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ORIGINAL ARTICLE

Linear extent of positive surgical margin impacts biochemical recurrence after robot-assisted radical prostatectomy in a high-volume center

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Abstract

The objective of this study is to evaluate if surgeon volume and stratifying positive surgical margins (PSM) into focal and non-focal may differentially impact the risk of biochemical recurrence (BCR) after robot-assisted radical prostatectomy (RARP). Between January 2013 and December 2017, 732 consecutive patients were evaluated. The population included negative cases (control group) and PSM subjects (study group). PSMs were stratified as focal (≤ 1 mm) or non-focal (> 1 mm). A logistic regression model assessed the independent association of factors with the risk of PSM. The risk of BCR of PSM and other factors was assessed by Cox's multivariate proportional hazards. Overall, 192 (26.3%) patients had PSM focal in 133 patients; non-focal in 59 cases. Focal PSM was associated with the percentage of biopsy positive cores (BPC; OR 1.011; $p = 0.015$), extra-capsular extension (pT3a stage; OR 2.064; $p = 0.016$), seminal vesicle invasion (pT3b; OR 2.150; $p = 0.010$), body mass index (odds ratio, OR 0.914; $p = 0.006$), and high surgeon volume (OR 0.574; $p = 0.006$). BPC (OR 1.013; $p = 0.044$), pT3a (OR 4.832; $p < 0.0001$) and pT3b stage (OR 5.153; $p = 0.001$) were independent predictors of the risk of non-focal PSM. Surgeon volume was not a predictor of non-focal PSM ($p = 0.224$). Independent factors associated with the risk of BCR were baseline PSA (hazard ratio, HR 1.064; $p = 0.004$), BPC (HR 1.015; $p = 0.027$), ISUP biopsy grade group (BGG) 2/3 (HR 2.966; p 0.003) and BGG 4/5 (HR 3.122; $p = 0.022$) pathologic grade group 4/5 (HR 3.257; $p = 0.001$), pT3b (HR 2.900; $p = 0.003$), and non-focal PSM (HR 2.287; $p = 0.012$). Surgeon volume was not a predictor of BCR ($p = 0.253$). High surgeon volume is an independent factor that lowers the risk of focal PSM. Surgeon volume does not affect non-focal PSM and BCR. Negative as well as focal PSM are not associated with BCR.

Keywords Prostate cancer · Radical prostatectomy · Robotic surgery · Focal-positive surgical margins · Non-focal-positive surgical margins

Introduction

Prostate cancer (PCa) is the most common non-cutaneous malignancy and the second leading cause of cancer-related deaths in men [1]. Robot-assisted radical prostatectomy (RARP) remains a common and widely available radical

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treatment option for PCa [2]. Although utilized frequently, unfavorable outcomes after radical prostatectomy (RP) continue to occur, including the detection of positive surgical margins (PSM), which is an important predictor of biochemical recurrence (BCR) and loco-regional recurrences [3–5]. Therefore, patients with PSM require close follow-up and/or additional treatment after surgery [3, 6]. In contemporary cohorts of patients, it is important to evaluate factors associated with the risk of PSM after RARP to decide if adjuvant treatments are needed. In our previous experience, we demonstrated that PSM can be related to tumor biology according with testosterone levels [7], percentage of biopsy positive cores, extra-capsular extension, seminal vesicle invasion, and low surgical experience [8]. Actually, there is no consensus in the literature regarding how to describe a positive surgical margin in the pathological report. In this context, it could be important to evaluate the linear extent of PSMs, because this information could be prognostic. Indeed, patients with a PSM can be categorized into two groups that include focal and non-focal PSM, which could have different associations with the risk of disease recurrence. Different cut-offs have been proposed in the literature to describe focal PSM as linear extent. However, the risk of biochemical recurrence (BCR) by PSM stratified by linear extent is a novel subject, which has not been appropriately investigated by the literature. Particularly, Servoll and associates have shown that a PSM length > 3 mm was an independent predictor of cancer recurrence after open radical prostatectomy [9]. Using a cut-off of 1 mm, Sammon et al. found that the BCR-free rate was higher in patients with PSM less than 1 mm after radical perineal prostatectomy during a long follow-up [10]. Lee et al. demonstrated that a PSM less than 3 mm after RP did not significantly affect BCR-free survival [11].

This study tested the hypothesis if the stratification of PSM into focal and non-focal according to a linear extent within 1 mm impacts the risk of biochemical recurrence after RARP in a contemporary cohort of patients.

Materials and methods

Study features

The present study is a retrospective analysis of prospectively collected data. It was approved by the Institutional Review Board and included a period ranging from January 2013 to December 2017. Each patient provided informed-signed consent for use of clinical data for analysis. Low-, intermediate-, high-risk and locally advanced patients were included in the study if the clinical T stage was ≤ T3b (and the prostate volume was ≤ 80 cc). Patients with cT4 stage or metastatic disease or who were under androgen blockade and/or had prior treatments were excluded. Additionally, patients with any prior surgical treatment of the prostate were excluded. Patients presenting pT2 + according with the Stanford protocol were excluded [12].

Clinical features

Preoperatively, patients were evaluated for age (years), body mass index (BMI; kg/m^2), and plasma levels of PSA (ng/mL), which were determined by radioimmunoassay methods. Prostate biopsies had the following features: (i) at least 12–14 cores; (ii) reported number of positive cores; (iii) measurement of prostate volume (TPV; mL); (iv) cancer grade group classification according to the 2014 International Society of Urologic Pathology (ISUP) system. All surgical specimens evaluated before January 2015 were retrospectively re-classified according to the ISUP 2014 classification [12].

In each case, the number of positive cores and the total number of cores sampled (BPC; percentage) were computed. Patients were clinically staged according the European Society of Urology (EAU) guidelines [6]. Tumors were staged by digital rectal exam (DRE) and/or by multiparametric resonance imaging (mMRI). Pelvic lymph nodes were assessed by computerized tomography (CT) or by multiparametric resonance imaging (mpMRI). Enlarged pelvic nodes measuring more than 1 cm in diameter were staged as cN1. The metastatic status was investigated by CT and/or mMRI as well as by total bone scan. Furthermore, the presence of a median lobe was assessed by reviewing radiological and/or surgical reports. Patients were then classified into risk groups according to the EAU guideline on PCA [6].

Peri-operative features

Surgeons performing RARP utilized the da Vinci Robotic System (Intuitive Surgical, Inc, Sunnyvale, CA, USA) employing a trans-peritoneal approach with anterograde prostatic dissection [13]. When the risk of lymph-node invasion (LNI) was greater than 5% an extended lymph-node dissection (ePLND) was performed [14]. In low-risk patients, the decision to perform an ePLND was based and clinical factors indicating increased risk of tumor upgrading in the surgical specimen [15–19].

Nodal packets were grouped according to a standard template and submitted in separate packages. Nerve sparing RP (NSRP) was performed when indicated [20]. The prostate was dissected by the intrafascial, interfascial, or extrafascial technique on the right side and/or left side according to nerve sparing principles, and guided by the clinical stage and cancer location and its relation to the capsule [21]. An extrafascial dissection was performed when nerve sparing was contraindicated. Five experienced surgeons performed RARP with a neck bladder sparing technique [22].

The single high-volume surgeon performed more than 500 RARPs before patient enrolment began. The other four surgeons (low-volume surgeons) performed between 50 and 60 procedures at the commencement of patient enrolment. The criteria used to define an experienced surgeon were according to a previous publication that reported that among surgeons with > 30 RARP procedures, there was no difference in PSM rates [23]. The high-volume surgeon (WA) performed 66% of the procedures. Preoperatively, patients were evaluated for surgical risk by the American Anesthesiologists Score (ASA) system [24]. Intra-operatively, operating time (OT, minutes) and blood loss (BL, milliliters) were measured. Postoperatively, length of hospital stay (LOHS) was recorded. Patients were followed for a period of 6 months to detect hospital re-admission and complications which were classified according to the Clavien–Dindo scoring (CDS) system [25].

Pathological features

Dedicated pathologists evaluated surgical specimens according to the Stanford protocol [26]. Prostate weight (PW, grams) was calculated. Tumors were classified according to the ISUP grade group (PGG) system [12]. Lymph nodes were assessed for histopathology after hematoxylin and eosin staining. Immunohistochemistry staining was performed when appropriate. In each case, the number of removed and metastatic nodes was computed. Specimens were staged as suggested according to EAU guidelines on PCA [6].

Surgical margins were considered positive when cancer invaded the inked surface of the specimen. When the linear extension of cancer involvement on the inked surface was less than or equal to 1 mm, the surgical margin was classified as focal; otherwise, it was coded as non-focal (Fig. 1). PSM was classified as apical, posterolateral (left and right), posterior, anterior, and bladder neck according to the region of invasion.

Follow-up, adjuvant treatments, and biochemical recurrence (BCR)

Our surveillance schedule for assessment of biochemical recurrence (BCR) after RP was based on EAU standard criteria [3, 6] and adapted to our internal protocol. Particularly, after RP, early adjuvant RT was offered to patients with non-focal PSM and pT ≥ 3a. Patients with focal PSM and pT ≥ 3a and focal or non-focal PSM patients with pT < 3a were monitored with 3 monthly PSA for the first 2 years, and every 6 months from 2 to 5 years after surgery. Salvage RT was proposed if a rising PSA was found. To exclude metastatic disease, patients with BCR (defined as PSA > 0.2 ng/ml after RP) were followed with MRI (if PSA > 0.5 ng/ml) and or PET/CT with choline (if PSA > 1 ng/ml). In the last few years, according to the machine availability, PET PSMA was also performed by some patients with PSA > 0.2 ng/ml. Additionally, PSA doubling time (PSADT) was considered. In patients with favorable histology and PSADT > 12 months, active surveillance was considered. Patients with a shorter PSADT underwent salvage RT.

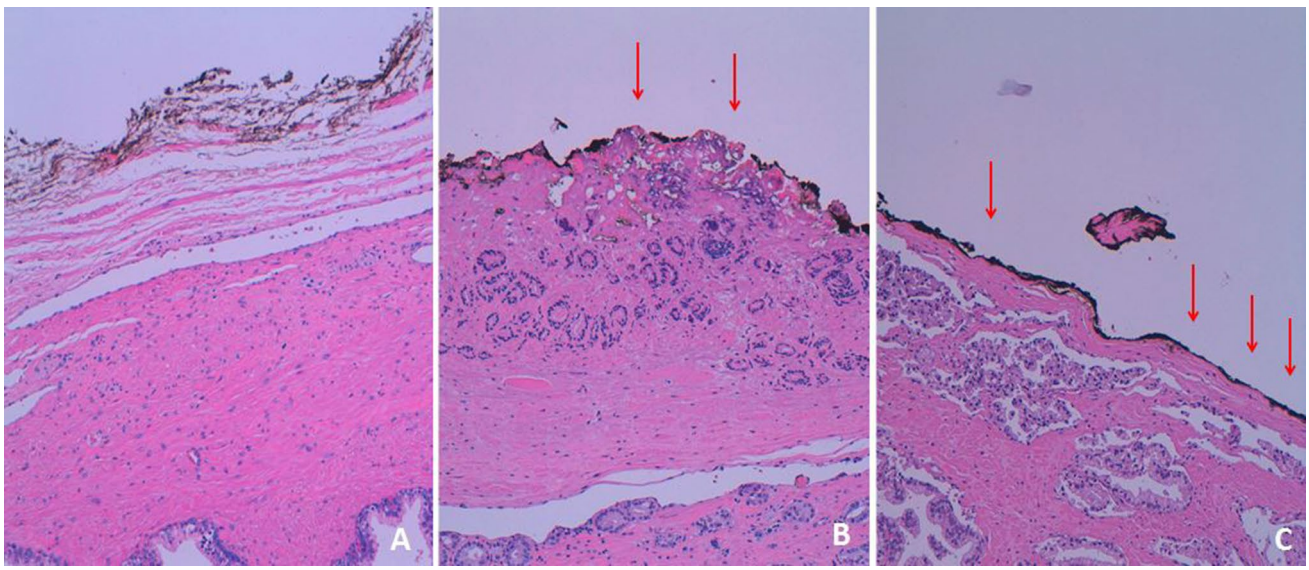

Fig. 1 Histopathologic depiction of focal and non-focal-positive surgical margins. A: the inked margin is free from neoplastic cells (H&E, ×10).B: the inked margin is focally (less than 1 mm) involved by neoplastic cells (H&E, ×10). C: the inked margin (more than 1 mm) is involved by neoplastic cells (H&E, ×10)

Study design

The aim of the study was to verify the hypothesis that a qualitative stratification of PSM into focal and non-focal might have an improved prognostic potential on biochemical recurrence in modern cohorts of patients undergoing RARP. The association of independent parameters with different PSM outcomes was first evaluated. Then, the association of factors with the risk of BCR was assessed.

Statistical analysis

Factors associated with the risk of focal and non-focal PSM

Summary statistics and distributions of factors among groups were assessed. Data on continuous variables are reported as medians with their respective interquartile ranges (IQR). Data on categorical variables are presented as frequencies with relative percentages. Associations of factors between groups were analyzed by test of Kruskal–Wallis for continuous variables and by the Pearson's chi-squared test or Fisher's exact test as appropriate. Significant factors were entered into the multivariate model. The multinomial logistic regression model evaluated associations of factors with the risk of PSM outcome, which were coded as negative (control group) as well as focal and non-focal (study groups).

Additionally, the presence of a median lobe was described in the ultrasound or MRI report and/or surgical report in a total of 42 patients (5.7% of the overall population), but it was not related to the presence of focal- or non-focal PSMs.

Factors associated with the risk of BCR

Patients were classified into two groups according to BCR. Summary statistics and distributions of factors between groups were assessed. Data on continuous variables are reported as medians with their respective interquartile ranges (IQR). Data on categorical variables are presented as frequencies with relative percentages. Associations of factors with the risk of BCR were first evaluated by univariate Cox proportional hazard model. Significant parameters were entered into the multivariate Cox proportional hazard model to detect independent factors associated with the risk of BCR.

The software used to run the analysis was IBM-SPSS version 20. All tests were two-sided with $p < 0.05$ considered to indicate statistical significance.

Results

Factors associated with positive surgical margins (PSM)

The overall study cohort included 732 patients whose demographics are reported in Table 1. Of the patient population, 34.2% were low risk, 50.1% intermediate risk, and 15.7 high risk/locally advanced according to EAU classification [6]. In the surgical specimen, extraprostatic extension was present in 21.9% of cases and showed high-grade issues (PGG 4–5) in 19.5% of subjects. Among the 342 patients who had an ePLND, the median number of dissected nodes was 26 and lymph-node invasion was detected in 49 cases (14.3%). The high-volume surgeon performed 66.1% of the procedures. Nerve sparing surgery was performed in 82% of cases. Major complications (CDS > 2) were detected in 2.9% of cases. Overall, 192 subjects had PSM (26.3%) which were classified as focal in 133 patients (18.2%) and non-focal in 59 cases (8.1%) (the anatomical distribution of focal- and non-focal PSM is reported in the supplementary Table 1). Table 2 shows independent factors associated with the risk of focal and non-focal PSM compared to controls. As shown, BMI, BPC, pathologic stage, and high-volume surgeon were independent predictors of focal PSM; moreover, the association was inverse for BMI (odds ratio, OR 0.914; $p = 0.006$) and high-volume surgeon (OR 0.574; p 0.006), but was positive for BPC (OR 1.011; $p = 0.015$), pT3a (OR 2.064; $p = 0.016$) and pT3b (OR 2.150; $p = 0.010$). Meanwhile, only BPC (OR 1.013; $p = 0.044$), pT3a (OR 4.832; $p < 0.0001$) and pT3b (OR 5.153; $p = 0.001$) were independent predictors of the risk of non-focal PSM. Therefore, the main differences between the risk factors for focal and non-focal PSM are related to BMI and high-volume surgeon. High surgeon volume reduces the risk of focal PSM, but does not reduce the risk of non-focal PSM.

In our cohort, the presence of a median lobe was reported in the ultrasound, MRI, or surgical reports in 42 patients (5.7% of the overall population), and it was not related to the presence of focal- or non-focal PSMs (data not shown).

Independent factors associated with the risk of biochemical recurrence (BCR)

The study population included 458 patients whose demographic details are reported in Table 3. Of these, the distribution was low risk in 158 patients (34.5%), intermediate risk in 228 (49.8%), and high risk/locally advanced in 72 (15.7%). Extended PLND was performed in 217 subjects

Table 1 Clinical, pathologic, and peri-operative factors in 732 patients who underwent robot-assisted radical prostatectomy (RARP)

Clinical factors		Pathological factors		Peri-operative factors	
Age, years; median (IQR)	65 (60–69)	Prostate weight (PW)		Operating time (OT)	
				OT, minutes; median (IQR)	200 (160–240)
Body mass index (BMI)		PW, g; median (IQR)	50 (41–63)		
BMI, kg/m^2; median (IQR)	25.8 (23.8–28)			Blood Lost (BL)	
		Dissected nodes; median (IQR)	26 (21–33)	BL, mL; median (IQR)	300 (200–500)
Prostate-specific antigen (PSA)					
PSA, ng/mL; median (IQR)	6.3 (4.9–8.7)	Pathology grade group (PGG)		Extended pelvic lymph-node dissection (ePLND)	
		PGG 1; *n* (%)	126 (17.2)	No ePLND; *n* (%)	390 (53.3)
Total prostate volume (TPV)		PGG 2–3; *n* (%)	463 (63.3)	ePLND; *n* (%)	342 (46.7)
PV, mL; median (IQR)	39 (30–50)	PGG 4–5; *n* (%)	143 (19.5)		
				Nerve sparing surgery (NSS)	
Biopsy positive cores (BPC)		Pathologic tumor stage (pT)		No NSS; *n* (%)	87 (11.9)
BPC, %; median (IQR)	29 (17–45.7)	pT2; *n* (%)	572 (78.1)	NSS; *n* (%)	600 (82)
		pT3a; *n* (%)	77 (10.5)	Unknown NSS; *n* (%)	45 (6.1)
Clinical tumor stage (cT)		pT3b; *n* (%)	83 (11.4)		
cT1c; *n* (%)	517 (70.6)			Surgeon	
cT2; *n* (%)	194 (26.5)	Pathologic nodal stage (pN)		Surgeon low volume; *n* (%)	248 (33.9)
cT3; *n* (%)	21 (2.9)	pN0; *n* (%)	293 (40)	Surgeon high volume; *n* (%)	484 (66.1)
		pNx; *n* (%)	390 (53.3)		
Clinical nodal stage (cN)		pN1; *n* (%)	49 (6.7)	American score of anaesthesiologists (ASA)	
cN0; *n* (%)	710 (97)			ASA 1–2; *n* (%)	675 (92.2)
cN1; *n* (%)	22 (3)	Positive surgical margins (PSM)		ASA 3–4; *n* (%)	57 (7.8)
		No PSM; *n* (%)	540 (73.8)		
Biopsy grade group (BGG)		PSM; *n* (%)	192 (26.2)	Length of hospital stay (LOHS)	
BGG 1, *n* (%)	343 (46.9)	Focal PSM; *n* (%)	133 (18.2)	LOHS, days; median (IQR)	4 (4–6)
BGG 2–3, *n* (%)	315 (43)	Non-focal PSM; *n* (%)	59 (8.1%)		
BGG 4–5, *n* (%)	74 (10.1)			Clavien–Dindo Score (CDS)	
				CDS 0; n (%)	557 (76.1)
				CDS 1–2; *n* (%)	154 (21)
				CDS > 2; *n* (%)	21 (2.9)
				No re-admission; *n* (%)	711 (97.1)
				Re-admission; *n* (%)	21 (2.9)

BMI body mass index, *PSA* prostate-specific antigen, *PV* prostate volume, *BPC* biopsy positive cores, *cT* tumor clinical stage, *cN* clinical nodal stage, *BGG* tumor biopsy grade group, *PW* prostate weight, *PGG* pathological grade group, *pT* tumor pathological stage, *pN* pathological nodal stage, *OT* operative time, *BL* blood lost, *ePLND* extended pelvic lymph-node dissection, *NSS* nerve sparing surgery, *ASA* American Society of Anesthesiolgists score, *LOHA* length of hospital stay, *CDS* Clavien–Dindo system, *IQR* interquartile range, *OR* odds ratio, *CI* confidence interval

*Adjusted odds ratios

**Model considering independent factors of clinical, pathological, and peri-operative models wih adjusted odds ratios

(47.4%). The median number (IQR) of nodes removed was 26 (21–33). Median LOHS was 4 (4–6) days. Biochemical recurrence was diagnosed in 40 patients (8.7%) of the follow-up population.

Median follow-up was 26 (14–40) months. Hospital re-admission was reported in 16 (3.5%) patients. BCR was diagnosed after a median time of 29.5 (17.2–42) months.

Early adjuvant RT was delivered in 31 cases (6.8%) and salvage RT in 9 (2.2%). Androgen deprivation therapy (ADT) was given in 48 cases (10.5%). All patients were alive at the time of censoring. Adjuvant RT was more frequently delivered in patients with BCR (11 cases; 27.5%) than controls (20 subjects; 4.8%). Adjuvant androgen blockade was more frequently delivered in patients with BCR (10 cases; 25%) than controls (23 cases; 5.5%). Androgen blockade was administrated as primary or combined treatment in 15 cases (37.5%) that recurred. When indicated, adjuvant hormonal therapy was started after a median time of 2.6 (1.8–3.1) months after surgery. BCR was

Table 2 Independent factors associated with the risk of focal and non-focal-positive surgical margins in 732 patients who underwent robot-assisted radical prostatectomy (RARP)

Factors	Population	Surgical margins			Focal positive vs negative surgical margins (*)			Non-focal positive vs negative surgical margins(*)		
		Negative	Focal positive	Non-focal positive	OR	95%CI	*p* value	OR	95% CI	*p* value
Number, *n* (%)	732	540 (73.8)	133 (18.2)	59 (8.1)						
BMI, kg/m^2; median (IQR)	25.8 (23.8–28)	26 (24–28)	25.1 (23.3–27.2)	25.3 (23.4–28.4)	0.914	0.857–0.974	0.006			
BPC, %; median (IQR)	29 (17–45.7)	28 (17–42)	33 (21–50)	35 (21–57)	1.011	1.002–1.021	0.015	1.013	1.000–1.023	0.044
pT2; *n* (%)	572 (78.1)	453 (83.9)	91 (68.4)	28 (47.5)	Ref			Ref		
pT3a; *n* (%)	77 (10.5)	43 (8)	20 (15)	14 (23.7)	2.064	1.145–3.722	0.016	4.832	2.348–9.943	<0.0001
pT3b; *n* (%)	83 (11.4)	44 (8.1)	22 (16.5)	17 (28.8)	2.150	1.196–3.864	0.010	5.153	2.541–10.450	0.001
Surgeon low volume; *n* (%)	248 (33.9)	168 (31.1)	57 (42.9)	23 (39)	Ref			Ref		
Surgeon high volume; *n* (%)	484 (66.1)	372 (68.9)	76 (57.1)	36 (61)	0.574	0.385–0.855	0.006	0.709	0.407–1.134	0.224

See Table 1; *IQR* interquartile range, *CI* confidence interval

*Adjusted OR

associated with an imaging recurrence in 15 cases (37.5%), which included involvement of retroperitoneal lymph nodes in 6 cases (40%), bone metastases in 5 cases (33.4%), visceral metastases in 2 cases (13.3%), and bladder neck invasion in 2 cases (13.3%).

Differences between groups are detailed in Table 3. As shown, BCR occurred in 40 patients (8.7%). The risk class distribution between groups (BCR vs controls) was significant and was as follows: low risk 7 (17.5%) vs 151 (36.1%), intermediate risk 21 (52.5%) vs 207 (49.5%), and high risk/locally advanced 12 (30%) vs 60 (14.4%). Patients who recurred had higher rates of aggressive disease than controls that showed higher rates of low-risk disease. Extended PLND was performed in 23 (57.5%) patients with BCR and in 194 (46.4%) cases in the control group, but the difference was not significant ($p=0.180$) neither was the median number of removed nodes ($p=0.095$).

On univariate analysis, factors that were associated with the risk of BCR included PSA (hazard ratio, HR 1.090; $p<0.0001$), BPC (HR 1.021; $p=0.003$), BGG 2/3 (HR 3.023; $p=0.003$), and BGG 4/5 (HR 5.156; $p<0.001$) for clinical factors as well as PGG 4/5 (HR 23.740; $p=0.002$), pT3a (HR 2.968; $p=0.015$), pT3b (HR 6.317; $p<0.0001$), non-focal PSM (HR 3.771; $p\leq0.0001$), and pN1 (HR 4.333; $p=0.001$) for pathological factors. Focal PSM and peri-operative parameters did not show any significant association with the risk of BCR.

Among the clinical parameters, multivariate analysis confirmed PSA, BPC, BGG 2/3, and BGG 4/5 as independent predictors of BCR and PGG 4/5, pT3b, and non-focal PSM among pathological parameters while PGG 2/3, pT3a, and pN1 lost significance. The final multivariate model of clinical and pathological factors associated with the risk of BCR with adjusted HR is reported in Table 4. Among clinical parameters, PSA (HR 1.064; $p=0.004$), BPC (HR 1.015; $p=0.027$), BGG 2/3 (HR 2.966; $p=0.003$), and BGG 4/5 (HR 3.122; $p=0.022$) remained significant independent predictors of the risk of BCR. Among pathological parameters, PGG 4/5 (HR 3.257; $p=0.001$), pT3b (HR 2.900; $p=0.003$), and non-focal PSM (HR 2.287; $p=0.012$) were independent predictors of the risk of BCR.

Interestingly, as shown in Fig. 2, the cumulative risk of BCR was higher in patients with non-focal PSM than patients with negative surgical margins or focal PSM. Furthermore, no differences in terms of BCR cumulative risk were found between patients with negative surgical margins or focal PSM after a median of 26 month follow-up (Fig. 2).

Table 3 Associations of factors with the risk of biochemical recurrence after robot-assisted radical prostatectomy in 458 cases

Factors	Population	Biochemical recurrence		Univariate analysis (*)	*p* value	Multivariate analysis*	*p* value
		No	Yes	HR (95% CI)		HR (95% CI)	
n (%)	458	418 (91.3)	40 (8.7%)				
Clinical factors				Clinical model		Clinical model	
Age, years; median (IQR)	65 (60–69)	65 (60–69)	65 (60–69)	1.023 (0.970–1.079)	0.405		
BMI, kg/m^2; median (IQR)	25.6 (23.5–27.8)	25.8 (23.8–27.8)	25.2 (23.5–27.5)	0.921 (0.826–1.027)	0.140		
PSA, ng/mL; median (IQR)	6.2 (4.7–8.7)	6.1 (4.7–8.2)	8.3 (5.2–12.3)	1.090 (1.050–1.132)	< 0.0001	1064 (1.020–1.110)	0.004
TPV, mL; median (IQR)	39 (30–49.5)	39 (29.7–50)	35 (30–44)	0.984 (0.961–1.008)	0.984		
BPC, %; median (IQR)	29 (17–43)	28.5 (17–42)	43 (20–56.7)	1.021 (1.007–1.035)	0.003	1.015 (1.002–1.029)	0.027
cT1c; *n* (%)	317 (69.2)	291 (69.6)	26 (65)	Ref	0.232		
cT2; *n* (%)	128 (27.9)	116 (27.8)	12 (30)	Ref			
cT3; *n* (%)	13 (2.8)	11 (2.6)	2 (5)	2.256 (0.663–11.448)	0.163		
cN0; *n* (%)	444 (96.9)	404 (96.7)	40 (100)	Ref			
cN1; *n* (%)	14 (3.1)	14 (3.3)	0	0.447 (0.000–159.073)	0.462		
BGG 1, *n* (%)	220 (48)	208 (49.8)	12 (30)	Ref		Ref	
BGG 2–3, *n* (%)	190 (41.5)	170 (40.6)	20 (50)	3.023 (1.473–6.203)	0.003	2.966 (1.441–6.106)	0.003
BGG 4–5, *n* (%)	48 (10.5)	40 (9.6)	8 (20)	5.156 (2.096–12.683)	< 0.0001	3.122 (1.176–8.289)	0.022
Pathological factors				Pathological model		Pathological model	
PW, gr; median (IQR)	50 (41–63)	50 (41–63)	50.5 (42.5–68.7)	1.009 (0.991–1.027)	0.314		
PGG 1; *n* (%)	73 (15.9)	72 (17.2)	1 (2.5)	Ref		Ref	
PGG 2–3; *n* (%)	296 (64.7)	277 (66.2)	19 (47.5)	5.984 (0.801–44.719)	0.081	Ref	
PGG 4–5; *n* (%)	89 (19.4)	69 (16.6)	20 (50)	23.740 (3.184–177.025)	0.002	3.257 (1.656–6.406)	0.001
pT2; *n* (%)	359 (78.4)	341 (81.6)	18 (45)	Ref		Ref	
pT3a; *n* (%)	47 (10.3)	40 (9.6)	7 (17.5)	2.968 (1.239–7.108)	0.015	1.611 (0.647–4.011)	0.305
pT3b; *n* (%)	52 (11.4)	37 (8.9)	15 (37.5)	6.317 (3.163–12.614)	< 0.0001	2.900 (1.440–5.838)	0.003
SM negative; *n* (%)	344 (75.1)	321 (76.8)	23 (57.1)	Ref		Ref	
SM focal positive; *n* (%)	76 (16.3)	70 (16.7)	6 (15)	2.126 (0.858–5.268)	0.103	Ref	
SM non-focal positive; *n* (%)	38 (8.3)	27 (6.5)	11 (27.5)	3.771 (1.834–7.751)	< 0.0001	2.096 (1.016–4.327)	0.045
pN0; *n* (%)	188 (41)	171 (40.9)	17 (42.5)	Ref		Ref	

Table 3 (continued)

Factors	Population	Biochemical recurrence		Univariate analysis (*)	*p* value	Multivariate analysis*	*p* value
		No	Yes	HR (95% CI)		HR (95% CI)	
pNx; *n* (%)	241 (52.6)	224 (53.6)	17 (42.5)	Ref		Ref	
pN1; *n* (%)	29 (6.3)	23 (5.5)	6 (15)	4.333 (1.809–10.379)	0.001	1.251 (0.479–3.268)	0.647
Peri-operative factors				Peri-operative model		Peri-operative model	
OT, minutes; median (IQR)	205 (162.2–240)	205 (162.2–240)	210 (161.2–244.5)	1.005 (0.999–1.011)	0.080		
BL, mL; median (IQR)	300 (200–500)	300 (200–500)	325 (150–500)	0.999 (0.998–1.000)	0.157		
No NSS; *n* (%)	52 (11.4)	50 (12)	2 (5)	Ref			
Unknown NSS; *n* (%)	14 (3.1)	13 (3.1)	1 (2.5)	Ref			
NSS; *n* (%)	392 (85.6)	355 (84.9)	37 (92.5)	1.182 (0.363–3.847)	0.702		
Surgeon low volume; *n* (%)	151 (33)	142 (34)	9 (22.5)	Ref			
Surgeon high volume; *n* (%)	307 (67)	276 (66)	31 (77.5)	0.734 (1.542–3.241)	0.253		
ASA 1–2; *n* (%)	427 (93.3)	391 (93.5)	36 (90)	Ref			
ASA 3–4; *n* (%)	31 (6.7)	27 (6.5)	4 (10)	1.249 (0.444–3.513)	0.674		
CDS 0; *n* (%)	352 (76.9)	322 (77)	30 (75)	Ref			
CDS 1–2; *n* (%)	95 (20.7)	86 (20.6)	9 (22.5)	1.552 (0.735–3.276)	0.249		
CDS > 2; *n* (%)	11 (2.4)	10 (2.4)	1 (2.5)	1.557 (0.211–11.476)	0.664		

See Table 1; *IQR* interquartile range, *HR* hazard ratio, *CI* confidence interval

*Cox proportional hazards

Table 4 Final multivariate models of factors associated with the risk of biochemical recurrence after robot-assisted radical prostatectomy in 458 cases

Factors	Multivariate analysis (Cox proportional hazards)		
	HR	95% CI	*p* value
Clinical model			
PSA	1.064	1.020–1.110	0.004
BPC	1.015	1.002–1.029	0.027
BGG 1	Ref		
BGG 2–3	2.966	1.441–6.106	0.003
BGG 4–5	3.122	1.176–8.289	0.022
Pathological model			
PGG 1	Ref		
PGG 2–3	Ref		
PGG 4–5	3.257	1.656–6.406	0.001
pT2	Ref		
pT3a	Ref		
pT3b	2.900	1.440–5.838	0.003
SM negative/focal positive	Ref		
Non-focal positive	2.096	1.016–4.327	0.045

See Table 1; *HR* hazard ratio, *CI* confidence interval

*Adjusted OR

Discussion

Factors associated with the risk of PSM

The detection of PSM after radical prostatectomy is an important predictor of BCR as well as of loco-regional cancer recurrences [3–5]. According with the contemporary data within the literature, PSM rates after RARP range from between 15 and 29.5% [27–33], and have been associated with tumor biology, including tumor staging and grading as well as surgical technique and the level of surgeon experience [3–5].

In our study, PSM rates were 26.2%, and clinical and pathological predictors of PSM also confirmed the results reported by others. However, additional factors including BMI and operative load of experienced surgeons emerged both as independent parameters associated with the risk of focal PSM. BPC, pT3a, and pT3b stage were independent predictors of the risk of non-focal PSM. Importantly, surgeon volume was not found to be an independent predictor of non-focal PSM.

The influence of elevated BMI during radical prostatectomy is unclear and controversial. In our previous experience, we found that high BMI is associated with high-grade complications as well as worse oncological outcomes [34–36] According to the surgical margins status, reports in the literature show that the association might be absent or

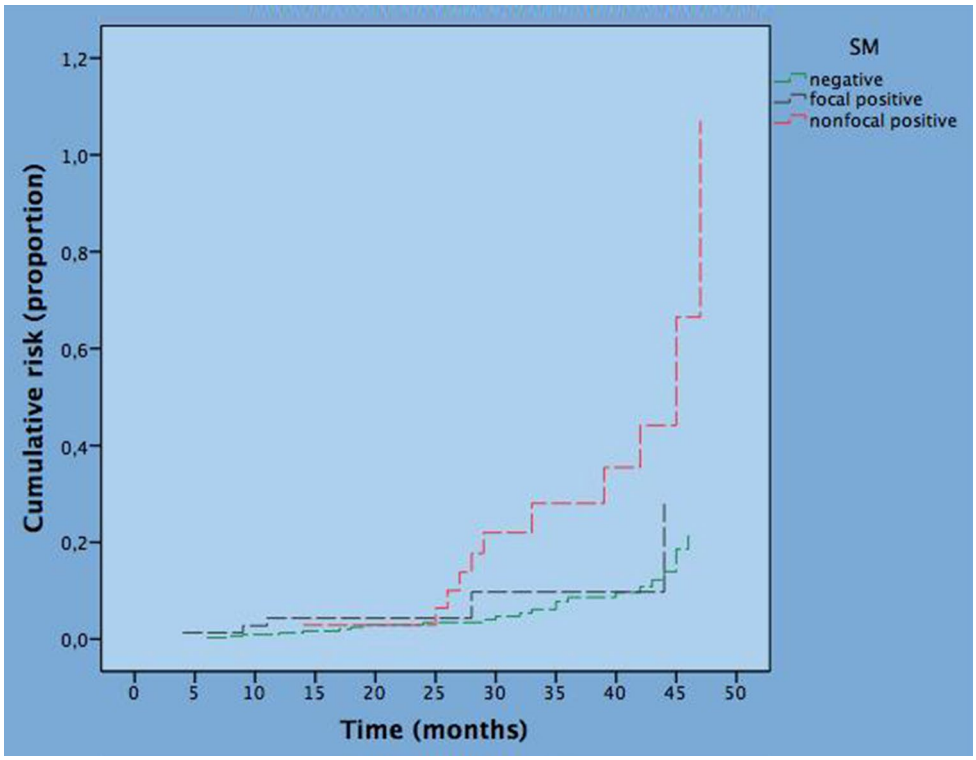

Fig. 2 Cumulative risk of biochemical recurrence (BCR): it was higher in patients with non-focal PSM than patients with negative surgical margins or focal PSM. No differences in terms of BCR cumulative risk were found between patients with negative surgical margins or focal PSM after a median of 26 month follow-up

positive. Particularly, Patel et al. found a positive correlation between high BMI and risk of PSM, and suggested that it might be related to the reduced vision and limited angle of movement during RARP in obese patients [28]. Here, we showed that BMI was an independent factor that associated with a reduced risk of focal PSM. This might be explained by peri-prostatic fat tissue thickness, which is more represented in obese patients who are then less likely to have focal PSM during RARP as demonstrated during CT scan studies [37].Our study has shown that, in a high-volume center, the high-volume experienced surgeon specifically and independently decreased the risk of focal PSM. The operating load of the experienced surgeon is an important parameter in robotic surgery. Indeed, Steinsvik et al. demonstrated that high-volume surgeons reduced overall risk of PSM after RARP [38]. Furthermore, a systematic review has shown that overall oncological outcomes are improved by increasing surgeon volume during RARP [39]. Additionally, Hu and associates have shown that patients treated by high-volume surgeons were less likely to undergo salvage therapy after RARP [40].

Among pathological factors, we found that BPC during the biopsy evaluation as well as p T3a and p T3b stages were associated with PCa high probability having non-focal PSM. Indeed, we previously demonstrated that the number of positive cores is strongly associated with more aggressive prostate cancer according to tumor upgrading and upstaging as well as uni-lateral or bi-lateral lymph-node metastasis and seminal vesical invasion [15, 16, 18, 19, 41, 42].

In our cohort, the presence of a median lobe was reported in the ultrasound, MRI, or surgical report in 5.7% of the overall population, and it was not related to the presence of focal- or non-focal PSMs.

Our data confirm the results provided by Hamidi et al. who found that the presence of a median lobe did not affect peri-operative PSM rate and BCR following RARP [43]. However, the data from another study seem to contradict this, particularly if the median lobe protrusion is greater than 10 mm [44].

Factors associated with the risk of BCR

When RARP is performed with radical intent, PSA levels are supposed to decrease to undetectable levels according to EAU guidelines on PCa [3, 6]. However, although PSA levels decline to undetectable levels, unfavorable pathological outcomes after RARP include extra-capsular extension, seminal vesicle invasion, and PSM [3, 6]. Indeed, all these parameters are associated with an increased risk of BCR [3–5]. On the other hand, the detection of PSM with or without other pathological features and an associated detectable PSA level after surgery is an even more pivotal issue because of further treatments can be needed [3, 6].

Considering a modern cohort of patients who underwent RARP, a few studies specifically consider the role of PSM as one of the several parameters predicting BCR after undetectable PSA. Rajan et al. reported PSM rates of 23.1% with BCR occurring in 18.9% of cases. However, they did not consider factors predicting PSM, but found that BGG > 1 as well as pT3a, pT3b, and PSM > 3 mm were associated with the risk of BCR after radical prostatectomy [31]. Interestingly, they evaluated the linear extent of PSM and demonstrated that it is an important parameter for differentiating which patients could develop BCR. In this context, different cut-offs have been used in the literature to describe focal PSM. Particularly, Servoll and associates have shown that a PSM length > 3 mm was an independent predictor of cancer recurrence in 303 patients who underwent open radical prostatectomy [9]. Sammon et al. used 1 mm as a cut-off in 794 patients undergoing radical perineal prostatectomy, and they found that at a median follow-up of 54 months, the 5-year BCR-free probability was 90.8% in patients with negative margins, 77.5% in patients with focal (≤ 1 mm) PSM, and 47.5% in patients with non-focal (> 1 mm) PSM [10]. Lee et al. demonstrated that focal (less than 3 mm) PSM after RP does not significantly affect BCR-free survival in 1733 prostate cancer patients [11]. Because RARP was performed in our cohort, we have chosen 1 mm as cut-off and evaluated the linear extent of PSM in two groups that were simple to compute and allowed a division of the population of patients into two subsets. In our study, we detected BCR rates of 8.7% with basal PSA, BPC, BGG 2/3, and BGG 4/5 as clinical independent predictors as well as extra-capsular extension, seminal vesicle invasion, and PSM as pathological independent factors associated with the risk of BCR. BMI and high load experienced surgeon did not predict the occurrence of BCR, probably because they were not directly associated with such risk but indirectly instead by lowering the rates of PSM, which were independently and directly associated with BCR, as previously shown. An important feature that emerged from the results of our investigation was that the linear extent of PSM is an important parameter for stratifying patients after surgery. Indeed, patients having focal PSM, as well as patients with negative surgical margins, have comparable risk of BCR compared to cases with non-focal PSM (Fig. 2). This result has a pivotal role in clinical practice, because patients who present with focal PSM, which represents 18.2% of patient population (69% among patients with PSM), may be managed expectantly after RARP.

General considerations

Our study shows that surgeons performing a large number of procedures can reduce the risk of focal PSM after RARP in a high-volume center, and importantly, we demonstrated

that this parameter is not related to BCR. In this way, we have proven that surgical experience does not affect the rate of non-focal PSM and thus is not related to BCR. This information is important when counseling patients who inquire about the experience of a surgeon and the details concerning his operating load and how it may affect pathologic outcomes including focal and non-focal PSM rates and BCR in contemporary series of patients.

Additionally, evaluation of PSM by linear extent to code PSM as focal (≤ 1 mm) and non-focal (> 1 mm) is a simple measurement that stratifies the risk of BCR, and thus, it should be considered in the BCR risk classifications after surgical radical treatment. Furthermore, these results represent a new way to approach robotic surgery in PCa patients, and as such, it is a novel parameter, which differentiates our study from other contemporary series.

Overall, our findings need to be further investigated and validated to be utilized in daily clinical practice.

Limits and strengths of the study

Although our study has strengths, it also presents several limitations. First, although our data were collected prospectively, data were analyzed retrospectively and thus suffer from the limitations related to such investigations. Second, follow-up was limited, and thus, oncological outcomes are not available for all patients, but data continue to be collection in this respect. Third, prostate volumes and biopsies performed elsewhere were not re-evaluated; however, their features had good standard quality to support the analysis. However, beyond these limits, our study has also many strengths that include the large contemporary cohort of patients in a high-volume center, all specimens evaluated by dedicated pathologists.

Conclusions

In high-volume centers, features related to host, tumor, and experienced surgeon load are pivotal factors that are associated with the risk of focal PSM. However, focal PSM is not an independent predictor of BCR after RARP. In contrast, non-focal PSM is an independent predictor of BCR after RARP. The high load experienced surgeon is not an independent factor that lowers the risk of non-focal PSM and as such the risk of BCR does not change based on surgeon volume. This issue is pivotal when counseling contemporary patients making informed decisions among PCa treatment modalities including robotic surgery as primary radical treatment for PCa.

Author contributions ABP: project development, data analysis and interpretation, manuscript writing, and supervision. AT and MS: project development, data collection, data analysis and interpretation, and manuscript writing. PC, MP, TP, NA, RR, RB, CC, and LT: data collection. AS: language and critical revision. MB, VDeM, FM, GN, SS, MAC, AA, and WA: other (supervision and critical revision).

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Compliance with ethical standards

Conflict of Interest All authors declare that they have not conflict of interest.

Informed consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all individual participants included in the study.

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