

High surgeon volume and positive surgical margins can predict the risk of biochemical recurrence after robot-assisted radical prostatectomy

Antonio Benito Porcaro , Alessandro Tafuri , Marco Sebben, Nelia Amigoni, Tania Processali, Marco Pirozzi, Riccardo Rizzetto, Aliasger Shakir, Paolo Corsi, Leone Tiso, Clara Cerrato, Filippo Migliorini, Giovanni Novella, Matteo Brunelli, Riccardo Bernasconi, Vincenzo De Marco, Salvatore Siracusano and Walter Artibani

Abstract

Background: The aim of this study was to determine whether any clinical factors are independent predictors of positive surgical margins (PSM), and to assess the association of PSM and biochemical recurrence (BR) after robot-assisted radical prostatectomy (RARP).

Methods: The population included cases with negative surgical margins (control group) and patients with PSM (study group). Tumor grade was evaluated according to the International Society of Urologic Pathology (ISUP) system. A logistic regression model assessed the independent association of factors with the risk of PSM. The risk of BR was assessed by Cox's multivariate proportional hazards.

Results: A total of 732 consecutive patients were evaluated. Extend pelvic lymph node dissection (ePLND) was performed in 342 cases (46.7%). Overall, 192 cases (26.3%) had PSM. The risk of PSM was positively associated with the percentage of biopsy positive cores (BPC; odds ratio, OR = 1.012; $p = 0.004$), extracapsular extension (pT3a; OR = 2.702; $p < 0.0001$), invasion of seminal vesicle (pT3b; OR = 2.889; $p < 0.0001$), but inversely with body mass index (OR = 0.936; $p = 0.021$), and high surgeon volume (OR = 0.607; $p = 0.006$). Independent clinical factors associated with the risk of BR were baseline prostate-specific antigen (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 factors associated with the risk of BR were ISUP group 4/5 (HR = 3.257; $p = 0.001$), pT3b (HR = 2.900; $p = 0.003$), and PSM (HR = 2.096; $p = 0.045$).

Conclusions: In our cohort, features related to host, tumor, and surgeon volume are associated with the risk of PSM, which is also an independent parameter predicting BR after RARP. The surgical volume of the operating surgeon is an independent factor that decreases the risk of PSM, and, as such, the risk of BR.

Keywords: biochemical recurrence, positive surgical margins, prostate cancer, robot-assisted radical prostatectomy, surgical volume

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Introduction

Prostate cancer (PCa) is the most common non-cutaneous malignancy, and the second leading

cause of cancer-related deaths in men.¹ Once PCa has been diagnosed and staged, the urologist will counsel the patient in order to decide the

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Correspondence to:
Antonio Benito Porcaro
Department of Urology
Azienda Ospedaliera
Universitaria Integrata
Verona, Piazzale Stefani 1,
Verona, 37126, Italy
drporcaro@yahoo.com
copartment

Alessandro Tafuri
Department of Urology,
University of Verona,
Azienda Ospedaliera
Universitaria Integrata
Verona, Verona, Italy
USC Institute of Urology,
and Catherine & Joseph
Aresty Department of
Urology, University of
Southern California, Los
Angeles, CA, USA

Marco Sebben
Nelia Amigoni
Tania Processali
Marco Pirozzi
Riccardo Rizzetto
Paolo Corsi
Leone Tiso
Clara Cerrato
Filippo Migliorini
Giovanni Novella
Vincenzo De Marco
Salvatore Siracusano
Walter Artibani
Department of Urology,
University of Verona,
Azienda Ospedaliera
Universitaria Integrata
Verona, Verona, Italy

Aliasger Shakir
USC Institute of Urology,
and Catherine & Joseph
Aresty Department of
Urology, University of
Southern California, Los
Angeles, CA, USA

Matteo Brunelli
Riccardo Bernasconi
Department of Pathology,
University of Verona,
Azienda Ospedaliera
Universitaria Integrata
Verona, Verona, Italy

most appropriate management, which includes active surveillance (AS), radical prostatectomy (RP), and radiation therapy (RT).^{2,3} In developed countries, RP is most frequently performed by the robot-assisted (RARP) approach. An unfavorable outcome after RARP is the detection of positive surgical margins (PSM), which is an important negative prognostic factor for cancer locoregional recurrence.^{2,3} So far, patients who show unfavorable pathologic outcomes in the surgical specimen, including high-grade tumors with disease extending beyond the prostate, and PSM need accurate counseling for further management options that include immediate RT (after recovery of the urinary function) or close PSA monitoring with salvage RT before PSA approaches values of 0.5 ng/ml.^{2,3} These issues impair the quality of life of affected patients because of anxiety as well as the toxicities related to adjuvant or salvage treatments, which may include androgen blockade.^{2,3} PSM after RARP may be related to tumor biology or to the physician's surgical experience.³⁻¹⁰ In high-volume centers, the rates of PSM were similar among surgeons with similar surgical volumes.⁹

In a contemporary cohorts of patients, it is important to evaluate factors associated with the risk of PSM after RARP because, when a PSM is detected, the next step is to decide whether adjuvant treatments should be delivered in order to reduce the risk of biochemical recurrence (BR). From this perspective, it is important to evaluate the actual effect of PSM as well as other clinical and pathological parameters on the risk of BR after RARP.

The aim of this study was to test the hypothesis that PSM among other clinical parameters impacts the risk of BR 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 data collection and analysis. Low, intermediate, and high risk, and locally advanced patients were included in the study if the clinical T stage was \leq T3b and the prostate volume was

\leq 80 cc. Patients with previous surgical prostate treatments, with cT4 stage or metastatic disease or who were under androgen blockade or had prior treatments were excluded. Patients with pT2+ (defined as 'positive margins in the setting of intra-prostatic or intra-tumoral incision') according to the Stanford protocol, were excluded.¹¹

Clinical features

Preoperatively, patients were evaluated for age (years) body mass index (BMI; kg/m²) and plasma levels of PSA (ng/ml), which were determined by radioimmunoassay methods. Prostate biopsies had the following features: at least 12–14 cores; reported number of positive cores; measurement of prostate volume (TPV; ml); and cancer grade group classification according to the 2014 International Society of Urologic Pathology (ISUP) system.¹² In each case, the percent of positive cores (BPC; percentage) was computed. Patients were clinically staged according the European Society of Urology (EAU) guidelines.² Tumors were staged by digital rectal exam (DRE) or by multiparametric resonance imaging (mMRI). Pelvic lymph nodes were assessed by computed 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 or mMRI as well as by total bone scan. Patients were then classified into risk groups according to the EAU guidelines on PCA.²

Perioperative features

RARP was executed by the da Vinci Robot System (Intuitive Surgical, Inc, Sunnyvale, CA, USA) and performed through the transperitoneal approach with anterograde prostatic dissection.¹³ The decision to perform an extended lymph node dissection (ePLND) was taken when the risk of lymph node invasion (LNI) was greater than 5%.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 When indicated, ePLND was performed according to an anatomical template including bilateral external iliac (extending proximally to the crossing of the ureter), obturator, Marcille's, common iliac, and Cloquet's nodal stations. The external iliac LN group was dissected laterally to the genitofemoral nerve at the lateral edge of the internal iliac artery

and vein from the node of Cloquet to the ureteric crossing of the internal iliac artery, as reported previously.^{20,21}

Nerve sparing RP (NSRP) was performed when indicated.¹⁵ When the nerve sparing technique was used, clinical stage, cancer localization, and its proximity to the capsule, were recorded. In particular, NSRP surgery was performed by the intrafascial or interfascial technique. Extrafascial dissection was performed when nerve sparing was not indicated.²² Five experienced surgeons performed RARP with a bladder neck sparing technique.²³ Surgeon experience was defined according to a previous publication that reported that among surgeons with >30 RARP procedures, there was no difference in PSM rates.²⁴ All surgeons had completed the RARP learning curve before the beginning of patient enrolment. Our high-volume experienced surgeon had performed more than 500 RARPs; our other four low-volume experienced surgeons had performed between 50 and 60 RARPs. A single high-volume experienced surgeon (WA) performed two-thirds of the procedures in our dataset. Preoperatively, patients were evaluated for surgical risk by the American Anesthesiologists Score (ASA) system.²⁵ Intraoperatively, operating time (OT, minutes) and blood lost (BL, milliliters) were measured. Postoperatively, length of hospital stay (LOHS) was recorded in each patient. Patients were followed for a period of 6 months in order to detect hospital readmission and complications that were classified according to the Clavien–Dindo classification system.²⁶

Pathological features

The dedicated pathologists prepared surgical specimens according to the Stanford protocol.²¹ Prostate weight (PW, grams) was calculated. Tumors were classified according to the ISUP grade group (PGG) system.¹² Nodal packets were grouped according to a standard template and submitted in separate packages. 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.²

Surgical margins were defined as positive when cancer invaded the inked surface of the specimen. Locations were coded as follows: apical,

posterior–lateral (left and right), posterior, anterior, and bladder neck. The pathologist evaluated the linear extent of PSM according to a qualitative pattern, which stratified positive surgical margins into two groups as focal and nonfocal. Accordingly, PSM were classified as focal when the linear extent was less than or equal to 1 mm, and nonfocal otherwise. In this report, we did not consider analysis related to stratification of PSM according to linear extent.

Follow up

Follow up, adjuvant treatments, and BR after RARP were evaluated according to EAU standard criteria.^{2,3} Overall, 580 out of 732 (79%) were available for follow up. Patients with follow up shorter than 4 months were excluded. Overall, BR was evaluated in 458 patients (79%). The median (IQR) follow up was 26 (14–40) months.

Study design

The aim of the study was to verify the hypothesis that qualitative stratification of surgical margins (PSM *versus* negative) might have different prognostic potential on BR in modern cohorts of patients undergoing RARP. The association of independent clinical parameters with PSM outcome was first evaluated. The association of factors with the risk of BR was then assessed.

Statistical analysis

Factors associated with PSM. Patients were classified into two groups according to PSM (PSM *versus* control). Summary statistics and distributions of factors between groups were assessed. Data on continuous variables are reported as medians with their respective interquartile ranges (IQRs). Data on categorical variables are presented as frequencies with relative percentages. Associations of factors between groups were analyzed by Mann–Whitney *U* test for continuous variables and by the Pearson's chi-squared test or Fisher exact test as appropriate for the categorical ones. Significant factors were entered into the multivariate model. The logistic regression model evaluated the association of factors with the risk of PSM.

Factors associated with BR. Patients were classified into two groups according to BR (BR *versus* control). Summary statistics and distributions of factors between groups were assessed. Data on continuous variables are reported as medians

with their respective IQRs. Data on categorical variables are presented as frequencies with relative percentages. Associations of factors with the risk of BR were first evaluated by univariate Cox proportional hazard model. Significant parameters were entered into the multivariate Cox proportional hazard model in order to detect independent factors associated with the risk of BR.

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

Results

Independent factors associated with the risk PSM

The overall study cohort included 732 patients whose demographics are reported in Table 1. Of the patient population, 34.2% was low risk, 50.1% intermediate risk, and 15.7% high risk or locally advanced according to EAU classification.² In the surgical specimen, extra prostatic extension was present in 21.9% of cases and showed high-grade disease (PGG 4-5) in 19.5% of subjects. Extend pelvic lymph node dissection was performed in 342 cases; among these, lymph node invasion was detected in 49 cases (14.3%) and 293 (85.7%) were pN0. Among the remaining 390 patients, pathological N stage was not investigated. The median number of dissected nodes was 26. 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%). The association of factors with the risk of PSM has been previously reported.²⁷ Table 2 shows independent factors associated with the risk of PSM compared with controls. BMI, BPC, pathologic stage, and high-volume surgeon were independent predictors of PSM; moreover, the association was inverse for BMI (odds ratio, OR = 0.936; $p = 0.021$) and high-volume surgeon (OR = 0.607; $p = 0.006$) as well as positive for BPC (OR = 1.012; $p = 0.004$), pT3a (OR = 2.702; $p < 0.0001$) and pT3b (OR = 2.889; $p < 0.0001$).

Independent factors associated with the risk of BR

The study population included 458 patients whose demographic details are reported in Table 3. Median (IQR) follow up was 26 (14–40) months.

Risk class 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 (47.4%). The median number (IQR) of removed nodes was 26 (21–33). Median (IQR) LOHS was 4 (4–6) days. Hospital readmission was reported in 16 (3.5%) patients. 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 time of censoring. Adjuvant RT was more frequently delivered in patients with BR (11 cases; 27.5%) than controls (20 subjects; 4.8%). Adjuvant androgen blockade was more frequently delivered in patients with BR (10 cases; 25%) than controls (23 cases; 5.5%). Adjuvant androgen blockade was administered alone or combined treatment in 15 cases (37.5%) that recurred. BR was associated with imaging recurrence in 15 patients (37.5%), which included retroperitoneal lymph nodes involvement in 6 patients (40%), bone metastases in 5 patients (33.4%), visceral metastases in 2 patients (13.3%), and bladder neck invasion in 2 patients (13.3%).

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

On univariate analysis, clinical factors associated with the risk of BR were prostate-specific antigen (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; $p < 0.001$). Pathological factors associated with the risk of BR were PGG 4/5 (HR = 23.740; $p = 0.002$), pT3a (HR = 2.968; $p = 0.015$), pT3b (HR = 6.317; $p < 0.0001$), PSM (HR = 2.041; $p = 0.035$), and pN1 (HR = 4.333; $p = 0.001$). Perioperative parameters did not show any significant association.

Table 1. Clinical, pathologic and perioperative factors in 732 patients who underwent RARP.

Clinical Factors	
Age, years; median (IQR)	65 (60–69)
BMI, kg/m ² ; median (IQR)	25.8 (23.8–28)
PSA, ng/ml; median (IQR)	6.3 (4.9–8.7)
TPV, ml; median (IQR)	39 (30–50)
BPC, %; median (IQR)	29 (17–45.7)
cT	
cT1c; <i>n</i> (%)	517 (70.6)
cT2; <i>n</i> (%)	194 (26.5)
cT3; <i>n</i> (%)	21 (2.9)
cN	
cN0; <i>n</i> (%)	710 (97)
cN1; <i>n</i> (%)	22 (3)
BGG	
BGG 1, <i>n</i> (%)	343 (46.9)
BGG 2–3, <i>n</i> (%)	315 (43)
BGG 4–5, <i>n</i> (%)	74 (10.1)
Pathological Factors	
PW (g); median (IQR)	50 (41–63)
Dissected nodes; median (IQR)	26 (21–33)
PGG	
PGG 1; <i>n</i> (%)	126 (17.2)
PGG 2–3; <i>n</i> (%)	463 (63.3)
PGG 4–5; <i>n</i> (%)	143 (19.5)
pT	
pT2; <i>n</i> (%)	572 (78.1)
pT3a; <i>n</i> (%)	77 (10.5)
pT3b; <i>n</i> (%)	83 (11.4)
pN	
pN0; <i>n</i> (%)	293 (40)
pNx; <i>n</i> (%)	390 (53.3)
pN1; <i>n</i> (%)	49 (6.7)

*(Continued)***Table 1.** (Continued)

Clinical Factors	
PSM	
No PSM; <i>n</i> (%)	540 (73.8)
PSM; <i>n</i> (%)	192 (26.2)
Perioperative Factors	
OT (min); median (IQR)	200 (160–240)
BL (ml); median (IQR)	300 (200–500)
no ePLND; <i>n</i> (%)	390 (53.3)
ePLND; <i>n</i> (%)	342 (46.7)
NSS	
No NSS; <i>n</i> (%)	87 (11.9)
NSS; <i>n</i> (%)	600 (82)
Unknown NSS; <i>n</i> (%)	45 (6.1)
Surgeon	
Surgeon low volume; <i>n</i> (%)	248 (33.9)
Surgeon high volume; <i>n</i> (%)	484 (66.1)
ASA score	
ASA 1–2; <i>n</i> (%)	675 (92.2)
ASA 3–4; <i>n</i> (%)	57 (7.8)
LOHS	
days; median (IQR)	4 (4–6)
CDS	
CDS 0; <i>n</i> (%)	557 (76.1)
CDS 1–2; <i>n</i> (%)	154 (21)
CDS > 2; <i>n</i> (%)	21 (2.9)
No readmission; <i>n</i> (%)	711 (97.1)
Readmission; <i>n</i> (%)	21 (2.9)
ASA, American Score of Anaesthesiologists; BL, blood lost; BGG, biopsy grade group; BMI, body mass index; BPC, biopsy positive cores; CDS, Clavien–Dindo score; cN, clinical nodal stage; cT, clinical tumor stage; ePLND, extended pelvic lymph node dissection; IQR, interquartile range; LOHS, length of hospital stay; NSS, nerve sparing surgery; OT, operating time; PGG, pathology grade group; pN, pathologic nodal stage; PSA, prostate-specific antigen; PSM, positive surgical margins; pT, pathologic tumor stage; PW, prostate weight; RARP, robot-assisted radical prostatectomy; TPV, total prostate volume.	

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

Factors	Population	Surgical margins		Multivariate analysis (*)	
		negative	positive	OR (95% CI)	<i>p</i> value
<i>n</i> (%)	732	540 (73.8)	192 (26.2)	Overall model (**)	
BMI, kg/m²; median (IQR)	25.8 (23.8–28)	26 (24–28)	25.2 (23.4–27.8)	0.936 (0.886–0.990)	0.021
BPC, %; median (IQR)	29 (17–45.7)	28 (17–42)	33 (21–50)	1.012 (1.004–1.020)	0.004
pT2; <i>n</i> (%)	572 (78.1)	453 (83.9)	28 (47.5)	Ref	
pT3a; <i>n</i> (%)	77 (10.5)	43 (8)	14 (23.7)	2.702 (1.631–4.474)	<0.0001
pT3b; <i>n</i> (%)	83 (11.4)	44 (8.1)	17 (28.8)	2.889 (1.752–4.765)	<0.0001
Surgeon low volume; <i>n</i> (%)	248 (33.9)	168 (31.1)	80 (41.7)	Ref	
Surgeon high volume; <i>n</i> (%)	484 (66.1)	372 (68.9)	112 (58.3)	0.607 (0.425–0.865)	0.006

See Table 1; IQR, interquartile range; OR, odds ratio; CI, confidence interval; (*), overall model of independent factors; (**); adjusted OR.

Multivariate analysis confirmed PSA, BPC, BGG 2/3 and BGG 4/5 as independent predictors of BR for clinical parameters as well as PGG 4/5, pT3b and PSM for 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 BR with adjusted HR is reported in Table 4. Considering 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; $p = 0.022$) are independent predictors of the risk of BR. Considering pathological parameters, PGG 4/5 (HR = 3.257; $p = 0.001$), pT3b (HR = 2.900; $p = 0.003$), and PSM (HR = 2.096; $p = 0.045$) were independent predictors of the risk of BR. Figure 1 depicts the risk curves of BR stratified by PSM; as shown, the risk of BR is increased by the presence of PSM.

We also evaluated the association between PSA and pathological factors in the prediction of BR and we found that PSA (HR = 1.058; $p = 0.007$), PSM (HR = 2.401, $p = 0.020$), and pT3b (HR = 2.631, $p = 0.015$) were independent predictors of BR. In addition, when the statistically significant factors were compared, all remained significant (see Table 4 ‘final PSA-pathological factors combined model’).

Discussion

Factors associated with the risk of PSM

In large contemporary series, PSM rates after RARP range from 15% to 29.5%.^{28–34} Surgery and tumor biology are factors that are associated with a PSM; the former is related to technique and surgeon’s experience, while the latter depends on the stage and grade of the tumor.^{3–10} The risk of PSM after RARP has been associated with clinical and pathological factors.^{28–30}

In our study, PSM rates were 26.2%, which confirmed findings in the literature; moreover, similar clinical and pathological predictors of PSM were also reported by other studies. In our previous experience, we found that higher preoperative total testosterone serum levels were predictive of positive surgical margins after RP.³⁵ However, unusual factors, including BMI and operative load of experienced surgeons, emerged as independent parameters associated with the risk of PSM. These findings represent a novelty and need to be explained. The influence of BMI during RARP is unclear, controversial, and the subject has been investigated to show that the association might be absent or positive.^{32,36–38} We previously found that BMI is associated with major postoperative complications after RARP.¹⁹

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 (*)		Multivariate analysis (*)	
		no	yes	HR (95% CI)	p value	HR (95% CI)	p value
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	4.478 (0.591–33.954)	0,147
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 positive; n (%)	114 (24.9)	97 (23.2)	17 (42.5)	2.041 (1.051–3.963)	0.035	2.287 (1.197–4.370)	0,012
pN0; n (%)	188 (41)	171 (40.9)	17 (42.5)	Ref		Ref	

(Continued)

Table 3. (Continued)

Factors	Population	Biochemical recurrence		Univariate analysis (*)		Multivariate analysis (*)	
		no	yes	HR (95% CI)	p value	HR (95% CI)	p value
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
Perioperative Factors				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 for abbreviations; IQR, interquartile range; HR, hazard ratio; CI, confidence interval; (*), Cox proportional hazards.

Patel and associates suggest that the positive association between BMI and PSM might be related to both reduced vision and angle movements during RARP in obese patients.²⁹ The present study shows that higher BMI is an independent factor that is associated with a reduced risk of PSM. This might be explained by periprostatic fat tissue thickness, which is more represented in obese patients, who are then less likely to have focal PSM during RARP. Although this hypothesis needs to be verified, it is supported by a study showing a significant correlation between BMI and periprostatic fat thickness ($r = 0.37$), which was measured by CT scans.³⁹ Our study has shown that, in a high-volume center, the high-volume experienced surgeon specifically and independently decreased the risk of PSM. The operating load of the experienced surgeon is an

important parameter, which is ongoing and being amplified in robotic surgery. Indeed, a systematic review of the literature concerning the volume–outcome relationship for RP has studied the subject dealing with surgeon volume and oncological outcomes.⁴⁰ The review has shown that overall oncological outcomes are improved by increasing surgeon volume. Hu and associates have shown that patients operated by high-volume surgeons were less likely to undergo salvage therapy after RARP.⁴¹ Moreover, Steinsvik and associates demonstrated that high-volume surgeons reduced overall risk of PSM after RARP.⁴² The identification of high-volume surgeons in high-volume centers might be a point to consider when counseling patients before RARP. With both BMI and high-load experienced surgeon emerging as independent factors together with other known

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	3.194	1.575–6.058	0.001
pT2	Ref		
pT3a	Ref		
pT3b	3.091	1.575–6.058	0.001
Negative surgical margin	Ref		
Positive surgical margin	2.287	1.197–4.370	0.012
PSA-Pathological combined model			
PSA	1.058	1.015–1.102	0.007
PGG 1-3	Ref		
PGG 4-5	1.961	0.911–4.222	0.085
pT2	Ref		
pT3a	Ref		
pT3b	2.631	1.210–5.719	0.015
Negative surgical margin	Ref		
Positive surgical margin	2.401	1.119–5.018	0.020
Final PSA-Pathological combined model (*)			
PSA	1.066	1.024–1.109	0.002
pT2-3a	Ref		
pT3b	3.053	1.428–6.525	0.004
Negative surgical margin	Ref		
Positive surgical margin	2.680	1.312–5.476	0.007
See Table 1 for abbreviations; (*) adjusted HR.			

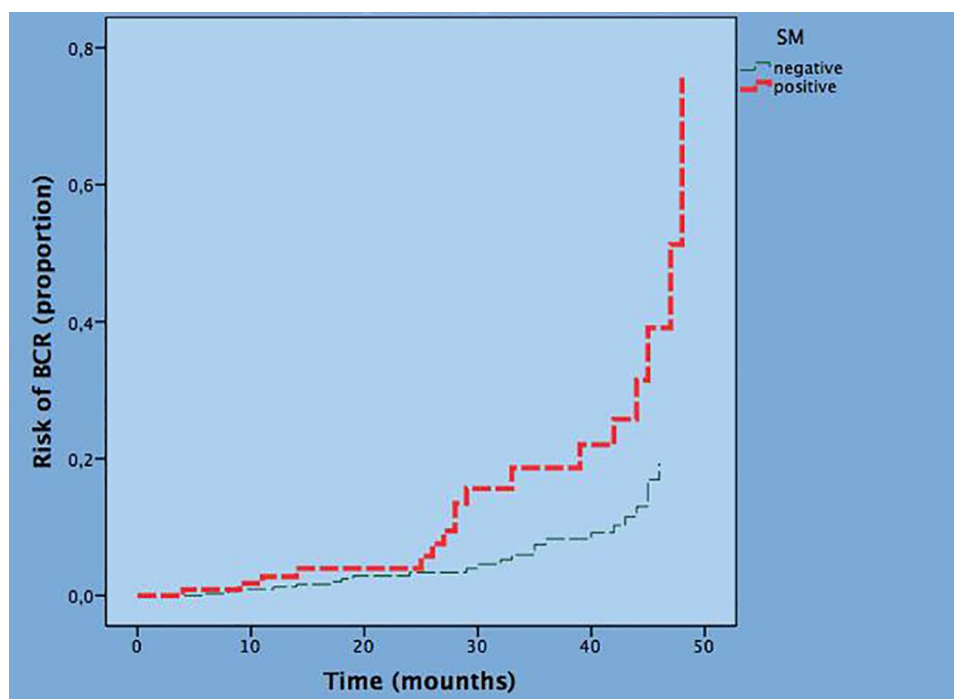


Figure 1. Risk curve of BR by surgical margins status. BR, biochemical recurrence.

parameters representing a novel finding, this association needs to be confirmed by further studies.

Factors associated with the risk of BR

When RARP is performed with radical intent, PSA levels are thought to decrease to undetectable levels according to EAU guidelines on PCA.^{2,3} However, although PSA levels may decline to undetectable levels, unfavorable pathological outcomes after RARP, including extracapsular extension, seminal vesicle invasion, high PGG, and PSM, may surface.^{2,3} Indeed, all these parameters are associated with an increased risk of BR.³⁻¹⁰ On the other hand, the detection of PSM with or without other pathological features in combination with detectable PSA levels after surgery is an even more pertinent issue because further treatments are mandatory.^{2,3}

Considering modern cohorts of patients who underwent RARP, few studies consider specifically the role of PSM as one of the several parameters able to predict BR after undetectable PSA.³²⁻³⁴ Rajan and colleagues reported PSM rates of 23.1% with BR occurring in

18.9% of cases; however, factors predicting PSM were not assessed, and parameters associated with the risk of BR were evaluated instead.³² In this study, the authors found that independent parameters associated with the risk of BR were baseline PSA > 10 ng/ml and BGG 1 > 1 for clinical factors as well as pT3a, pT3b, and PSM > 3 mm or multifocal for pathological factors. Jo and coworkers reported PSM rates of 20.5%, with BR detected in 18.7% of patients; as in the previous study, factors predicting PSM were not evaluated but factors predicting BR were assessed instead.³⁴ The authors reported independent factors associated with the risk of BR were age, cT > 2, PSA > 10 ng/ml, BGG > 1, BPC > 50% among clinical factors as well as extracapsular extension, seminal vesicle invasion, and PSM at the apex among pathological factors in the study. So far, in these two studies, the assessment of PSM was one of the independent pathological factors predicting the risk of BR. In our study, we detected BR rates of 8.7% with basal PSA, BPC, BGG 2/3, and BGG 4/5 as independent clinical predictors as well as extracapsular extension, seminal vesicle invasion, and PSM as pathological independent predictors of BR. Further, when we combined PSA with

pathological factors, PSA, PSM, and pT3b persisted as independent predictors of BR. BMI and high-volume experienced surgeon did not predict the occurrence of BR, 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 BR, as previously shown.

The main features that differentiate our study from the two previously mentioned studies include the contemporaneous evaluation of factors associated with the risk of both PSM and BR. Our study shows that the high-volume experienced surgeons can reduce the risk of PSM after RARP in high-volume centers, and thus avoid treatments related to managing this unfavorable event. This information is important when counseling patients who are specifically concerned about their surgeon's experience and operative volume and how it relates to their oncologic outcomes as well as PSM rates. Overall, these results represent a new way to approach robotic surgery in PCA patients, and, as such, it is a novelty, which differentiates our study from other contemporary series. However, further confirmatory studies are required.

Strengths and limitations and of the study

While our study has strengths, it also presents several limitations. First, although data was collected prospectively, it is retrospective and thus suffers from all the limitations related to this type of study. Second, follow-up was limited. Third, 152 (21%) of patients were lost during follow up because many patients traveled to our tertiary center from long distances and some patients chose to continue their follow up with their local physician. Despite multiple attempts to contact them, many remained unreachable. Third, prostate biopsies performed at outside institutions were not re-evaluated; however, their features had good standard quality to support their analysis. However, beyond these limits, our study has also many strengths, which include the large contemporary cohort of patients in a high-volume center, and all specimens being evaluated by a dedicated pathologist.

Conclusion

In high-volume centers, features related to host, tumor, and experienced surgeon volume are pivotal factors associated with the risk of PSM,

which is also an independent parameter predicting BR after RARP. A high-volume experienced surgeon is an independent factor that decreases the risk of PSM and therefore the risk of BR. This issue is pivotal when counseling patients who elect to undergo robotic surgery as primary active treatment for PCA.

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Antonio Benito Porcaro and Alessandro Tafuri contributed equally.

Author contributions

ABP performed project development, data Analysis and interpretation, and manuscript writing. AT performed project development, data collection, data analysis and interpretation, and manuscript writing. MS, MP, TP, NA, RR, PC, LT, and CC performed data collection. AS performed data collection, English language and critical revision, and manuscript writing. FM, GN, MB, VDM, SS, and WA performed supervision and critical revision.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

ORCID iDs

Antonio Benito Porcaro  <https://orcid.org/0000-0002-7890-040X>

Alessandro Tafuri  <https://orcid.org/0000-0003-1404-2925>

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