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ORIGINAL ARTICLE

Prognostic value of unifocal and multifocal positive surgical margins in a large series of robot-assisted radical prostatectomy for prostate cancer

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Abstract

Purpose To evaluate the prognostic value of positive surgical margins (PSM) focality for the prediction of biochemical recurrence (BCR) in patients undergoing robotic-assisted radical prostatectomy (RARP) for prostate cancer.

Methods All men with clinically localized prostate cancer undergoing RARP in our tertiary referral centre between May 2005 and August 2016 were retrospectively identified. Patients with neoadjuvant therapy were excluded. Comparisons were made between cases with negative surgical margins (NSM), unifocal PSM (uPSM), and multifocal PSM (mPSM).

Results From a total of 973 patients available for analysis, 315 (32%) had a PSM. In these patients, 190 had uPSM and 125 had mPSM. Focality of PSM was significantly associated with tumour stage and grade, preoperative PSA, and postoperative PSA persistence (all $p < 0.001$), but not with nerve sparing (NS) ($p = 0.15$). PSA persistence was found in 120 (12%) patients, resulting in 853 patients available for survival analyses with a median follow-up of 52 months. Both uPSM and mPSM were found to be independent predictors of BCR, conferring a hazard ratio of 1.9 (95% CI 1.3–3.0; $p = 0.002$) and 3.4 (95% CI 2.1–5.6; $p < 0.001$), respectively, when compared to NSM. In subgroup analyses, PSM was particularly predictive for BCR when patients underwent unilateral or bilateral NS ($p \leq 0.003$).

Conclusions Based on a large case series of RARP, we found PSM focality to be an independent predictor of BCR, with a 1.9- and 3.4-fold risk increase for BCR in case of uPSM and mPSM, respectively. PSM seems to be of particular prognostic relevance when NS has been performed.

Keywords Prostate cancer · Radical prostatectomy · Surgical margins · Focality · Prognosis · Biochemical recurrence

Introduction

Radical prostatectomy (RP) is a common treatment method for clinically localized prostate cancer (PCa) [1]. Surgical approaches to RP have steadily evolved over the last decades [2]. Sufficient benign tissue should separate the tumour from the resection plane to ensure a complete removal of malignant cells, while urethral sphincter muscle and adjacent neurovascular should be spared for sustained continence and erectile function [3, 4]. Achieving this dual oncological and functional aim remains a challenge and entails the risk of leaving tumour tissue behind. In such case, tumour cells would outline the superficial layer of the prostatectomy specimen, reported as a positive surgical margin (PSM). The probability for PSM occurrence mostly depends on tumour characteristics, accuracy of preoperative disease burden

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assessment, surgeons skills, and strategy with respect to nerve-sparing (NS) technique, as well as on the pathological assessment [5, 6].

PSM are reported in 6.5–32% of patients in contemporary series of RP [7] and represent an established independent risk factor for biochemical recurrence (BCR), defined as a prostate-specific antigen (PSA) relapse after surgery [6, 8, 9]. Ultimately, a PSM may lead to clinical progression and premature cancer-related death [10–13]. Nevertheless, the prognostic value of detailed characterization of PSM in the era of robot-assisted RP (RARP) remains less investigated [6, 14, 15].

In the present study, we aimed to evaluate the association between PSM focality, clinicopathological characteristics, and the risk for BCR in a large contemporary series of men undergoing RARP.

Patients and methods

Study population and design

All men with clinically localized prostate cancer undergoing RARP in our tertiary referral centre between May 2005 and August 2016 were identified. Data were retrieved from electronic medical records and, if necessary, from referring urologist or patient's general practitioner. From 2008, a part of the identified men were included in our prospective single-centre cohort study (prostate cancer outcomes cohort study: proCOC [16, 17]). The study was approved by the local ethics committee (StV KEK-ZH-Nr. 25-2008 & StV KEK-ZH-Nr. 06/08).

Patients who received a neoadjuvant therapy before surgery were excluded from analysis. A PSA value of 0.1 ng/ml or higher was defined as BCR. Men with a PSA persistence after RARP were excluded from analysis of BCR. Patients were censored from the analysis of BCR whenever any secondary therapy was performed before evidence of BCR. Patients with BCR and possible local recurrence were offered early salvage radiotherapy when the PSA raised over 0.1 ng/ml.

Surgical technique

RARP were performed with the four-arm daVinci® Surgical System (Intuitive Surgical Inc., Sunnyvale, CA, USA). Bilateral extended pelvic lymph-node dissection was performed as described earlier in patients with either PSA ≥ 10 ng/ml at diagnosis or Gleason score (GS) ≥ 7 at biopsy [18]. A unilateral or bilateral nerve-sparing (uNS or bNS) technique was discussed with patients and, if appropriate, offered to patients with clinically organ-confined GS ≤ 7 tumour at biopsy. A uNS was offered to cases with GS 8 and low contralateral tumour burden at biopsy. No nerve sparing (nNS) was performed in all the other patients. Grade of nerve sparing referring to fascial layers was not documented and was not specifically standardized among the surgeons. However, nerve sparing was always performed by an experienced surgeon (> 80 radical prostatectomy performed).

Pathological analysis

All surgical specimens were analysed by specialized uropathologists in our institution using standardized whole-mount sections. Tumour characteristics were obtained from pathology reports. Tumour grading was reported according to the current Prognostic Grade Groups (PGG) and GS from pathology reports were matched accordingly [19, 20]. Surgical margins were deemed positive whenever cancer cells touched the surface of the RP specimen on light microscopy (tumour on ink) [17]. For this study, location of the PSM was systematically reviewed from the original pathology report and classified according to Fontenot et al.: posterior, posterolateral, lateral, and anterior at the apex, apical, and mid portions of the prostate or bladder neck [15]. PSM of one of these locations was defined as a unifocal PSM (uPSM), irrespective of PSM length. Whenever two of these locations were positive or bilateral PSMs were present, the PSM was deemed as multifocal (mPSM).

Statistical analysis

Continuous variables are presented as median and interquartile ranges (IQR) and analysed using the Kruskal–Wallis test. The results for categorical variables are presented as percentage and were analysed using Fisher's exact test or Chi-square test whenever appropriate. Estimates of BCR-free survival (RFS) were calculated with the Kaplan–Meier method and compared with the log-rank test. A stepwise reverse multivariable Cox regression analysis (entry level at $p \leq 0.05$ and removal cut-off at $p \geq 0.1$) was modelled to evaluate PSM focality as a predictor of BCR, including established predictors of BCR as covariates. Proportional hazard assumption was assessed for each variable with the plot of a log-negative–log-survival distribution and by the plot of Schoenfeld's residuals over time. Predictive accuracy of the Cox regression model was estimated using the Harrell's concordance index (c index). All analyses were performed with IBM SPSS Statistics Release 24.0.0.1 (IBM Corp., Armonk, NY, USA). All p values were two-sided with p values < 0.05 considered statistically significant.

Results

A total of 982 patients undergoing RARP were identified. Nine patients were excluded because of neoadjuvant androgen deprivation therapy. Table 1 summarizes patients' characteristics of the remaining 973 cases available for the final analysis. Median age was 64 years and median preoperative PSA was 7.3 ng/ml. A majority of patients had organ-confined disease (684/973 = 70%) without lymph-node invasion (898/973 = 92%) and a PGG ≤ 3 (785/973 = 81%). Postoperatively, 120/973 (12%) patients had a PSA persistence and were excluded from survival analyses regarding RFS. Median follow-up time for the remaining 853 patients was 52 months (IQR 15–72). During follow-up, BCR occurred in 117/853 (14%) patients after a median follow-up of 24 months (IQR 12–44).

From 973 patients, 315 (32%) had a PSM. Of these, 190 (60%) were reported to have uPSM, whereas 125 (40%) were reported to have mPSM (Table 1). Patients with mPSM had significantly higher preoperative PSA, higher tumour stage, higher PGG, and higher rate of postoperative PSA persistence than patients with uPSM or negative surgical margins (NSM) (all $p < 0.001$).

Around two-thirds of all patients underwent surgery with NS technique (627/973 = 64%), of which 319 (51%) had uNS and 308 (49%) had bNS (Table 1). No significant association was found between NS and surgical margins status ($p = 0.15$).

The estimated RFS at 5 years was 86% (95% confidence interval (CI) 83–90%) for NSM, 70% (95% CI 62–79%) for uPSM, and 60% (95% CI 47–74%) for mPSM, respectively ($p < 0.001$) (Fig. 1).

In a multivariable analysis, both uPSM and mPSM remained significant predictors for BCR, independently of tumour stage, nodal stage, PGG, and application of NS (Table 2). There was a 1.9-fold risk increase for BCR between NSM and uPSM (95% CI 1.3–3.0; $p = 0.002$), and a 3.4-fold risk increase for BCR between NSM and mPSM (95% CI 2.1–5.6; $p < 0.001$). Of note, bNS remained an independent predictor for BCR, with a 2.1-fold risk increase for BCR compared to nNS (95% CI 1.3–3.4; $p = 0.003$). The

Table 1 Clinicopathological characteristics of the study population with stratification for surgical margins status

Variable	Total	Surgical margins status			*p*
		NSM	uPSM	mPSM	
Patients, no. (%)	973 (100)	658 (68)	190 (19)	125 (13)	
Age, years, median (IQR)	64 (59–68)	64 (59–68)	63 (58–69)	65 (61–69)	0.40
Preoperative PSA, ng/ml, median (IQR)	7.3 (5.0–19.4)	6.8 (4.7–9.8)	7.9 (5.2–12.6)	10.7 (6.4–17.2)	**< 0.001**
pT stage, no. (%)					**< 0.001**
≤ pT2	684 (70)	525 (80)	113 (60)	46 (37)	
≥ pT3	289 (30)	133 (20)	77 (40)	79 (63)	
pN stage, no. (%)					**< 0.001**
cN0	280 (29)	208 (32)	50 (26)	22 (18)	
pN0	618 (63)	414 (63)	123 (65)	81 (64)	
pN1	75 (8)	36 (5)	17 (9)	22 (18)	
PGG, no. (%)					**< 0.001**
≤ 3	785 (81)	553 (84)	150 (79)	82 (66)	
≥ 4	188 (19)	105 (16)	40 (21)	43 (34)	
NS technique, no. (%)					0.15
nNS	346 (36)	218 (33)	72 (38)	56 (45)	
uNS	319 (33)	226 (34)	58 (30)	35 (28)	
bNS	308 (32)	214 (33)	60 (32)	34 (27)	
PSA persistence, no. (%)					**< 0.001**
No	853 (87)	609 (94)	165 (87)	79 (63)	
Yes	120 (12)	49 (7)	25 (13)	46 (37)	
Follow-up, months, median (IQR)	52 (15–72)	52 (14–72)	56 (16–73)	42 (12–70)	0.52

Data are presented as number (percent) or median (interquartile range)

p values < 0.05 were considered statistically significant

NSM negative surgical margins, *uPSM* unifocal positive surgical margin, *mPSM* multifocal positive surgical margins, *IRQ* interquartile range, *PSA* prostate-specific antigen, *PGG* Prognostic Grade Group, *NS* nerve sparing, *nNS* no nerve sparing, *uNS* unilateral nerve sparing, *bNS* bilateral nerve sparing

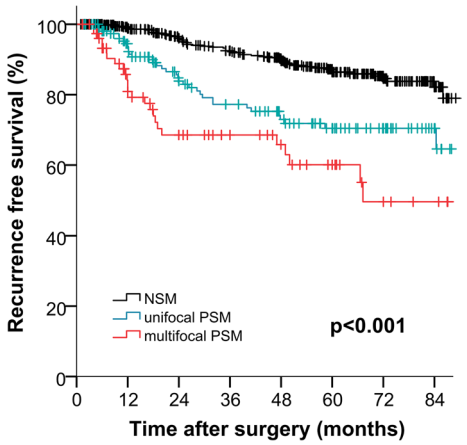

Fig. 1 Kaplan–Meier estimates of biochemical recurrence-free survival by surgical margins status. *NSM* negative surgical margins, *PSM* positive surgical margins

Table 2 Cox regression analyses of predictors for biochemical recurrence

Variable	Univariable		Multivariable	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Surgical margins				
NSM	1.0 (Ref.)		1.0 (Ref.)	
uPSM	2.5 (1.6–3.8)	**< 0.001**	1.9 (1.3–3.0)	**0.002**
mPSM	4.5 (2.8–7.3)	**< 0.001**	3.4 (2.1–5.6)	**< 0.001**
Tumour stage				
≤ pT2	1.0 (Ref.)		1.0 (Ref.)	
≥ pT3	5.7 (3.9–8.1)	**< 0.001**	3.3 (2.2–5.0)	**< 0.001**
Nodal stage				
pN0	1.0 (Ref.)		1.0 (Ref.)	
pN1	6.5 (3.7–11.6)	**< 0.001**	3.9 (2.1–7.2)	**< 0.001**
cN0	0.48 (0.31–0.75)	**0.001**	0.5 (0.3–0.9)	**0.02**
PGG				
≤ 3	1.0 (Ref.)		1.0 (Ref.)	
≥ 4	3.7 (2.5–5.4)	**< 0.001**	2.1 (1.3–3.3)	**0.002**
NS technique				
nNS	1.0 (Ref.)		1.0 (Ref.)	
uNS	0.78 (0.50–1.23)	0.29	1.3 (0.8–2.1)	0.28
bNS	0.96 (0.62–1.48)	0.84	2.1 (1.3–3.4)	**0.003**
Preoperative PSA				
< 10 ng/ml	1.0 (Ref.)		–	–
≥ 10 ng/ml	1.5 (1.01–2.2)	**0.04**	–	–

p values < 0.05 were considered statistically significant

HR hazard ratio, *95% CI* 95% confidence interval, *NSM* negative surgical margins, *uPSM* unifocal positive surgical margin, *mPSM* multifocal positive surgical margins, *PGG* Prognostic Grade Group, *NS* nerve sparing, *nNS* no nerve sparing, *uNS* unilateral nerve sparing, *bNS* bilateral nerve sparing, *PSA* prostate-specific antigen

preoperative PSA reached the removal level cut-off ($p \geq 0.1$) and was thus not included in the multivariable Cox regression model.

The predictive accuracy of the Cox regression model was 0.781 for the conventional NSM versus PSM stratification versus 0.783 for NSM, uPSM, and mPSM stratification. When surgical margin status was removed from the model, the c-index was 0.734.

The Cox regression model was tested for interaction between above-mentioned covariates. A significant interaction was found between surgical margin status and PGG, as well as between surgical margin status and NS technique (data not shown). This prompted us to conduct a subgroup analysis stratifying for PGG and NS technique (Fig. 2a–e). To further complete the subgroup analysis, a stratification for tumour stage was also performed (Fig. 2f, g).

In patients with PGG ≤ 3, both uPSM and mPSM showed lower RFS estimates than NSM (Fig. 2a), whereas only mPSM had denotatively lower RFS estimates in patients with PGG ≥ 4 (Fig. 2b). This observation was verified by a multivariable Cox regression analysis (Table S1; all $p < 0.001$). Neither uPSM nor mPSM was predictive for BCR when patients did not receive any NS (Fig. 2c, Table S2, all $p > 0.05$). Contrarily, both uPSM and mPSM were predictive for BCR in patients who had undergone nerve sparing (Fig. 2d, e, Table S2; all $p \leq 0.003$).

In the subgroup analysis for tumour stage, both uPSM and mPSM remained independent predictors for BCR in both ≤ pT2 and ≥ pT3 tumours (Fig. 2f, g and Table S3, all $p \leq 0.04$).

Patients with BCR were treated by the early salvage radiotherapy in 19 of 25 (76%) cases when mPSM was present, in 19 of 31 cases (61%) when uPSM was noted and in 29 of 51 (57%) cases with NS. Data on therapy decision after BCR were missing in ten patients (0, 4, and 6 cases in the mPSM, uPSM, and NSM groups, respectively). Adjuvant radiotherapy was performed before evidence of BCR in three patients, which were censored from the RFS analysis at the time of secondary therapy.

Discussion

The present study consists of a large contemporary consecutive series of RARP performed over more than a decade. Of all cases, 32% were deemed positive for surgical margins and differentiation for PSM focality was significantly associated with worse clinicopathological parameters. Most importantly, focality of PSM was found as an independent predictor of BCR, with an HR of 1.9 and 3.4 for uPSM and mPSM, respectively, when compared to NSM.

In a systematic review on RARP series, Novara et al. found a mean PSM rate of 15% (range 6.5–32) and reported

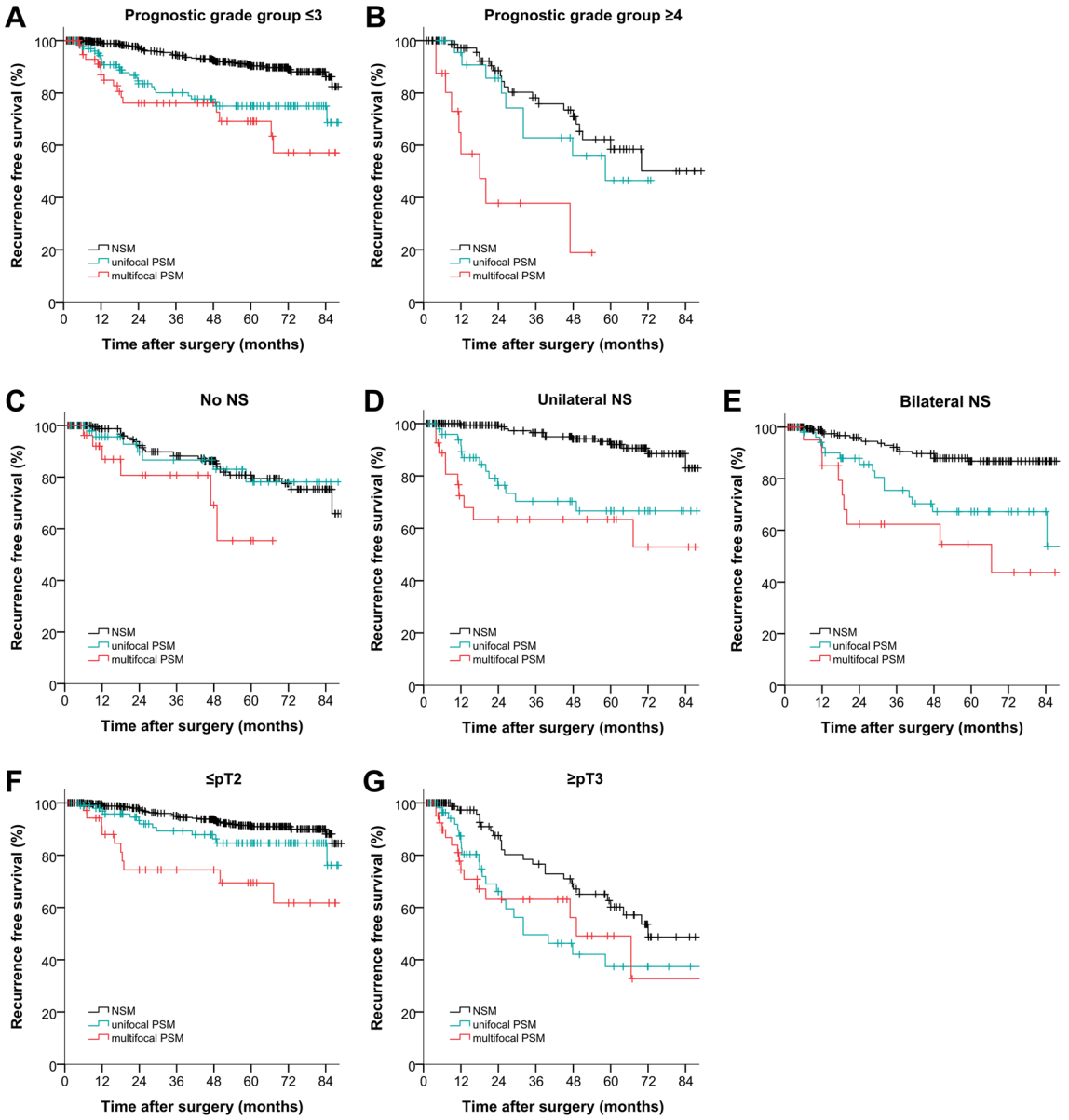

Fig. 2 Subgroup analyses with Kaplan–Meier estimates of biochemical recurrence-free survival by surgical margins status

tumour stage and grade to be strong predictors of PSM [7]. Comparatively, the PSM rate in the present study was at the upper range limit (32%), despite a relatively low rate of extracapsular tumour extension (≥ pT3: 30%) and that of high-grade disease (PGG ≥ 4: 19%). This discrepancy may come from interobserver variability concerning PSM evaluation, which has been reported by several studies and was particularly high between non-academic pathologists and dedicated academic uro-pathologists [21–23]. The relatively high PSM rate in our series may thus be attributable to the meticulous evaluation of all prostatectomy samples by specialized uro-pathologists, who reported a uPSM even when only one tumour cell touched the ink surface.

To the best of our knowledge, this is the first study based on a case series including only RARP and reporting both uPSM and mPSM as independent predictors of BCR. Multiple prior studies have investigated the role of PSM in RP and showed results that were in line with our findings. In a case series of 1712 open RP, Mauermann et al. found an adjusted HR for BCR of 1.2 and 1.6 for uPSM and mPSM ($p = 0.001$ and $p < 0.001$), respectively, when compared to NSM [24]. Sammon et al. reported an adjusted HR for BCR of 3.6 for mPSM ($p < 0.001$), but the authors did not specify the risk entailed by patients with uPSM [25]. When directly comparing mPSM with uPSM, an adjusted HR for BCR of 1.4 ($p = 0.002$) and 2.3 ($p < 0.001$) has been reported by

Stephenson et al. and Lee et al., respectively [26, 27]. A few studies found mPSM, but not uPSM as an independent predictor of BCR in patients after RP [28–31]. The other reports showed that PSM focality was not an independent predictor for BCR [15, 32–37]. However, these reports had either low patient sample size (< 500), low overall PSM rate (< 10%), and short follow-up period (median ≤ 12 months), or did not include a comparison with NSM cases. In summary, the current literature–including our study—suggests that PSM stratified by focality is of prognostic value in patients after RP for prostate cancer.

Of interest, subgroup analyses included in the present study revealed a denotative role for PSM focality in patients with PGG ≤ 3 as well as in patients who had undergone NS. Because the area of nerve sparing is particularly prone to PSM [38], it appears conceivable that a relevant amount of tumour tissue may have been left behind, even when seemingly minimal uPSM was reported. In contrast, we were not able to show any significant association between uPSM and BCR in patients with PGG ≥ 4 as well as in patients who had not undergone NS. Besides lack of analytical power, a potential explanation may be that the two later subgroups are characterized by a selection of high-risk patients, for whom other tumour characteristics (e.g., micrometastases) may have outweighed the risk entailed by uPSM.

Whether the application of NS bears a higher risk for PSM and would, therefore, impact on prognosis is debated [38, 39]. In the present study, no association was found between NS technique and surgical margins status. Although not significant in univariable analysis, bNS was found as an independent predictor for BCR in multivariable analysis, which may be the consequence of interaction between NS and surgical margin status [40]. Such association has not been reported previously in the literature and, thus, deserves further assessment in the other large cohorts. One explanation may be that the disease burden was underestimated in this patient group, leading to an inadequate selection of patients who were offered a bNS technique. Underestimation of disease burden prior RP has been shown to be relevant in a previous study from our centre [41]. In that study, tumour undergrading at biopsy frequently occurred in a group of community pathologists and was found as an independent predictor for both PSM and BCR. In light of these results, implementation of preoperative tumour delineation by multiparametric MRI as well as strategies of intraoperative fresh-frozen tissue analysis are promising tools to overcome the potential oncological risk of NS [42–45].

The present study has limitations. PSM length and GS at PSM were not consistently documented in pathological reports available for this study and could, therefore, not be analysed. Due to an insufficient number of cases accounting for disease progression or death events, these oncological outcomes were not evaluated in this study.

Conclusions

PSM focality is significantly associated with worse clinicopathological features and remains a significant independent predictor for BCR in patients after RARP. PSM seems to be of particular prognostic relevance when NS has been performed. Clinicians should be aware of the prognostic impact of PSM focality for further patient counselling.

Author contributions EXK protocol/project development, data collection or management, data analysis, and manuscript writing/editing. JB data collection or management, and manuscript writing/editing. AJB data collection or management, and manuscript writing/editing. KS data collection or management, data analysis, and manuscript writing/editing. AM data collection or management, data analysis, and manuscript writing/editing. BK data collection or management, and manuscript writing/editing. CDF data collection or management, data analysis, and manuscript writing/editing. PW protocol/project development, data analysis, and manuscript writing/editing. TS protocol/project development, data analysis, and manuscript writing/editing. TH protocol/project development, data analysis, and manuscript writing/editing. DE protocol/project development, data analysis, and manuscript writing/editing. CP protocol/project development, data collection or management, data analysis, and manuscript writing/editing.

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Compliance with ethical standards

Conflict of interest The authors disclose no potential conflicts of interest.

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

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