

# Impact of intraoperative frozen section by location: Does it really predict significant positive surgical margins after robot-assisted laparoscopic prostatectomy?

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## Abstract

**Objectives:** We investigated the relationship between positive surgical margin (PSM)-related factors and biochemical recurrence (BCR) and the ability of intraoperative frozen sections to predict significant PSM in patients with prostate cancer.

**Methods:** The study included 271 patients who underwent robot-assisted laparoscopic prostatectomy with bilateral nerve sparing and maximal urethra preservation. Intraoperative frozen sections of the peri-urethra, dorsal vein, and bladder neck were analyzed. The ability of PSM-related factors to predict BCR and significant PSM were assessed by logistic regression.

**Results:** Of 271 patients, 108 (39.9%) had PSM and 163 (60.1%) had negative margins. Gleason score  $\geq 8$  (18.9% vs 7.5%,  $p=0.015$ ) and T stage  $\geq T3a$  (51.9% vs 24.6%,  $p<0.001$ ) were significantly more frequent in the PSM group. Multivariate analysis showed that Gleason pattern  $\geq 4$  (vs  $<4$ ; hazard ratio: 4.386,  $p=0.0004$ ) was the only significant predictor of BCR in the PSM cohort. Peri-urethral frozen sections had a sensitivity of 83.3% and a specificity of 84.2% in detecting PSM with Gleason pattern  $\geq 4$ . Multivariate analysis showed that membranous urethra length (odds ratio [OR]: 0.79,  $p=0.0376$ ) and extracapsular extension of the apex (OR: 4.58,  $p=0.0226$ ) on MRI and positive peri-urethral tissue (OR: 17.85,  $p<0.0001$ ) were associated with PSM of the apex.

**Conclusions:** PSM with Gleason pattern  $\geq 4$  is significantly predictive of BCR. Intraoperative frozen sections of peri-urethral tissue can independently predict PSM, whereas sections of the bladder neck and dorsal vein could not. Pathologic examination of these samples may help predict significant PSM in patients undergoing robot-assisted laparoscopic prostatectomy with preservation of functional outcomes.

**Keywords:** Biochemical recurrence, Frozen section, Positive surgical margin, Robotic-assisted prostatectomy

## I. Introduction

- Positive surgical margin (PSM)  $\uparrow$   $\approx$  biochemical recurrence (BCR)  $\uparrow$

PSM  $\leftarrow$  extracapsular extension of the tumor  
 technical error in the operating room or histology laboratory  
 surgeon's experience  
 aggressiveness of nerve sparing

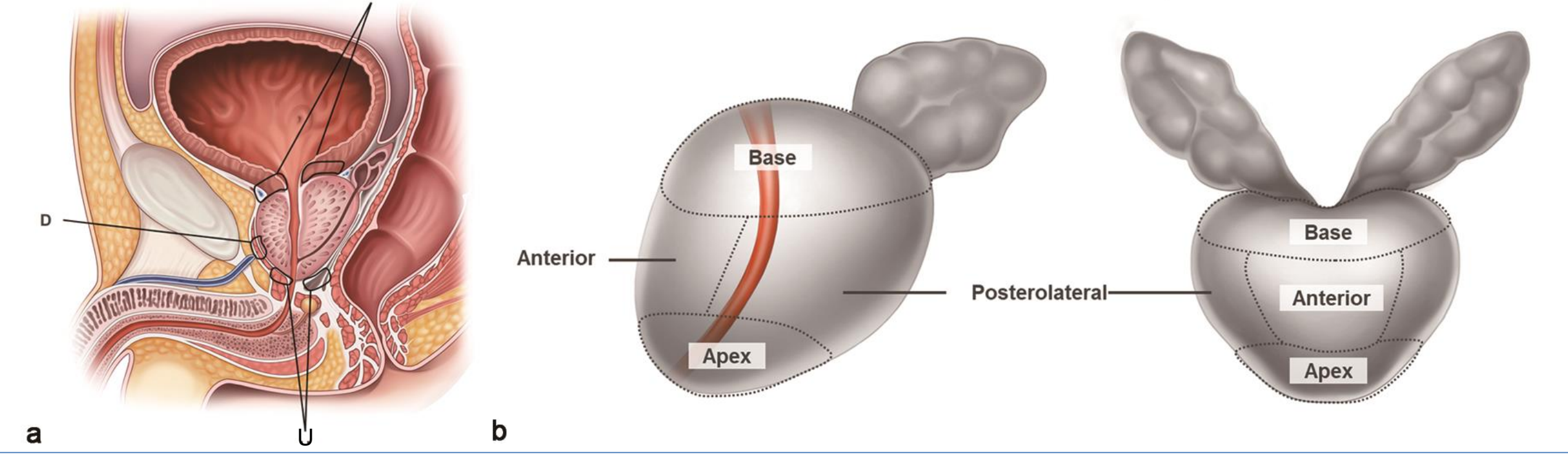
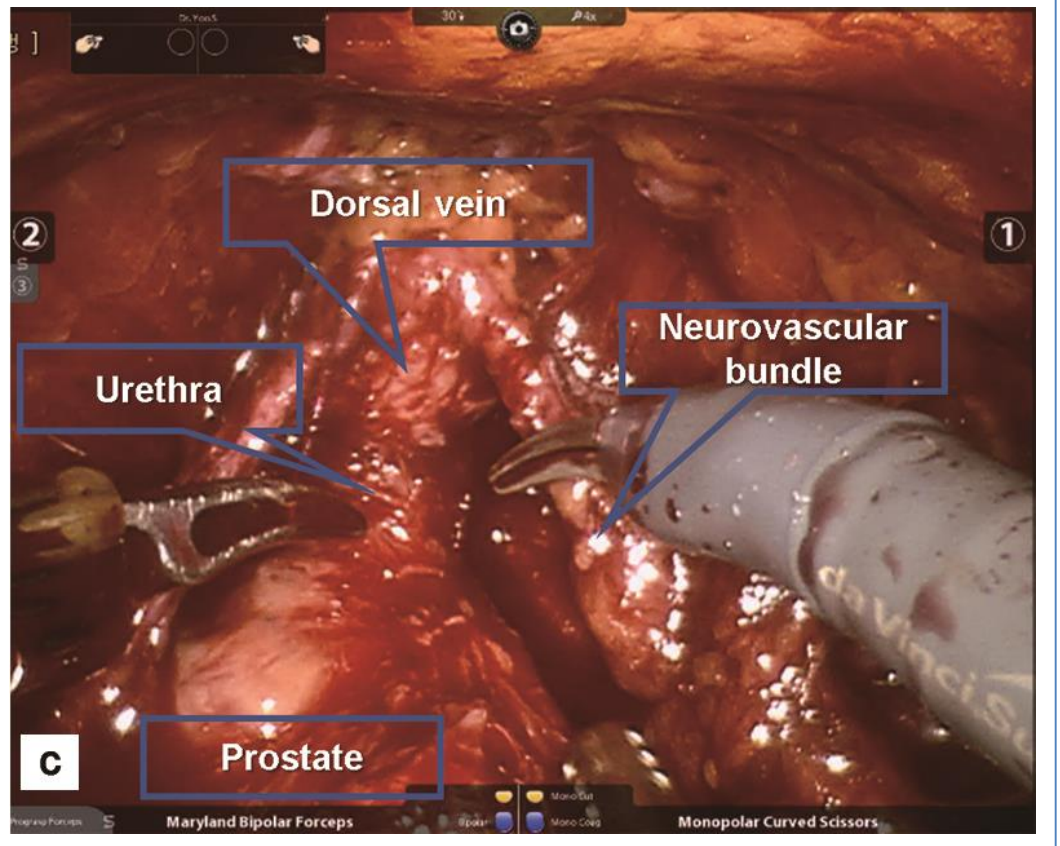
- Intraoperative frozen section assessment may reduce PSM rates
- negative conversion after positive frozen may improve oncologic outcome

- Objective**
- $\rightarrow$  identify significant PSM-related factors predictive of BCR
- $\rightarrow$  confirm that intraoperative frozen section can predict significant PSM

## II. Materials & Methods

- 271 patients with prostate cancer (2008~2016)
- RALP with intraoperative frozen sections
- Exclusion : Neoadjuvant therapy
- Mean follow-up : 30.2 months (15.4-39.8)

- Comparing continuous variables: t-test
- Comparing categorical variables: chi-square test
- Cox hazards regression & Logistic regression
- Survival graph: Kaplan-Meier method /c log-rank test



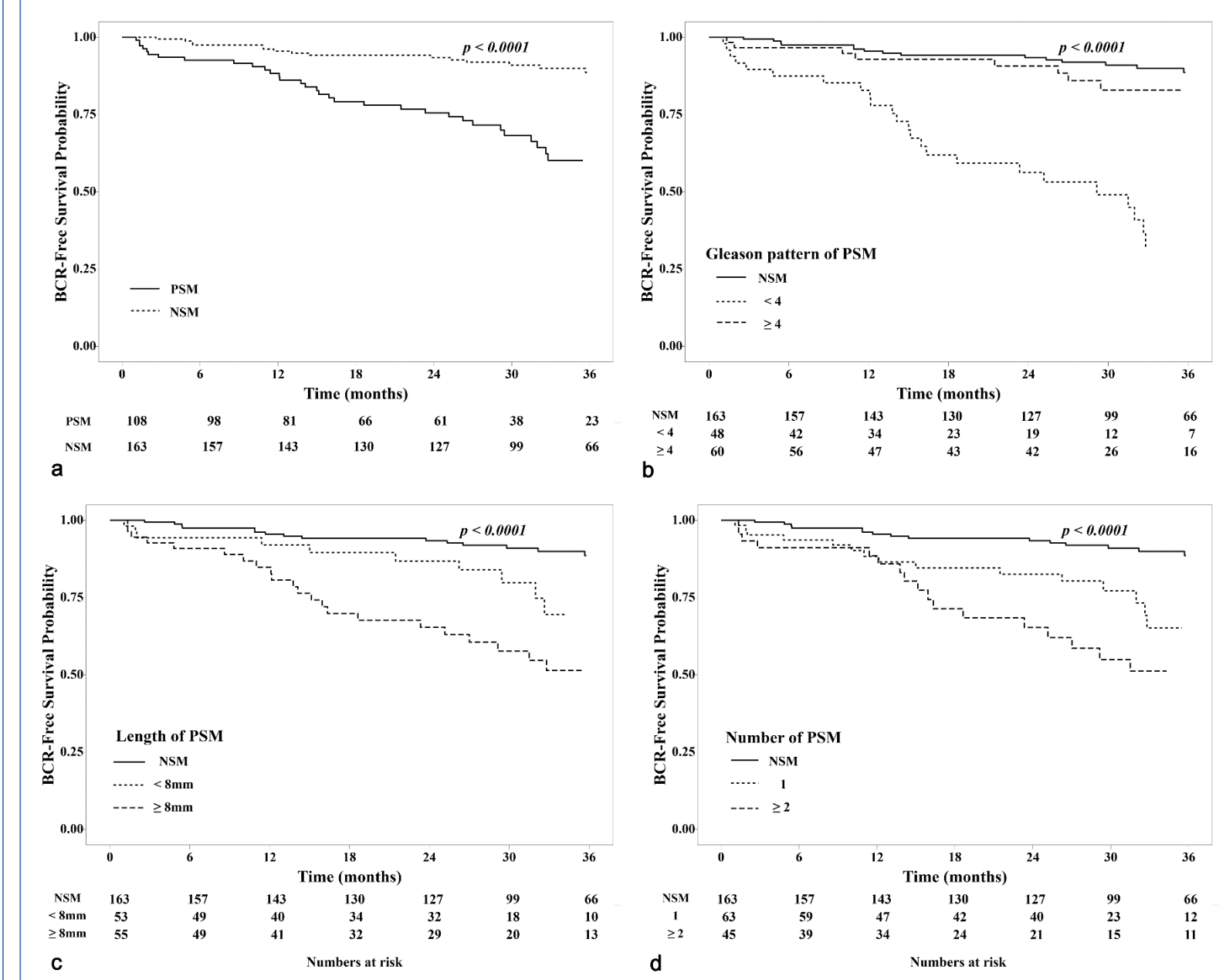
## III. Results

### Basic characteristics of patients and tumors

Mean $\pm$ SD or number (%)	PSM (N=108)	NSM (N=163)	Total (N=271)	p
Age (yr)	63.8 $\pm$ 7.3	65.6 $\pm$ 6.7	64.9 $\pm$ 7.0	<b>0.039</b>
Initial PSA (ng/ml)	9.2 $\pm$ 7.5	7.1 $\pm$ 4.8	7.9 $\pm$ 6.0	<b>0.013</b>
Body mass index (kg/m <sup>2</sup> )	24.3 $\pm$ 3.3	24.7 $\pm$ 2.6	24.5 $\pm$ 2.9	0.315
Hypertension	70 (64.8%)	89 (54.6%)	112 (41.3%)	0.122
Diabetes mellitus	23 (21.3%)	29 (17.8%)	52 (19.2%)	0.576
Charlson comorbidity index				0.720
- 0	9 (8.3%)	18 (11.0%)	27 (10.0%)	
- 1	62 (57.4%)	94 (57.7%)	156 (57.6%)	
- $\geq 2$	37 (34.3%)	51 (31.3%)	88 (32.5%)	
D'Amico risk				<b>0.032</b>
- Low	2 (1.9%)	15 (9.2%)	17 (6.3%)	
- Intermediate	14 (13.0%)	14 (8.6%)	28 (10.3%)	
- High	92 (85.2%)	134 (82.2%)	226 (83.4%)	
Clinical T2 stage	78 (72.2%)	133 (81.6%)	211 (77.9%)	0.095
Extracapsular invasion on MRI	30 (27.8%)	24 (14.7%)	54 (19.9%)	0.144
Seminal vesicle invasion on MRI	7 (6.5%)	12 (7.4%)	19 (7.0%)	0.454
Clinical Gleason score				<b>0.014</b>
- 6	30 (27.8%)	52 (31.9%)	82 (30.3%)	
- 7	48 (44.4%)	81 (49.7%)	129 (47.6%)	
- 8	14 (13.0%)	25 (15.3%)	39 (14.4%)	
- $\geq 9$	16 (14.8%)	5 (3.1%)	21 (7.7%)	
Prostate volume on TRUS (cc)	34.1 $\pm$ 10.1	34.9 $\pm$ 14.5	34.6 $\pm$ 12.9	0.675
Membranous urethra length, MRI (mm)	12.0 $\pm$ 4.0	12.1 $\pm$ 2.8	12.1 $\pm$ 3.4	0.919
Positive core percent (%)	57.8 $\pm$ 33.5	51.4 $\pm$ 37.0	53.9 $\pm$ 35.7	0.155
Max tumor percent of positive core (%)	51.3 $\pm$ 31.0	39.1 $\pm$ 25.3	44.0 $\pm$ 28.3	<b>0.001</b>
Prostate volume (cc)	29.4 $\pm$ 9.7	31.0 $\pm$ 13.1	30.4 $\pm$ 11.8	0.264
Tumor volume (cc)	6.6 $\pm$ 7.7	2.6 $\pm$ 2.6	4.2 $\pm$ 5.6	<b>&lt;0.001</b>
Pathologic Gleason score				<b>0.015</b>
- 6	12 (11.9%)	36 (22.5%)	48 (18.4%)	
- 7	70 (69.3%)	112 (70.0%)	182 (69.7%)	
- 8	4 (4.0%)	3 (1.9%)	7 (2.7%)	
- $\geq 9$	15 (14.9%)	9 (5.6%)	24 (9.2%)	
Pathologic T stage				<b>&lt;0.001</b>
- T2	52 (48.1%)	123 (75.5%)	175 (64.6%)	
- T3a	41 (38.0%)	28 (17.2%)	69 (25.5%)	
- T3b	15 (13.9%)	12 (7.4%)	27 (10.0%)	
Length of PSM (mm)	11.1 $\pm$ 15.0		11.1 $\pm$ 15.0	
Number of PSMs				
- 1	63 (58.3%)		63 (23.2%)	
- $\geq 2$	45 (41.7%)		45 (16.6%)	
Gleason pattern of PSM				
- $<4$	48 (44.4%)		48 (17.7%)	
- $\geq 4$	60 (55.6%)		60 (22.1%)	
Location of PSM				
- Apex	62 (57.4%)	0 (0.0%)	62 (22.9%)	
- Base	21 (19.4%)	0 (0.0%)	21 (7.7%)	
- Anterior	37 (34.3%)	0 (0.0%)	37 (13.7%)	
- Posterolateral	41 (38.0%)	0 (0.0%)	41 (15.1%)	
Positive frozen section				
- Peri-urethra tissue	44 (40.7%)	19 (11.7%)	63 (23.2%)	<b>&lt;0.001</b>
- Bladder neck	6 (5.6%)	2 (1.2%)	8 (3.0%)	0.090
- Dorsal vein site	15 (13.9%)	2 (1.2%)	17 (6.3%)	<b>&lt;0.001</b>

## IV. Results

### Kaplan-Meier analysis of BCR-free survival according to characteristics of surgical margins



## V. Results

### Cox hazard analysis of factors associated with BCR-free survival

	Total cohort				PSM cohort							
	Univariate		Multivariate model 1 <sup>1</sup>		Multivariate model 2 <sup>2</sup>							
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p			
PSM vs NSM	3.310	1.900	5.740	<b>&lt;0.0001</b>	2.681	1.474	4.878	<b>0.0012</b>				
Gleason pattern of PSM (vs NSM)												
- Gleason pattern $<4$	1.440	0.660	3.140	0.3640	1.212	0.522	2.813	0.6551	1.000	(reference)		
- Gleason pattern $\geq 4$	6.670	3.670	12.100	<b>&lt;0.0001</b>	4.434	2.347	8.380	<b>&lt;0.0001</b>	4.386	1.938	9.928	<b>0.0004</b>
Length of PSM (vs NSM)												
- $<8$ mm	2.310	1.110	4.840	<b>0.0260</b>	2.497	1.156	5.394	<b>0.0198</b>	1.000		(reference)	
- $\geq 8$ mm	4.160	2.230	8.090	<b>&lt;0.0001</b>	2.804	1.441	5.456	<b>0.0024</b>	1.236	0.536	2.854	0.6191
Number of PSMs (vs NSM)												
- 1	2.670	1.390	5.140	<b>0.0030</b>	2.448	1.240	4.828	<b>0.0098</b>	1.000		(reference)	
- $\geq 2$	4.250	2.230	8.090	<b>&lt;0.0001</b>	3.056	1.471	6.347	<b>0.0027</b>	1.147	0.445	2.955	0.7767
Location of PSM (vs NSM)												
- Apex	3.660	1.990	6.730	<b>&lt;0.0001</b>	3.861	1.919	7.768	<b>0.0002</b>	1.000		(reference)	
- Base	5.210	2.370	11.420	<b>&lt;0.0001</b>	1.826	0.742	4.491	0.1898	1.294	0.272	6.160	0.7464
- Anterior	3.120	1.500	6.480	<b>0.0020</b>	2.727	1.162	6.400	<b>0.0212</b>	0.765	0.131	4.467	0.7663
- Posterolateral	3.560	1.800	7.040	<b>&lt;0.0001</b>	2.691	1.300	5.570	<b>0.0076</b>	0.908	0.158	5.219	0.9143

1 In multivariate model 1, each variable was adjusted for initial PSA, pathologic Gleason score, and pathologic T stage.  
 2 In multivariate model 2, all variables related to PSM were entered into the PSM cohort.

## VI. Results

### Sensitivity, specificity, and predictive values of intraoperative frozen sections showing PSMs at each site

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All PSMs				
- Peri-urethra tissue	64.5	89.0	63.5	89.4
- Bladder neck	19.0	98.4	50.0	93.5
- Dorsal vein site	24.3	96.6	52.9	89.0
PSM with Gleason pattern $\geq 4$				
- Peri-urethra tissue	83.3	84.2	39.7	97.6
- Bladder neck	9.1	97.3	12.5	96.2
- Dorsal vein site	31.3	95.3	29.4	95.7

## VII. Results

### Multivariate logistic regression of factors predicting PSMs including Gleason pattern $\geq 4$ at each location

	Apex				Base				Anterior				
	OR	95% CI	p		OR	95% CI	p		OR	95% CI	p		
Initial PSA (continuous)													
Membranous urethra length on MRI (continuous)	0.79	0.63	0.99	<b>0.0376</b>					NA	0.84	0.65	1.05	0.1516
Prostate volume (continuous)													
Clinical Gleason score ( $\geq 9$ vs $\leq 8$ )													
Positive core percent (continuous)													
Maximal tumor percent of positive core (continuous)	1.02	1.00	1.04	0.0834	1.05	1.02	1.10	<b>0.0023</b>					
Extracapsular extension of each site on MRI (yes vs no)	4.58	1.24	17.32	<b>0.0226</b>					6.26	1.42	25.33	<b>0.0106</b>	
Seminal vesicle invasion on MRI (yes vs no)												NA	
Positive frozen section of peri-urethra tissue (yes vs no)	17.85	5.40	73.25	<b>&lt;0.0001</b>								NA	
Positive frozen section of bladder neck (yes vs no)												NA	
Positive frozen section of dorsal vein site (yes vs no)												NA	

## VIII. Conclusions

- PSM with Gleason pattern  $\geq 4$  was significantly predictive of BCR in patients who underwent robot-assisted laparoscopic prostatectomy with bilateral nerve sparing and maximal urethra preservation.
- Positive frozen sections of peri-urethral tissue were an independent predictor of significant PSM with high sensitivity and specificity, whereas positive frozen sections of the bladder neck and dorsal vein site were not significantly predictive.
- Intraoperative frozen sections of peri-urethral tissue may help to predict significant PSM and preserve functional outcomes.