Predictors of biochemical recurrence after robot-assisted radical prostatectomy: single-centre analysis

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Introduction We evaluated risk factors for biochemical recurrence (BCR) after robot-assisted radical prostatectomy (RARP) based on our department database.

Material and methods Patients who underwent RARP between 2018 and 2020 were identified and included in our retrospective study. Patients who received neoadjuvant treatment, patients with positive lymph nodes, salvage prostatectomies, and patients with missing data were excluded. BCR was defined as PSA ≥0.2 ng/ml. Parameters that were investigated were the International Society of Urological Pathologists (ISUP) score, stage, and positive surgical margins (PSM) as they were reported in the pathology report. A subgroup analysis based on the tumour stage was performed.

Results A total of 414 patients were included in the analysis. Seventy-seven of them experienced BCR. Based on multivariable analysis, ISUP grade was a strong predictor for BCR with odds ratio (OR): 2.86 (CI: 1.49–5.65; p = 0.002), OR: 5.90 (CI: 1.81–18.6; p = 0.003), OR: 4.63 (CI: 1.79–11.9; p = 0.001) for ISUP grade 3, 4, 5, respectively. Regarding tumour stage, pT2 and pT3a did not show any significant difference in predicting BCR (p = 0.11), whereas pT3b stage was a predictor for BCR with OR: 6.2 (CI: 2.25–17.7; p < 0.001). In the subgroup analysis for 206 patients with pT2 disease, ISUP group and PSM were predictors for BCR. On the other hand, when patients with pT3 disease were inspected, the only parameter that was predictive of BCR was pT3b disease (OR: 4.68, CI: 1.71–13.6; p = 0.003). ISUP grade, the extent of T3 disease, and the extent and ISUP grade of surgical margins were not predictors of BCR.

Conclusions The most important risk factors for BCR after RARP are ISUP grade and tumour stage. In pT2 disease, PSM is a significant predictor of BCR, along with high ISUP grade. The substage pT3b can be considered a predictor of BCR in pT3 cases.

Key Words: prostatectomy ‹› radical prostatectomy ‹› recurrence ‹› positive margin ‹› PSM ‹› surgical margin

INTRODUCTION

Prostate cancer (PCa) constitutes the second most common type of cancer in men, and it is estimated that one in six men will be diagnosed with prostate cancer during their lifetime [1]. Nowadays, there is a plethora of options to manage patients with PCa, including surveillance and active treatments [2]; in the latter scenario, robot-assisted radical prostatectomy (RARP) has rapidly become one of the leading procedures in PCa surgery [3, 4].

Overall, RARP may offer superior or similar outcomes compared to open and laparoscopic radical prostatectomy (RP); however, the debate is still ongoing, especially considering the rate of biochemical recurrence (BCR) after the procedure [5].

It is known that 20–40% of men after RP will develop a biochemical recurrence [6]. In the literature, high Gleason grade, high stage, positive surgical margins (PSM), and positive lymph nodes are considered adverse pathological features and risk factors for BCR after RARP [7].
In this study, we aim to identify the role of different predictors for BCR based on the pathological results after RARP.

MATERIAL AND METHODS

Study population

We used our prospectively maintained database to identify patients who underwent RP between January 2018 and December 2020. The total number of patients was 612. From that number, we excluded patients who received neoadjuvant treatment, patients with positive lymph nodes, salvage prostatectomies, and patients with missing data. Thus, 414 men were included in the final analysis. The dataset included preoperative prostate-specific antigen (PSA), biopsy, and MRI data as well as postoperative biopsy results and PSA. BCR was defined as 2 consecutive PSA values >0.2 ng/ml after RARP.

Surgical procedure

RARP was performed with the Da Vinci Xi Surgical System by 6 expert urologists (more than 200 robotic cases each). The operation was facilitated by 6 transperitoneal ports. Bilateral or unilateral nerve sparing was performed according to the biopsy and MRI results if it was not contraindicated to the guidelines [9]. Nerve sparing procedure was primarily recommended in men with adequate erectile function, and with low-risk of extracapsular extension on the side-of nerve-sparing surgery. Extracapsular extension and ISUP grade >3 at prostate gland biopsy were contraindications to ipsilateral nerve-sparing approach. Pelvic lymph node dissection was decided based on Briganti's nomogram [10].

Pathology evaluation

The pathology report involved histopathological type of tumour, Gleason grade, and ISUP stage. In cases of T3 disease and PSM, it included the extent, the site and grade of extraprostatic extension (EPE), and PSM, respectively. PSM were defined as focal if <3 mm and extended if ≥3 mm or multifocal.

Statistical analysis

This is a retrospective study. Patients were stratified into 2 groups according to BCR status: patients without BCR (study group) and patients with BCR (control group) at the last follow-up. Demographics and surgical and postoperative outcomes of the study group were compared with the control group.

Table 1. *Clinical characteristics of all patients in the study cohort who underwent robot-assisted radical prostatectomy classified according to biochemical recurrence*

	N	BCR		p-value*
		No	Yes	
N		337	77	
Age, median [IQR]	414	64 [59, 69]	65 [57, 69]	0.8
PSA pre-op (ng/ml)	414			0.002
<10		274 (81%)	49 (64%)	
10–20		55 (16%)	23 (30%)	
>20		8 (2.4%)	5 (6.5%)	
Prostate volume (cc), median [IQR]	414	40 [30, 50]	45 [40, 60]	0.030
ISUP biopsy	414			<0.001
1		42 (12%)	5 (6.5%)	
2		213 (63%)	30 (39%)	
3		53 (16%)	20 (26%)	
4		21 (6.2%)	17 (22%)	
5		8 (2.4%)	5 (6.5%)	
ISUP specimen	414			<0.001
1		3 (0.9%)	0 (0%)	
2		185 (55%)	17 (22%)	
3		118 (35%)	39 (51%)	
4		11 (3.3%)	7 (9.1%)	
5		20 (5.9%)	14 (18%)	
ISUP upgrade	414			0.022
No		169 (50%)	29 (38%)	
Up		136 (40%)	33 (43%)	
Down		32 (9.5%)	15 (19%)	
Pathological stage	414			<0.001
T2		189 (56%)	20 (26%)	
T3a		138 (41%)	42 (55%)	
T3b		10 (3.0%)	15 (19%)	
Surgical margin extent (mm)	414			0.004
None		246 (73%)	42 (55%)	
≤3		66 (20%)	23 (30%)	
>3		25 (7.4%)	12 (16%)	
Surgical margin ISUP	414			<0.001
None		250 (74%)	43 (56%)	
1		15 (4.5%)	1 (1.3%)	
2		33 (9.8%)	8 (10%)	
3		17 (5.0%)	8 (10%)	
4		21 (6.2%)	13 (17%)	
5		1 (0.3%)	4 (5.2%)	
Largest tumour diameter median [IQR]	414	20 [15, 26]	24 [20, 34]	<0.001
Follow-up time (months) median [IQR]	414	46 [35, 57]	47 [35, 59]	0.4

*Wilcoxon rank sum test; Fisher's exact test; Pearson's chi-squared test
BCR – biochemical recurrence; PSA – prostate-specific antigen; ISUP – International Society of Urological Pathology

Statistical analysis was conducted according to guidelines (https://www.europeanurology.com/article/S0302-2838(18)31002-9/fulltext). The Kolmogorov-Smirnov test was used to establish the distribution of the data. When normally distributed, mean ± standard deviation (SD) was used. On the other hand, the median and interquartile range were adopted to report non-normal distribution data. Frequency (%) was used to report categorical data. To compare the differences in the distribution of continuous and categorical variables between the 2 groups, Mann-Whitney U-test and Fisher's exact were used, respectively. When continuous variables showed parametric distribution, Student's t-test was used. Multivariable Cox regression analyses were used to identify independent predictors of BCR since time-dependent endpoint. Any variable having a significant univariate test and/or clinical significance was selected as a candidate for the multivariate analysis.

All statistical tests were performed with STATA, and statistical significance was set at $p \leq 0.05$.

RESULTS

Patients' characteristics

Table 1 summarises the clinical characteristics of the population of the study. Overall, 414 patients who underwent RARP were included in the analysis. From that number, 337 (81.4%) patients did not have BCR at the last follow-up, while 77 (18.6%) patients experienced BCR. The mean follow-up time was similar, at 46 and 47 months in the no-BCR and BCR groups, respectively ($p = 0.4$).

The BCR group had higher rates of ISUP grade 4 (9.1% vs. 3.3%) and 5 (18 vs. 5.9%) at the final histopathological report ($p < 0.001$), as well as the higher rate of T3a (55 vs. 41%) and T3b (19 vs. 3%, $p < 0.001$). 91 (27.4%) and 35 (46%) of patients had PSM in the no-BCR and BCR groups, respectively ($p = 0.004$).

Multivariable regression

Table 2 shows the uni- and multivariable Cox regression for the predictive factors of BCR for all cases. Regarding multivariable regression, ISUP group was an unequivocal predictor for BCR with OR: 2.86 (CI: 1.49–5.65; $p = 0.002$), OR: 5.90 (CI: 1.81–18.6; $p = 0.003$), OR: 4.63 (CI: 1.79–11.9; $p = 0.001$) for ISUP grade 3, 4, 5, respectively. Regarding tumour stage, pT2 and pT3a did not show any significant difference in predicting BCR ($p = 0.11$), whereas pT3b stage was a predictor for BCR with OR: 6.2 (CI: 2.25–17.7; $p < 0.001$). PSM, tumour diameter, prostate volume, age, and preoperative PSA did not show any significant predicting value for BCR.

Subgroup analysis

Table 3 shows the results of the subgroup analysis for 206 patients with pT2 disease. In this sub-cohort

Table 2. *Uni- and multivariable Cox regression for the predictive factors of biochemical recurrence in the whole study cohort*

Characteristic	Univariable				Multivariable			
	N	OR	95% CI	p-value	N	OR	95% CI	p-value
Age at therapy (years)	411	0.99	0.96, 1.03	0.7	411	0.96	0.92, 1.00	0.077
PSA (ng/ml)	411				411			
<10	Ref	–	–			–	–	
10–20		2.31	1.29, 4.08	0.004		1.37	0.69, 2.62	0.4
>20		3.46	1.01, 10.8	0.036		1.08	0.28, 3.95	>0.9
Prostate volume (cc)	411	1.01	1.00, 1.02	0.2	411	1.01	0.99, 1.03	0.2
ISUP specimen	411				411			
2	Ref	–	–			–	–	
3		3.60	1.98, 6.80	<0.001		2.86	1.49, 5.65	0.002
4		6.93	2.30, 20.1	<0.001		5.90	1.81, 18.6	0.003
5		7.62	3.26, 17.9	<0.001		4.63	1.79, 11.9	0.001
Pathological stage	411				411			
T2	Ref	–	–			–	–	
T3a		2.83	1.61, 5.12	<0.001		1.70	0.89, 3.31	0.11
T3b		13.9	5.63, 36.2	<0.001		6.20	2.25, 17.7	<0.001
Surgical margin	411				411			
Negative	Ref	–	–			–	–	
Positive		2.23	1.33, 3.70	0.002		1.55	0.85, 2.80	0.15
Largest tumour diameter (mm)	411	1.06	1.03, 1.09	<0.001	411	1.03	0.99, 1.07	0.10

OR – odds ratio; CI – confidence interval; PSA – prostate-specific antigen

of patients, ISUP grade played a major role for BCR. Moreover, PSM is also an important risk factor with an OR: 3.34 (CI: 1.08–10.3; p = 0.033).
Table 4 shows the analysis of patients with pT3 disease. The only parameter in this subgroup that can predict BCR is whether it is a pT3a or a pT3b disease (OR: 4.68; CI: 1.71–13.6; p = 0.003). Other parameters, such as age, PSA, ISUP grade, the extent of T3 disease, and the extent and ISUP grade of surgical margins were all insignificant predictors of BCR.

DISCUSSION

To the best of our knowledge, this analysis on BCR is one of the largest and most up-to-date cohort-based studies on RARP only, including 414 patients with a minimum follow-up of 3 years. A total of 206 men had a pT2 prostate cancer, while 205 had a pT3 disease. When the entire cohort was analysed, it was found that tumour grade was a significant risk factor for BCR. In addition, invasion of seminal vesicles (SVs) by tumour is another significant predictor for BCR. Surprisingly, our analysis showed that PSM was not a significant predictor for BCR. However, when only pT2 patients were analysed, both ISUP grade and PSM were significant risk factors for BCR. In pT3 disease, the only significant pathological feature was whether SVs were involved or not.
Multivariable analysis showed that pT2 and pT3a have similar risks for BCR (p = 0.11). On the other hand, pT3b is a stronger predictor for BCR in comparison to pT2 and pT3a. This notion is not in line with the literature, as pT3 disease is considered a locally advanced disease and high risk for BCR based on the EAU risk group stratification [8]. However, it is known that more than 50% of men with pT3 disease at RP specimens will not experience disease progression over a ten-year follow-up [11]. This observation led to several attempts to subdivide pT3 prostate cancer. These subdivisions often refer to the extent of EPE and its Gleason score. Based on our analysis, the extent of EPE and its characteristics (unifocal vs. multifocal) do not play a significant role in predicting BCR. However, Park et al. studied pT3a disease based on the number and radial distance of EPE and subcategorised pT3a disease into 3 categories using cut-off limits of 0.75 mm and 2 mm for radial distance and whether it is focal and multifocal. This proved to be a valuable predictor for BCR [12]. In addition, Jeong et al. in their paper divided pT3a disease into focal and non-focal based on the number of glands found outside the prostate and concluded that the extent of EPE is a risk factor for BCR but not for cancer-specific or overall survival [13]. In sharp contrast, Gupta et al. studied the distance, the Gleason grade, and the extent of EPE and found that none of them is a significant predictor for BCR in multivariable analysis [14].
Gleason score is considered the strongest predictor of BCR [15]. However, in our multivariable analysis, this seems to be less important when considering patients with pT3 disease. This is in contrast to the current literature. Hong et al. tried to identify the risk factors for BCR in pT3 disease to set up criteria for adjuvant radiotherapy. They concluded

Table 3. *Uni- and multivariable Cox regression for the predictive factors of biochemical recurrence in the patient with T2 disease*

Characteristic	Univariable				Multivariable			
	N	OR	95% CI	p-value	N	OR	95% CI	p-value
Age at therapy (years)	206	0.99	0.93, 1.06	0.9	206	0.93	0.85, 1.01	0.088
PSA (ng/ml)	206				206			
<10	Ref	–				–		
10–20		1.51	–	0.5		0.83	–	0.8
>20		0.00	0.41, 4.51	>0.9		0.00	0.18, 3.13	>0.9
Prostate volume (cc)	206	1.00	0.97, 1.02	>0.9	206	1.02	0.98, 1.06	0.3
ISUP specimen	206				206			
2	Ref	–	–			–	–	
3		6.43	2.05, 24.3	0.002		8.37	2.45, 34.7	0.001
4		23.6	3.71, 152	<0.001		53.4	6.82, 479	<0.001
5		13.5	2.31, 74.3	0.002		19.6	2.92, 131	0.002
Surgical margin	206				206			
Negative	Ref	–	–			–	–	
Positive		2.51	0.93, 6.51	0.060		3.34	1.08, 10.3	0.033
Largest tumour diameter (mm)	206	1.01	0.95, 1.07	0.7	206	1.02	0.94, 1.10	0.6

OR – odds ratio; CI – confidence interval; PSA – prostate-specific antigen

that Gleason score ≥8, preoperative PSA ≥10 ng/ml, and lymphovascular invasion were risk factors in pT3 disease, and they recommend adjuvant radiotherapy. However, their multivariable analysis showed that pT3b was the only significant risk factor for clinical progression, which resembles the finding of our study [16].

PSM is one of the recognised risk factors for BCR, but it is also one of the most controversial [17]. Our study showed that PSMs are a significant risk factor in predicting BCR in pT2 disease, but not for pT3. Like EPE, there is an ongoing attempt to identify which patients with PSM are most likely to experience BCR. In our study, the extent and grade of PSM do not seem to relate to higher risk of BCR. We chose to subcategorise PSM into limited and extensive for <3 mm and ≥3 mm, respectively, based on the paper of Koskas et al. However, our conclusion differs from theirs, as they found that extensive PSM is a risk factor for BCR in both pT2 and pT3 diseases [18]. Cao et al. considered extensive PSM >1 mm, and they concluded that PSM is indeed a risk factor for BCR, but in their subgroup analysis they concluded that PSM is only important in pT2 disease and not in pT3, which is similar to our outcomes [19]. Regarding tumour grade at the margins, there is evidence in the literature that suggests it is a significant predictor for BCR [20, 21, 22].

The present study is not without limitations. First, the retrospective design of the study may have introduced some biases in the analysis. In addition, the follow-up period after RARP was rather small and included cases performed during the COVID pandemic [23]; thus, further studies with longer follow-up are needed to support the results. Moreover,

Table 4. *Uni- and multivariable Cox regression for the predictive factors of biochemical recurrence in the patient with pT3 disease*

Characteristic	Univariable				Multivariable			
	N	OR	95% CI	p-value	N	OR	95% CI	p-value
Age at therapy (years)	209	0.97	0.92, 1.02	0.2	199	0.96	0.91, 1.02	0.2
PSA (ng/ml)	206				199			
<10	Ref	–	–			–	–	
10–20		2.28	1.13, 4.58	0.020		1.72	0.72, 4.05	0.2
>20		3.48	0.92, 13.2	0.060		1.67	0.35, 7.97	0.5
Prostate volume (cc)	209	1.01	1.00, 1.03	0.12	199	1.01	0.99, 1.04	0.3
ISUP specimen	210				199			
2	Ref	–	–			–	–	
3		1.95	0.95, 4.18	0.076		1.31	0.54, 3.28	0.6
4		2.73	0.64, 10.5	0.2		1.64	0.29, 8.66	0.6
5		4.04	1.48, 11.2	0.006		1.53	0.40, 5.64	0.5
Pathological stage	210				199			
T3a	Ref	–	–			–	–	
T3b		4.61	1.98, 11.0	<0.001		4.68	1.71, 13.6	0.003
Surgical margin extent (mm)	210				199			
None	Ref	–	–			–	–	
≤3		1.62	0.80, 3.24	0.2		1.15	0.05, 11.6	>0.9
>3		1.87	0.73, 4.61	0.2		0.69	0.02, 8.31	0.8
Surgical margin ISUP	210				199			
None	Ref	–	–			–	–	
1		0.00		>0.9		0.00	0.00, 803,472,065	>0.9
2		1.42	0.47, 3.88	0.5		2.13	0.17, 57.4	0.6
3		1.79	0.63, 4.78	0.3		1.37	0.11, 36.3	0.8
4		2.22	0.88, 5.39	0.082		1.56	0.14, 39.2	0.7
5		9.97	1.23, 205	0.050		4.32	0.11, 318	0.5
Largest tumour diameter (mm)	210	1.05	1.02, 1.09	0.005	199	1.01	0.97, 1.06	0.6
T3 focality	210				199			
Unifocal	Ref	–	–			–	–	
Multifocal		1.92	0.91, 3.97	0.081		1.89	0.79, 4.48	0.15
T3 extent (mm)	205	1.06	1.02, 1.11	0.003	199	1.05	0.99, 1.10	0.092

OR – odds ratio; CI – confidence interval; ISUP – International Society of Urological Pathologists; PSA – prostate-specific antigen

data for some patients were missing because they chose to have their follow-up at their local services. The cases were performed by 6 different surgeons with different levels of experience. Last, no specific details about post-operative details on functional outcomes were included in this analysis [24].

In clinical practice, our findings strongly suggest considering adjuvant treatments after RARP in cases of patients with pT2 stage and PSM and/or ISUP >2, as well as all the patients with pT3b. Further studies are needed to better address the behaviour of pT3a disease.

CONCLUSIONS

The most important risk factor for BCR after RARP is ISUP grade and tumour stage. These findings change slightly when considering patients with pT2 and pT3 stages only. Notably, PSM is a significant predictor of BCR in pT2 cases only, along with high ISUP grades. The substage pT3b, instead, can be considered a predictor of BCR in pT3 cases.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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