
No	334	12	
PNI			< 0.001*
Yes	369	904	
No	40	42	
Impact of surgical variability			
Surgeon			0.100
Surgical modality			0.121
RARP	263	780	
LRP	38	154	
ORRP	108	397	

*p value < 0.05, statistically significant; SVI = seminal vesicle involvement; PNI = peripheral neural involvement; RARP = robotic assisted radical prostatectomy; LRP = laparoscopic radical prostatectomy; ORRP = open radical retropubic prostatectomy; PSM = positive surgical margin

TABLE 3. **Multivariate logistic regression analysis of relation between predictors of positive surgical margin**

Factor	Comparisons	OR (95% CI)	p value
Preoperative factors			
Age	> 60 yrs versus ≤ 60 yrs	0.73 (0.56-0.95)	0.018*
Body mass index (kg/m^2)		1.10 (0.79-1.55)	0.542
Race		1.11 (0.83-1.49)	0.489
Preoperative PSA	≥ 10 ng/mL versus < 10 ng/mL	1.99 (1.35-2.95)	0.001*
Pathologic factors			
T-stage	T3/T4 versus T2	2.83 (1.38-5.83)	0.005*
Gleason	≥ 8 versus ≤ 6	1.56 (0.98-2.53)	0.060
	7 versus ≤ 6	0.99 (0.73-1.36)	0.994
Prostate weight	≥ 61 g versus ≤ 30 g	0.58 (0.35-0.96)	0.033*
	[31 g-60 g] versus ≤ 30 g	0.88 (0.66-1.18)	0.401
ECE	Unifocal versus none	1.31 (0.63-2.71)	0.474
	Multifocal versus none	1.21 (0.53-2.80)	0.653
PNI		2.89 (1.98-4.23)	< 0.001*
SVI		1.20 (0.74-1.94)	0.458
Impact of surgical variability			
Surgeon		0.99 (0.95-1.03)	0.711
Surgical modality	LRP versus RARP	0.95 (0.56-1.55)	0.850
	ORRP versus RARP	0.78 (0.54-1.12)	0.176

*p value < 0.05, statistically significant; ECE = extracapsular extension; PNI = peripheral neural involvement; SVI = seminal vesicle involvement; LRP = laparoscopic radical prostatectomy; RARP = robotic assisted radical prostatectomy; ORRP = open radical retropubic prostatectomy; PSM = positive surgical margin

LRP versus RARP), race, surgeon, and BMI were not associated with higher risk of PSM.

The Cox proportional hazard and regression analysis, Table 4 showed that Gleason sum 7 (HR: 7.77[2.17-27.86], p = 0.002), and Gleason sum ≥ 8 (HR: 3.78[1.14-12.59], p = 0.030) and PSM (HR: 2.29[1.02-5.15], p = 0.046) were significant risk factors for BCR. The Log Rank Test (p < 0.001) showed that there is a statistically significant

TABLE 4. **Multivariate Cox proportional hazard regression analysis of relation between pathologic factors and biochemical recurrence**

Factor	Comparisons	HR (95% CI)	p value
Preoperative PSA	≥ 10 ng/mL versus < 10 ng/ml	2.21 (0.77-6.40)	0.142
T-stage	T3/T4 versus T2	5.16 (0.57-46.43)	0.143
Gleason score	7 versus ≤ 6	7.77 (2.17-27.86)	0.002*
Gleason score ≥ 8	≥ 8 versus ≤ 6	3.78 (1.14-12.59)	0.030*
PSM	PSM versus none	2.29 (1.02-5.15)	0.046*
Unifocal ECE	Unifocal versus none	0.52 (0.07-4.14)	0.535
Multifocal ECE	Multifocal versus none	0.14 (0.01-2.15)	0.158
SVI	SVI versus none	0.96 (0.29-3.13)	0.943
PNI	PNI versus none	1.01 (0.12-8.72)	0.994
Prostate weight	≥ 61 g versus ≤ 30 g	0.00 (0.00-3.84)	0.978
	[31 g-60 g] versus ≤ 30 g	2.53 (0.94-6.81)	0.067

*p value < 0.05, statistically significant; PSM = positive surgical margin; ECE = extracapsular extension; SVI = seminal vesicle involvement; PNI = peripheral neural involvement

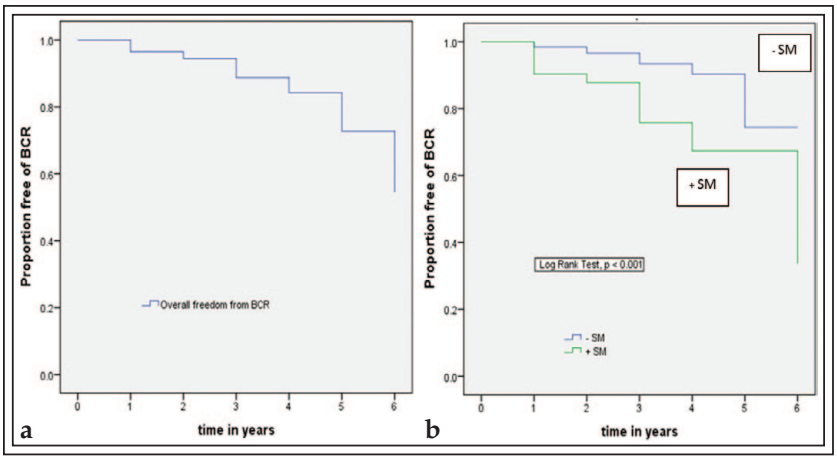

Figure 1. a) Overall freedom from biochemical recurrence (BCR) for selected patients; **b)** Freedom from biochemical recurrence (BCR) stratified by surgical margin (SM) status, p < 0.001.

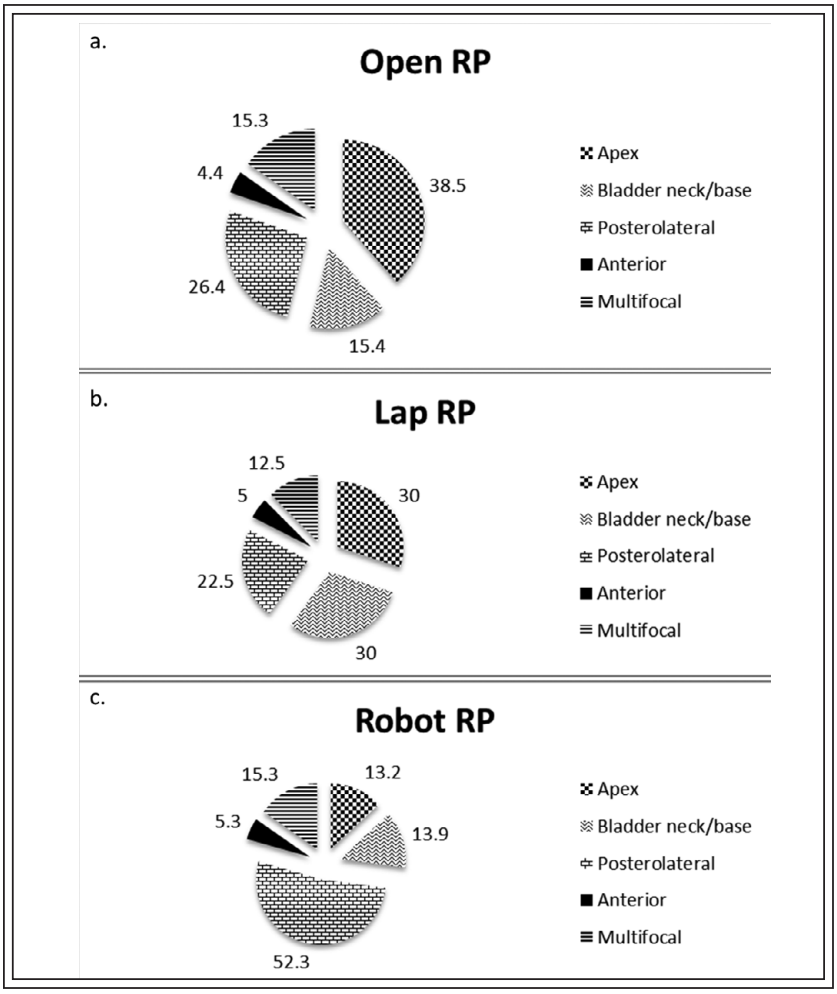

Figure 2. Positive surgical margin (PSM) location by radical prostatectomy (RP) technique, p < 0.001. **a)** PSM location in open RP; **b)** PSM location in laparoscopic RP; **c)** PSM location in robotic RP.

difference between the BCR-free survival curves of PSM and negative surgical margins, Figure 1.

Figure 2 defines the location of PSM by surgical technique. Although there was a fairly even distribution in LRP, the majority of PSM in open RP were apical (38.5%) and for RARP posterolateral (52.3%). Alternatively, apical PSM rate for RARP was 13.2% and posterolateral rate for open RP was 26.4% (p < 0.001).

For 53 patients undergoing LND in the LRP cohort, none were positive for involvement with prostate cancer. For the ORRP cohort, 12/435 (2.7%) were positive and for the RARP cohort, 9/965 (.09%) were positive.

Discussion

This large, single-institution analysis of PSM in RP spans across the evolution of our technique. Early in this series, we predominantly were performing open RP, briefly forayed into LRP, and currently our predominant technique is robotic. We, however, found no statistical difference in the incidence of PSM across techniques, which is contrary to a recent massive multinational, multi-institutional series evaluating the rate of PSM in these three modalities of RP over a similar time period.[12] This manuscript found a statistically decreased incidence of PSM for minimally invasive RP (both RARP and LRP) over open RP, with the lowest rate in the robotic cohort. Still, this study was multi-institutional and despite its large numbers, was subject to biases and drawbacks of such a study, including variation in surgical technique, pathologic processing, and data collection.

Multiple studies have correlated clinical and histopathological findings as predictive factors of PSM after ORRP. Much of this information is extrapolated to minimally invasive approaches.

TABLE 5. **Distribution of high risk (Gleason score ≥ 8 or T-stage ≥ T3) prostate cancer amongst all three surgical modalities**

Gleason score	**Techniques**		
	RARP	**ORRP**	**LRP**
≥ 8	80 (8%)	37 (7%)	9 (5%)
7	313 (30%)	27 (6%)	65 (34%)
≤ 6	650 (62%)	441 (87%)	118 (61%)
T-stages	**Techniques**		
	RARP	**ORRP**	**LRP**
T2	807 (77%)	372 (73%)	161 (84%)
T3/4	236 (23%)	133 (27%)	31 (16%)

RARP = robotic assisted radical prostatectomy; ORRP = open retropubic radical prostatectomy; LRP = laparoscopic radical prostatectomy

Few instances have specifically addressed predictive factors for PSM after robotic prostatectomy. We divided risk factors as preoperative, pathologic, and surgeon/technique dependent. Preoperative PSA was the only significant preoperative variable, and although almost all of the pathologic factors demonstrated significance in univariate analysis, only pathologic stage and PNI remained significant after multivariate logistical regression. Another interesting result in our analysis was in examining the percentage of high risk prostate cancer patients in each cohort; possibly a result of the changing recommendations in prostate cancer screening, we operated on many more GS 7-10 patients with RARP than both LR and ORRP, although the pathologic stages for RARP and ORRP were similar, Table 5. This contrasts to the single-surgeon experience by Coelho et al, who in a series of 876 patients who underwent RARP, observed that clinical stage was the only independent predictive factor for PSM.[13] These findings, however, are similar to a recent series attempting to identify which risk factors (clinical, pathological, and/or technical) would account for PSM in robotically assisted prostatectomy. Their PSM rate was 15.7% and included a total of 1277 out of 8095 patients operated on at seven different institutions. They concluded that preoperative PSA level and pathological stage were important risk factors for PSM. They also found that increasing prostate weight was associated with a lower risk of PSM after RARP.[14]

Arguing that PSM are only influenced by surgical technique, and as such might be used as quality indicator, Williams et al designed a population-based study to characterize which factors are associated with PSM in order to evaluate surgeon performance with RP. A similar subset of risk factors (which in addition included year of procedure, Charlson comorbidity index, race, marital status, geographical location and D'Amico risk group among others) was utilized. Overall they observed a 19.4% rate of PSM. A significant geographical and temporal variation in PSM was noted but neither surgeon volume nor surgical approach was associated with PSM.[15] Villamil et al's single-institution analysis looking at the incidence and location of PSM following open, pure laparoscopic and robotic-assisted radical prostatectomy also found that there was no statistically significant difference in PSM between these groups.[16] This is similar to our findings, and reinforces the notion that a minimally invasive prostatectomy program built on a sound open experience should not compromise oncological outcomes.

The significance of PNI on needle biopsy and radical prostatectomy specimens has long been discussed. Although some believe this to portend a poor prognosis, others have questioned this impression.[17-19] We found this pathologic feature on final specimen to be associated with an increased incidence of PSM, although this alone did not appear to affect the occurrence of BCR on multivariate analysis.

The association between smaller prostate weight, increased PSM and worse overall outcomes has been prior established, so there was no surprise when this proved to be significant in our multivariate analysis.[20] This did not prove significant, however, as a factor for BCR, although it is possible with longer follow up the association will be more tangible. We were surprised, however, of the observation that patients older than 60 had a lower incidence of PSM on our multivariate analysis, a correlation that does not have good representation in the literature. This link may disappear if the age cutoff were higher (e.g. 70 years old) but does require further study in this changing landscape of screening and treating prostate cancer in the elderly. Finally, the relationship between obesity and prostate cancer is not well defined and it has been associated with both increase and decrease in prostate cancer incidence. Overweight or obese patients did not have a higher incidence of positive surgical margins in our cohort. This finding is in agreement with Tomaszewski et al[21] who showed in a 12 year retrospective single-institution analysis that obesity was not associated with PSM or BCR. With obesity becoming a major health issue in the United States it warrants further investigation in trying to understand the prognostic effect of obesity in prostate cancer, PSM and recurrence.

PSM after RP portend a higher likelihood of BCR of the disease and may adversely affect cancer-specific survival. Recent studies indicate that the oncologic significance of PSM increases with higher risk disease; the biochemical progression-free survival (bPFS) in low risk disease patients was 99.6% for negative margins versus 94.9% for PSM, but for intermediate disease risk, bPFS was 93.5% with negative margins versus 83% percent with PSM; and even more significant in high risk disease patients: with bPFS of 78.5% with negative margins versus 57.1% with PSM.[22] Similar findings were evident in our cohort where patients with PSM were 2.29 times more likely to have BCR compared to patients without PSM.

Since the incipience of our institutional robotic surgery program, we have noticed a migration in the location of PSM during RP. Improved visualization and more delicate dissection around the prostatic apex undoubtedly have influenced the decreased number of apical PSM during RARP. On the other hand, more aggressive attempts at nerve spare, particularly in low risk patients, can explain the increased number of PSM at the posterolateral margin in this cohort. Patients were not considered for nerve spare if they had poor to no erectile function preoperatively and if they had a high volume of intermediate risk or any evidence of high risk disease. Because of the retrospective nature of the review, complete nerve spare records could not be obtained on cases done past approximately 8 years ago. This includes all of the LRP, most of the ORRP (87.8%) and few of the RARP (26.5%) cases given the evolution in our modality over the years. For those with complete records, the incidence of any nerve sparing technique was higher with RARP (84%) over ORRP (74%) but equivalent for bilateral nerve spare (68% versus 69%, respectively). These findings are contrary to a similar study published in 2007, in which apical PSM were the most common location for both techniques.[23] Accordingly, we also published early in our experience a trend toward higher apical PSM in RARP, and due to modifications in technique, have since noted a significant decrease in this location.[24] Finally, it should be noted that the incidence of bladder neck/base and anterior PSM for all three procedures were similar.

There are several strengths of this analysis, the foremost of which is the considerable patient number of 1740 patients in a single-institution, contemporary surgical experience. Additionally, the prostatectomy specimens, regardless of year performed, surgeon, or technique, underwent standard whole mount step sectioned pathologic analysis with second level pathologic review between surgeons and the genitourinary pathologists in a multidisciplinary weekly pathology conference, ensuring an elevated degree of accuracy and confidence in the reported results. The significant correlation of PSM and BCR on multivariate analysis in a subset of our patient with long term follow up is a final validating feature of this study.

Limitations of this study included the retrospective single institution nature of this review. There are multiple surgeons included with different levels of experience which may confound the data, although specific surgeon was not an independent risk factor for PSM. Additionally, other reported risk factors, such as PSA density, nodal status and site/location of PSM were not routinely recorded in this data set.

In our large, multi-surgeon, single-institution analysis of PSM in RP, preoperative PSA ≥ 10 ng/ml, pathologic stage ≥ T3, and PNI significantly predicted PSM. Additionally, the presence of a PSM on final pathologic specimen was an independent predictor of BCR. These results were not affected by surgeon or surgical approach. Patients with these adverse pathologic features should be considered for adjuvant treatment or monitored closely for early salvage treatment. □

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