ORIGINAL ARTICLE

Vol. 40 (3): 306-315, May - June, 2014
doi: 10.1590/S1677-5538.IBJU.2014.03.03

Radical prostatectomy and positive surgical margins: relationship with prostate cancer outcome

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ABSTRACT

Introduction: Positive surgical margins (PSMs) are an adverse factor that may predict a worse outcome in patients submitted to radical prostatectomy (RP). However, not all of these cases will evolve to biochemical (BCR) or clinical (CR) recurrence, therefore relationship between PSMs and these recurrent events has to be correlated with other clinical and pathologic findings to indicate complementary treatment for selected patients.

Materials and Methods: Of 1250 patients submitted to open retropubic radical prostatectomy (RRP), between March 1991 and June 2008, the outcome of 161 patients with PSMs and of 67 without PSMs as a control group, comprising a total of 228 cases were retrospectively reviewed. A minimum follow-up time of 2 years after surgery was considered. BCR was determined when PSA ≥ 0.2ng/mL. CR was determined whenever there was clinical evidence of tumor. Chi-square test was used to correlate clinical and pathologic variables with PSMs. Time interval to biochemical recurrence was analyzed by the Kaplan-Meier product limit analysis using the log-rank test for comparison between groups. Univariate and multivariate Cox stepwise logistic regression models were used to identify significant predictors of risk of shorter intervals to BCR.

Results: Prostate circumference margin was the most common site with 78 cases (48.44%). Regarding the outcome of 228 cases from both groups, BCR occurred in 68 patients (29.82%), and CR in 10 (4.38%). Univariate analysis showed statistically significant associations ($p < 0.001$) between presence of PSMs with BCR, but not with CR ($p = 0.05$). At follow-up of the 161 patients with PSMs, only 61(37.8%) presented BCR, while 100 (62.8%) did not. BCR correlated with pathologic stage; Gleason score; preoperative PSA; tumor volume in the specimen; capsular and perineural invasion; presence and number of PSMs. CR correlated only with angiolymphatic invasion and Gleason score. Considering univariate analysis of clinical and pathologic factors predicting progression-free survival at 5 years, prostate weight; preoperative PSA; Gleason score; pathologic stage; tumor volume; PSMs; capsular and perineural invasion were correlated with BCR. At multivariate analysis, only Gleason score and percentage of tumor volume correlated as significant independent predictors of BCR.

Conclusion: At univariate analysis, presence, number and location of PSMs have consistent correlation with BCR after RRP, but at follow-up BCR occurred only in 37.8% of patients with PSMs. However at multivariate analysis, the significant risk factors for BCR were percentage of tumor volume ($p = 0.022$) and Gleason score ($p < 0.005$) in the surgical specimen. Angiolymphatic invasion and Gleason score were significantly correlated with CR.

ARTICLE INFO

Key words:
Prostatic Neoplasms; Prostatectomy; Tumor Burden

Int Braz J Urol. 2014; 40: 306-15

Submitted for publication:
August 15, 2013

Accepted after revision:
October 13, 2013

INTRODUCTION

The finding of positive surgical margins (PSMs) after radical prostatectomy (RP) implies that cancer resection was not complete leading the surgeon to decide between complementary treatments such as: active surveillance, adjuvant radiotherapy or androgen-deprivation therapy. Many studies report that PSM represents an independent predictor of biochemical recurrence (BCR) after RP. Furthermore, these studies have also shown that most men with PSMs do not develop BCR (1-3). At multivariate analysis, Gleason score of specimen, pathologic stage, percentage of tumor volume in the surgical specimen and PSMs were all significant risk factors for BCR. Each of these factors has previously been associated with BCR (4). Another study shows that PSM is an independent predictor of BCR after RP, where BCR rates were similar for cases with unifocal and multifocal PSMs, and the risk of BCR was highly dependent on the PSM location. Cases of base and anterior margins of the prostate have a worse prognosis and should be considered candidates for adjuvant treatment due to the very high likelihood of BCR. Although PSMs are more common on the apex, posterior and posterolateral sites, they are associated with lower BCR rates (5). To verify the relationship between PSMs and BCR, we retrospectively analyzed the outcome of a group of patients submitted to RRP, for clinically localized prostate adenocarcinoma with PSMs, and studied the correlations of these results with clinical and pathologic variants.

MATERIALS AND METHODS

From a total of 1250 patients submitted to RRP to cure a clinically localized Prostate Cancer, by the team of the Division of Urology, Pelvic Surgery Department, A.C. Camargo Cancer Center, between March 1991 and June 2008, we retrospectively studied the outcome of 161 patients with PSMs, compared to a control group of 67 patients without PSMs, in a total of 228 cases. Our total number of patients with PSMs was of 298 cases (23.84%). We excluded from the study patients who received hormone therapy or radiotherapy before the surgery, 56 patients who have PSMs and involvement of seminal vesicles and/or inguinal or pelvic lymph nodes or stage T4 disease, and 81 patients who have PSMs with incomplete or missing follow-ups. Based upon their preoperative PSA, rectal digital examination, transrectal ultrasound, pelvic computerized tomography or nuclear magnetic resonance (high risk cases) results and the pathologic study from their prostate biopsies, all patients were considered bearers of organ-confined disease. We recorded patient age, race, preoperative PSA, clinical and pathologic stage, prostate surgical specimen weight, percentage of tumor volume, perineural and/or angiolymphatic invasion, capsular and extracapsular involvement, the number and site (urethral, bladder neck, prostate circumference) of PSMs in the surgical specimens. These were staged according to the 1997 American Joint Committee on Cancer System and graded using the Gleason system. All cases underwent the same protocol for pathologic evaluation, the prostate being analyzed as a whole. After removal of the seminal vesicles, surgical specimens were step sectioned at a constant interval obtaining variable number of transverse sections according to the prostate size. Each transverse section of the prostate was subdivided into 2 anterolateral and 2 posterolateral quadrants. From each quadrant it was obtained one slide unless too large to need a second slide. A visual estimate was used to evaluate tumor extent. After analysis of each quadrant a percentage was reached for the total tumor volume. Extraprostatic extension was evaluated whenever cancer was seen in adipose tissue being considered either focal or extensive. Surgical margins were considered positive when the tumor could be seen on the inked surface of the surgical specimen (6). Serum PSA levels after RRP were measured every 4 months for 2 years and then every 6 months for 2 more years and annually thereafter. BCR was considered when the PSA reached a level $\geq$ 0.2ng/mL. Thereupon the patient was referred for external pelvic and prostatic bed radiotherapy or radiation plus hormone therapy in selected cases with worse prognosis. CR was determined when clinical evidence of tumor was seen as a metastatic disease, or when PSA rose despite radiotherapy, hormone, or chemotherapy treatments. Minimum follow-up time was of 2 ye-

ars after surgery. The time interval to biochemical recurrence was analyzed by the Kaplan-Meier product limit analysis using the log-rank test for comparison between groups. The univariate and multivariate Cox stepwise logistic regression models were used to identify significant predictors of risk of shorter intervals to BCR. The Kaplan-Meier method was used to calculate the curves of biochemical-recurrence free survival (from the date of RRP until date of the first PSA measurement > 0.2ng/mL or to the date of the last follow-up) and clinical-recurrence free survival (from the date of the RRP until the date of detection of local or distant disease or until date of the last follow--up). The Chi-square test was used to correlate clinical and pathologic variables with PSMs. Time interval to biochemical recurrence was analyzed by the Kaplan-Meier product limit analysis using the log-rank test for comparison between groups. Univariate and multivariate Cox stepwise logistic regression models were used to identify significant predictors of risk of shorter intervals to BCR. All statistical tests were performed with $p < 0.05$ to indicate statistical significance with R free statistical software (www.r-project.org).

RESULTS

For the 228 patients, follow-up ≥ 5 years was available in 93 patients and ≤ 5 years in 135 patients. Minimum follow-up time after surgery was of 2 years, median follow-up 6.2 years (range 2-15 years). At diagnosis median age of patients was 64.5 years (range 43-81 years), race was 68.42% white, 19.29% black, and 12.29% mulatto, median preoperative PSA level was 8.47ng/mL (range 1.3-78.8ng/mL).

Prostate specimen weight ranged from 10 to 167g (mean 44.77g), and tumor volume was estimated as ranging from 0.5% to 100% of total prostate volume (mean 12.82%). Prostate capsule invasion (focal and extracapsular) was present in 123 cases and absent in 105, perineural invasion was present in 162 cases and absent in 66, angiolymphatic invasion was present in 18 cases and absent in 210.

Table-1 shows demographic, clinical and pathologic parameters correlated with presence of PSMs, age, preoperative PSA, specimen Gleason score, weight, pathologic stage, percentage of tumor volume, capsular and perineural invasion. Clinical stage and angiolymphatic invasion were not correlated. Patients younger than 50 and older than 70 years of age showed higher incidence of PSMs. Pre-treatment PSA ≥ 10ng/mL, specimen Gleason score ≥ 7, pathologic stage ≥ T2b, tumor volume ≥ 10% of specimen's total volume and presence of capsular and perineural invasion showed statistically significant associations with occurrence of PSMs.

Conversely, when weight of the prostate was ≤ than 60g it was more correlated with PSMs. From the total of 228 patients, 161 (71%) had PSMs, while 67 (29%) had negative surgical margins (NSMs). Of those with PSMs, 106 cases (46%) showed one margin, 44 (19%) two margins, and 11 (5%) three margins. The prostate circumference site was the most common PSM (48.44%) followed by prostatic+urethral (apical) (17.39%), urethral (apical) (13.66%), and bladder neck (6.21%) (Table-2).

Of the 228 patients BCR occurred in 68 (30%), and did not in 160 (70%), whereas clinical recurrence (CR) occurred in 10 (4%) and did not in 218 (96%).

Univariate analysis showed statistically significant ($p < 0.001$) association between presence of PSMs and BCR, however not with CR ($p = 0.06$).

BCR was found in 68 patients, wherein those with no PSMs corresponded to 7 (10.5%) cases, while PSMs were present in 61 (89.5%) cases.

Among 161 patients with PSMs, 61 (37.88%) presented BCR, while 100 (62.12%) did not (Table-3). COX univariate analysis of pathologic factors predicting progression-free survival of BCR and CR in 5 years after RRP (Table-4) correlated BCR progression-free survival with pathologic stage, Gleason score, pre-treatment PSA, tumor volume in specimen, capsular and perineural invasion, presence and number of PSMs.

Interestingly, the progression-free survival time for CR was correlated only with angiolymphatic invasion and Gleason score.

Table-5 shows univariate and multivariate regression analysis of clinical and pathologic

Table 1 - Demographic, clinical, and pathologic variables correlated with PSMs.

Variables	Categories	Negative PSMs N (%)	PSMs N (%)	p
Age (years)	40-50	2 (13)	13 (87)	< 0.001
	50-60	35 (43)	46 (57)	
	60-70	23 (22)	82 (78)	
	> 70	7 (26)	20 (74)	
Pre-operative PSA (ng/mL)	≤ 10	60 (34)	114 (66)	< 0.01
	10-20	5 (14)	32 (86)	
	> 20	1 (8)	12 (92)	
Specimen Gleason score	2-6	51 (40)	75 (60)	< 0.001
	7	11 (16)	59 (84)	
	8-10	5 (16)	27 (84)	
Clinical stage	< T2b	65 (31)	145 (69)	0.02
	≥ T2b	4 (22)	14 (78)	
Pathologic stage TNM	< T2b	63 (91)	6 (9)	< 0.001
	≥ T2b	4 (3)	155 (97)	
Tumor volume (% specimen)	≤ 10	65 (49)	68 (51)	< 0.001
	10-20	2 (4)	43 (96)	
	20-40	0 (0)	36 (100)	
	> 40	0 (0)	10 (100)	
Weight of specimen (g)	< 40	27 (23)	89 (77)	< 0.001
	40-60	22 (27)	59 (73)	
	> 60	18 (58)	13 (42)	
Capsular invasion	No	59 (56)	46 (44)	< 0.001
	Yes	8 (7)	115 (93)	
Perineural invasion	No	40 (60)	27 (40)	< 0.001
	Yes	27 (17)	134 (83)	
Angiolymphatic invasion	No	65 (31)	145 (69)	0.11
	Yes	2 (11)	16 (89)	

Table 2 - Sites of PSMs in prostate surgical specimen.

Sites of PSMs	N = 161	(%)
Prostatic (circunferential)	78	48.44
Urethral (apex)	22	13.66
Bladder neck (base)	10	6.21
Prostatic+urethral	28	17.39
Prostatic+bladder neck	6	3.72
Urethral+baldder neck	9	5.59
Prostatic+urethral+bladder neck	8	4.96

specimen Gleason score ≥ 7, smaller glands with weight ≤ 40g, pathologic stage ≥ pT2b, percentage of tumor volume higher than 10% of surgical specimen, capsular and perineural invasion with occurrence of PSMs, in accordance with several authors (7-9).

PSMs point to a greater risk of biochemical progression. D'Amico et al. (8) found that after RP failure rates of 2-year PSA were of 45-55% in patients with PSMs, when compared to 15-25% of those with organ confined disease. Several factors have been assessed to verify whether it is possible to further stratify risk of recurrence in patients with PSMs. In virtually all studies, multiple PSMs have signaled a worse prognosis. Number of PSMs

Table 3 - Correlation between PSMs and BCR and CR

	Category	No PSMs N(%)	PSMs N(%)	p
Biochemical recurrence	No	60 (38)	100 (62)	<0.001
	Yes	7 (10)	61 (90)	
Clinical recurrence	No	67 (31)	151 (69)	0.06
	Yes	0 (0)	10 (100)	

factors predicting BCR at 5 years post-RRP. At univariate analysis, prostate weight, preoperative PSA, Gleason score, pathologic stage, tumor volume, PSMs, capsular involvement, and perineural invasion were statistically significant.

Multivariate analysis correlated BCR only with Gleason score and tumor volume in surgical specimen as statistically significant independent predictors ($p < 0.005$ and $p = 0.022$ respectively).

DISCUSSION

In contemporary series, PSMs are reported in 11-38% of patients undergoing RP. The prognostic factors pointing at the presence of PSMs are many ranging from pathologic characteristics to the surgeons' expertise and surgical techniques.

Our results correlate younger and older age, pre-treatment PSA higher than 10ng/mL, (single vs. multiple) showed that there was a statistically significant higher risk of recurrence in patients with more than one PSM, with a hazard ratio of 2.19 at the 95% CI (9).

A similar result was reported by Obek et al. (10), who showed that at a mean follow-up of 25 months, the recurrence rate in patients with multiple PSMs was of 43% vs. 24% in those with a single focus. Furthermore, patients with two or more PSMs were 2.5 times more likely to have recurrence in a shorter period.

In our study, only 61 (37.88%) out of 161 patients with PSMs presented BCR. As in literature, various PSMs sites, bladder neck and prostate circumference, lead to worse outcome. In our cases with no PSMs, BCR was only found in 7 patients (10.5%).

It is extremely difficult to predict PSM outcome, and as patients with PSMs are at higher risk

Table 4 - COX proportional hazard regression analyses of pathologic factors predicting BCR and CR progression-free survival in 5 years following RRP.

Variables	Cathegory	N	BCR	p	N	CR	p
Age (years)	40-50	15	0.71		15	1.00	
	50-60	81	0.77	0.33	81	0.97	0.44
	60-70	105	0.61		105	0.93	
	> 70	27	0.84		27	1.00	
Clinical stage	< T2b	210	0.69	0.3	210	0.96	0.02
	≥ T2b	12	0.75		12	0.76	
Pathologic stage	< T2b	69	0.86	< 0.001	69	1.00	0.08
	≥ T2b	159	0.64		159	0.94	
Gleason score	2-6	126	0.79		126	0.98	
	7	70	0.62	< 0.001	70	0.94	< 0.01
	8-10	32	0.46		32	0.88	
Pre-operative PSA (ng/mL)	≤ 10	174	0.77		174	0.94	
	10-20	37	0.53	< 0.001	37	1.00	0.27
	> 20	17	0.31		17	0.92	
Tumor volume (% from specimen)	≤ 10	133	0.80		133	0.98	
	10-20	45	0.71	< 0.001	45	0.95	0.05
	20-40	36	0.46		36	0.94	
	> 40	10	0.30		10	0.80	
Weight (g)	≤ 40	116	0.62		116	0.94	
	40-60	80	0.83	0.03	80	0.97	0.57
	> 60	32	0.65		32	0.96	
Capsular invasion	No	106	0.84	< 0.01	106	0.99	0.05
	Yes	122	0.60		122	0.93	
Perineural invasion	No	66	0.86	0.01	66	0.97	0.24
	Yes	162	0.64		162	0.95	
Angiolymphatic invasion	No	210	0.70	0.83	210	0.96	0.01
	Yes	18	0.65		18	0.88	
Margins	No	67	0.89	< 0.01	67	1.00	0.08
	Yes	161	0.64		161	0.94	
Margins	None	67	0.89		67	1.00	
	Unique	106	0.66	<0.01	106	0.92	0.05
	Multiple	55	0.60		55	0.98	
Number of margins	0	67	0.89		67	1.00	
	1	106	0.66	< 0.01	106	0.92	0.11
	2	44	0.65		44	0.98	
	3	11	0.41		11	1.00	

Table 5 - Univariate and multivariate analyses of clinical and pathologic factors predictors of BCR in 5 years.

Characteristic		Univariate				Multivariate			
	n	RR	IC(95%)		Pr(>|z|)	RR	IC(95%)		Pr(>|z|)
Prostate weight	228	0.98	0.96	0.99	0.013	0.99	0.97	1.01	0.187
Patient age	228	0.99	0.96	1.03	0.737	0.99	0.95	1.02	0.489
Pre-operative PSA	228	1.039	1.021	1.056	0.0008	1.018	0.992	1.044	0.18
Gleason score					7.9E-05				0.005
≤ 6	124	1.00				1.00			
7	71	1.88	1.07	3.31	0.029	1.37	0.75	2.50	0.301
≥ 8	33	4.02	2.14	7.54	1.5E-05	3.13	1.57	6.25	0.001
Tumor Volume	228	1.02	1.01	1.03	3.2E-05	1.02	1.00	1.03	0.022
Margins					0.003				0.653
Negatives	67	1.00				1.00			
Positives	161	3.51	1.51	8.13	0.003	1.47	0.27	7.96	0.653
Pathologic stage					0.005				0.759
≤ pT2a	68	1.00				1.00			
≥ pT2b	160	3.09	1.41	6.77	0.005	0.78	0.16	3.81	0.759
Perineural invasion					0.009				0.533
No	67	1.00				1.00			
Yes	151	3.24	1.47	7.12	0.003	1.62	0.67	3.90	0.284
Extense	10	4.60	1.34	15.72	0.015	1.92	0.49	7.48	0.346
Capsular invasion					0.002				0.279
No	105	1.00				1.00			
Yes focal	82	2.42	1.30	4.49	0.005	1.76	0.86	3.61	0.124
Extracapsular	41	3.23	1.64	6.38	0.001	1.76	0.78	3.98	0.173
Angiolymphatic invasion					0.540				0.666
No	210	1.00				1.00			
Yes	18	1.30	0.56	3.03	0.540	0.82	0.33	2.04	0.666

of progression, the ability to stratify this risk needs improvement along with other factors that may affect disease progression and survival (11). Focal capsular or extensive extracapsular involvement, were both correlated with BCR in our study. Other studies found that men with PSMs and no extracapsular spread had a lower rate of recurrence than men with extracapsular disease, but this was contradicted by the SEARCH database study group (12), who found that men with PSMs and no extracapsular spread had a recurrence risk similar to those with extracapsular disease regardless of margin status.

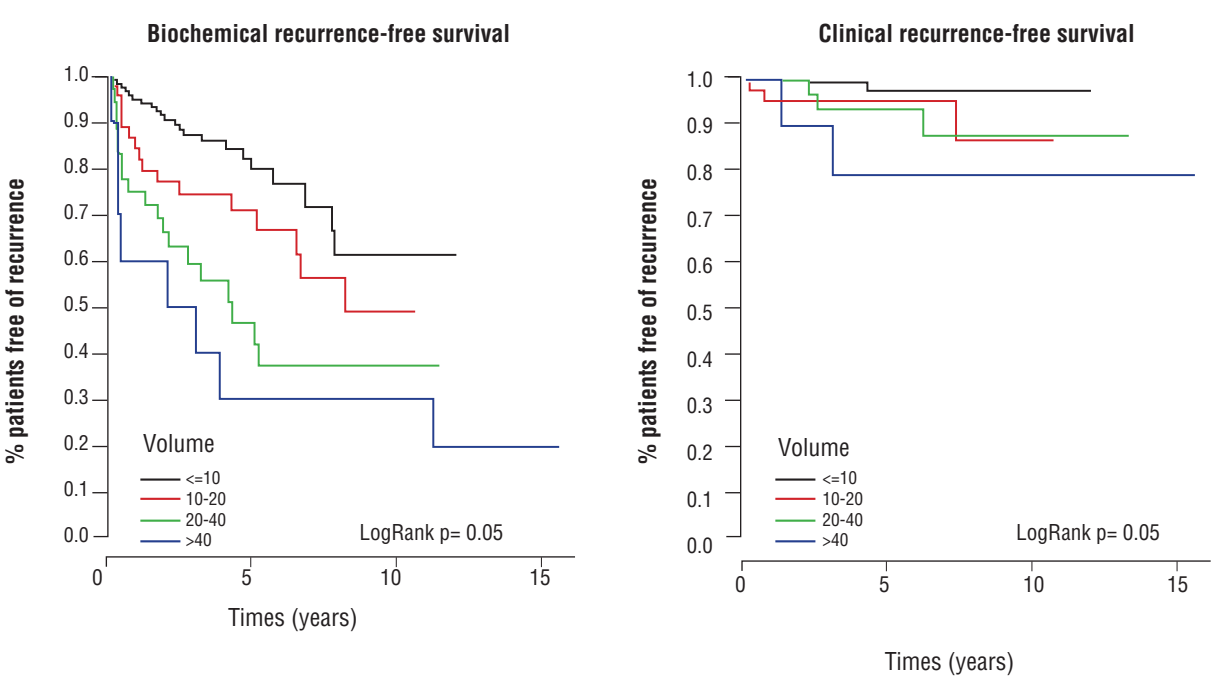
Similar to our results, Stephenson et al. (13) noted that 7-year progression-free probability was observed in 60% of patients with positive surgical margins. A positive surgical margin was significantly associated with biochemical recurrence (HR 2.3, $p < 0.001$) after adjustment of the following factors: age, prostate specific antigen, Gleason score, pathologic stage and year of surgery. An increased risk of biochemical recurrence was associated with multiple vs. single positive surgical margins (adjusted HR 1.4, $p = 0.002$) and extensive vs. focal positive surgical margins (adjusted HR 1.3, $p = 0.004$) at multivariate analysis. However, neither parameter improved the predictive accuracy of a nomogram compared to one in which surgical margin status was modeled as positive vs. negative (concordance index 0.851 vs.0.850 vs. 0.850).

In our results, at univariate analysis prostate weight, preoperative PSA, Gleason score, pathologic stage, tumor volume, PSMs, capsular and perineural invasion were correlated with BCR in full agreement with literature. Nevertheless at multivariate analysis only Gleason score and tumor volume were statistically significant independent predictors of BCR (Figure-1).

Guram et al. (14), conclude that patients with vascular invasion in the radical prostatectomy specimen are at high risk of recurrence after surgery, and that adjuvant systemic treatment should be considered for these patients. They further conclude that patients with negative surgical margins and no vascular invasion are likely to be cured by radical prostatectomy. Similarly, our results showed that angiolymphatic invasion and Gleason score were significantly correlated only with CR.

Gleason score reflects tumor aggressiveness, whereas cancer volume illustrates the extent of the lesion, as such it can be hypothesized that high-grade cancer volume and percentage simultaneously reflect cancer invasion ability to spread and their impact on outcome. Our results support the conclusions of other authors (15,16) that high-grade cancer volume had the highest impact on recurrence-free survival in patients with surgically treated and pathologicly organ-confined prostate cancer or that prostate volume has prognostic value in pathology T2 radical prostatectomy specimens (17). These facts highlight the importance of the percentage of tumor volume in the surgical specimen, rather than the presence of PSMs, as important predictor

Figure 1 - Probability of biochemical recurrence-free and clinical progression-free survival at 5-10 years according to percentage tumor volume in the specimen.



of BCR. Other studies, however, argued that tumor extent does not provide additional information beyond that of Gleason score and surgical margin status (18-20).

CONCLUSIONS

Our results agree with numerous previous reports that presence, number and site of PSMs have consistent correlation with BCR following RRP within other pathologic factors at univariate analysis. However, not all patients with PSMs will present tumor progression. As confirmed in our study, BCR occurred only in 37.8% of patients with PSMs. Overall, CR was very rare, as it represented 4% of the total number of cases (PSMs and no PSMs). At multivariate analysis, percentage of tumor volume ($p = 0.022$) and Gleason score ($p < 0.005$) in the surgical specimen were the independent significant prognostic risk factors for BCR, rather than the presence of PSMs, stressing the importance of these two pathologic factors. Furthermore, angiolymphatic invasion and Gleason score were significantly correlated only with CR.

ABBREVIATIONS

CaP = Prostate adenocarcinoma
PSMs = Positive surgical margins
RRP = Open retropubic radical prostatectomy
RP = Radical prostatectomy
BCR = Biochemical recurrence
CR = Clinical recurrence

CONFLICT OF INTEREST

None declared.

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