Comprehensive Analysis of Perioperative Factors Influencing the Risk of Biochemical Recurrence in Patients with Radical Prostatectomy

Mihnea Bogdan Borz[1,2], Vlad Horia Schitcu[1,2]*, Nicolae Crisan[2,3], Bogdan Petrut[1,2], Oliviu Cristian Borz[4], Paul Cristian Borz[5], Igor Duquesne[6], Jordan Nasri6, Ioan Coman[2]

Purpose: To analyze the perioperative factors that influence the risk of biochemical recurrence (BCR) in patients with localized PCa undergoing radical prostatectomy

Materials and Methods: A total of 457 patients, operated by 2 surgeons in our high-volume oncological center were included in the initial database. Patients who underwent RP for clinically localized PCa in our clinic from 2016 to 2021 were included in the study. Perioperative data were retrospectively reviewed for this study. Follow-up data including post-operative PSA and adjuvant treatment was prospectively gathered by contacting the patients or from the follow-up consultation. Final database was composed of 366 patients who underwent open or 3D laparoscopic RP. Statistical analysis was performed to emphasize the most powerful parameters that influence the BCR.

Results: Accounting for multivariable analysis, 4 parameters were statistically significant: initial PSA (iPSA), Gleason score, vascular involvement and positive surgical margins. For the group of patients with no positive margins, 3 parameters were statistically significant: iPSA above 10,98 ng/mL (AUC=0,71); lymph node involvement and Gleason score. Multivariable Cox regression showed that positive margins and iPSA had a significant impact on the time to BCR. Patients who received adjuvant therapy were excluded from the study. Out of the whole cohort, 27,3% of patients presented BCR.

Conclusion: Perioperative factors need to be carefully analyzed and a detailed follow-up needs to be conducted in order to assess the risk of biochemical recurrence, resulting in the optimal time for adjuvant treatment implementation.

Keywords: prostate; cancer; prostatectomy; biochemical; recurrence

INTRODUCTION

Prostate cancer (PCa) is the most common urological malignancy managed by a practicing urologist. According to the World Health Organization, the estimated number of incident cases and deaths worldwide, males, all ages in 2020 are as follows: prostate cancer stands as the second most common malignancy in men after lung cancer, with an incidence of 1,414,259, being the 5th most common death cause due to malignancy with 375,304 disease related deaths[1,2]. Incidence varies greatly depending on the ethnicity and geographic zone with intervals ranging from 11.5 per 100.000 in the Middle East[3], North America 97.2 per 100.000, South America 60.1 per 100.000[4] and the most frequently found in African Americans up to 195 per 100.000[5].
An increased incidence of PCa has resulted primarily from improved screening of prostate specific antigen (PSA) in the last years[6]. PCa represents a leading cause in cancer-related deaths in developed countries even though a continuous decline has been observed in PCa-related deaths[7] due to developments in the medical field and improvements in understanding of the pathology. Treatment strategies are varied, radical prostatectomy (RP) being the most commonly used option as a primary treatment for patients with PCa[8], which can be performed by open, laparoscopic or robotic-assisted approach.
Approximately 20-40% of patients undergoing RP develop biochemical recurrence (BCR)[9–11]. PSA represents the pivotal tool for follow-up and diagnosis of recurrence. After RP the PSA usually becomes undetectable, BCR being defined as two consecutive PSA values higher than the threshold value of 0,2 ng/mL[7,12].
A continuing challenge in the postoperative management and follow-up is the approach of a patient who presents with BCR after RP[12,13]. A rising PSA level usually precedes clinical recurrence with metastasis and PCa-specific mortality. Even though BCR may not

[1]Institute of Oncology „Prof dr. Ion Chiricuta" CLUJ NAPOCA.
[2]„Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj Napoca.
[3]Clinical Municipal Hospital, Cluj Napoca.
[4]Târgu Mureş County Emergency Clinical Hospital.
[5]Regional Institute of Gastroenterology and Hepatology Prof. Dr. Octavian Fodor, Cluj Napoca.
[6]Hopital Cochin – Port Royal, Paris.
*Correspondence: "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj Napoca, Romania.
Tel: +4 0742 309 213. E mail: schitcu@yahoo.com.
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Table 1. Univariate analysis of perioperative clinical data reported to biochemical recurrence

Parameters		No biochemical recurrence	Biochemical recurrence	*p* Value
PSA risk	Low	157 (83.95%)	30 (16.05%)	0.001
	Intermediate	75 (66.96%)	37 (33.04%)	
	High	22 (41.50%)	33 (58.50%)	
pT	Stage II	166 (88.77%)	21 (11.23%)	0.001
	Stage III/IV	92 (52.27%)	84 (47.73%)	
pN	pN0	186 (72.37%)	71 (27.63%)	0.001
	pN+	7 (24.13%)	22 (75.87%)	
Gleason score	7	182 (76.79%)	55 (23.21%)	0.001
	8	17 (54.83%)	14 (45.17%)	
	9	13 (30.23%)	30 (69.77%)	
Lymphatic	L0	232 (80%)	58 (20%)	0.001
involvement	L1	29 (38.15%)	47 (61.85%)	
Vascular involvement	V0	258 (75.43%)	84 (24.56%)	0.001
	V1	3 (12.5%)	21 (87.5%)	
Perineural	Pn0	94 (92.15%)	8 (7.85%)	0.001
involvement	Pn1	166 (63.11%)	97 (37.89%)	
Surgical Margin	R0	216 (80.59%)	52 (19.41%)	0.001
	R1	45 (45.91%)	53 (54.08%)	

pT= pathological tumor classification, pN= lymph node involvmenet, R= status of surgical margins

always be associated with clinical recurrence it can predate it by several years[10,12,14].

The issue of recurrence impairs the quality of life of affected patients inducing stress and anxiety, as well as toxicity or side effects of salvage therapy[15]. In case of BCR, no guidelines are established for the appropriate strategy, only recommendations can be followed[13]. Physicians are challenged with preventing or delaying the onset of adjuvant treatment in those at risk, while avoiding over-treatment in patients whose disease may not progress beyond the BCR[12], thus an optimal time to start the adjuvant therapy and best treatment option need to be standardized.

The paper's objective is to investigate the perioperative factors that influence the risk of BCR in patients with localized PCa undergoing radical prostatectomy. This research aims to assist urologists in identifying eligible patients for potential postoperative radiotherapy and considering adjuvant treatment even when it might not be traditionally recommended

METHODS

Study Population

A total of 457 patients, operated by 2 surgeons in our high-volume oncological center were included in the initial database. Patients who underwent RP for clinically localized PCa in our clinic between 2016 and 2022 were included in the study. Perioperative data were retrospectively reviewed for this study including demographic data, preoperative prostate-specific antigen (PSA) value, clinical stage, prostate needle biopsy (biopsy Gleason score, International Society of Urological Pathology (ISUP) grade), specimen pathological data after RP (Gleason score, ISUP grade, TNM classification, status of surgical margins (SM) and lymph node involvement). Follow-up data including post-operative PSA and adjuvant treatment was prospectively gathered by contacting the patients or from the follow-up consultation.

Inclusion and exclusion criteria

Patients who were lost at follow-up or had adjuvant treatment directly after surgery were excluded from the study. The final database was composed of 366 patients who underwent open or 3D laparoscopic RP.

Evaluations and data comparison

To strengthen and acknowledge the results obtained in the study, a PubMed search was conducted encompassing papers published between 2018 and 2022, with a focus on factors influencing BCR after RP. Keywords such as prostate cancer, biochemical recurrence, clinical recurrence, laparoscopic prostatectomy, and positive margins were used obtaining a list of 29 papers. After analyzing all the papers, 21 studies were included in the research analysis.

Statistical Analysis

All perioperative data was subjected to statistical analysis comparing the results for the BCR-negative and

Table 2. Multivariable analysis.

	Variables in the Equation			
			95% C.I.for OR	
	Sig.	Odds ratio	Lower	Upper
iPSA	0.01	1.73	1.13	2.64
pT	0.25	1.56	0.74	3.29
pN	0.06	3.02	0.95	9.58
Gleason Score	0.02	1.66	1.1	2,51
L	0.29	1.54	0.69	3.43
V	0.04	4.01	1	16.04
Pn	0.22	1.84	0.7	4.83
R	0.01	2.57	1.32	5.01

iPSA = initial PSA, pT = pathological tumor classification, pN = lymph node involvement, L = lymphatic involvement, V = vascular involvement, Pn = perineural involvement, R = surgical margin status

Table 3. Multivariable analysis of patients with negative surgical margins

	Variables in the Equation			
			95% C.I.for OR	
	Sig.	OR	Lower	Upper
iPSA above 10.98 ng/mL	0.027	2,588	1.111	6.029
pT	0.246	1.716	0.689	4.274
pN	0.026	5.88	1.242	27.831
Gleason score	0.047	1.765	1.006	3.096
L	0.467	1.488	0.509	4.35
V	0.166	3.651	0.585	22.786
Pn	0.778	1.167	0.397	3.431

iPSA= initial PSA, pT= pathological tumor classification, pN= lymph node involvmenet, L= lymphatic involvement, V=vascular involvmenet, Pn=perineural involvement

Table 4. Multivariable COX regression

	Cox Regression			
			95.0% CI for OR	
	Sig.	OR	Lower	Upper
iPSA	0.006	1.014	1.004	1.024
pT	0.11	1.678	0.889	3.17
pN	0.216	1.513	0.785	2.914
Gleason score	0.073	1.29	0.977	1.704
L	0.276	1.382	0.772	2.475
V	0.575	1.205	0.628	2.31
Peri N	0.113	1.987	0.85	4.646
R	0.047	1.64	1.008	2.669

iPSA= initial PSA, pT= pathological tumor classification, pN= lymph node involvmenet, L= lymphatic involvement, V=vascular involvmenet, Pn=perineural involvement, R=surgical margin status

BRC-positive groups and for the SM-negative and SM-positive groups. Minimum sample size was calculated at 385 to achieve a confidence interval of 95%. Mann-Whitney U, Fisher`s exact test and Pearson Chi-Square tests were applied to the database. ROC curve analysis was performed to determine the cutoff value, sensitivity and specificity ratios. A multivariable analysis was performed to emphasize the most powerful parameters that influence the BCR, the model building including variable selection algorithm were statistically significant parameters from the univariate analysis, which were selected using Bonferroni correction.. Cox regression analysis to evaluate the factors that significantly influenced time to BCR. For survival analysis, we defined the starting point as the date of intervention for patients who underwent radical prostatectomy between 2016 and 2021, and the endpoint as the date of their last follow-up, which had a mean duration of 49.6 months. For statistical analysis, IBM SPSS v26.0 program was used and a *p*-value < .05 was considered as significant.

RESULTS

The overall study cohort included 366 patients who underwent RP, no neoadjuvant therapy, for clinically localized prostate cancer. Table 1 represents a univariate analysis summarizing the perioperative clinical data. Median age was 66 (51 to 82) and median iPSA 9,89 ng/mL. Within a mean postoperative follow-up of 49,6 months, 100 patients (27,3%) experienced BCR. The majority of patients included in the study presented with low and intermediate risk PCa with iPSA under 10 and Gleason score of 7. The univariate analysis for all perioperative factors are presented in **Table 1**.

ROC curve analysis determined a cutoff value of 10,98 ng/mL with an associated AUC of 0,71 (95% CI: 0.65 - 0.78, $P < .001$), results shown in Figure 1. The multivariable analysis of factors that influence the BCR are listed in Table 2. Accounting for multivariable analysis, 4 of the parameters were statistically significant iPSA (95% CI : 1.13-2.64, OR = 1.73, $P = .01$); Gleason score (95% CI : 1.10-2.51, OR = 1.66, $P = .02$); vascular involvement (95%CI : 1.00-16.04, OR = 4.01, $P = .04$); positive resection margin (95% CI : 1.32 - 5.01, OR = 2.57, $P = .01$). High risk cases with iPSA greater than the cutoff value, Gleason score of 9, vascular involvement and positive SM had a BCR rate greater than 50%, all factors having a statistically significant association ($P < .001$). Patients with vascular involvement at the final specimen histopathological examination had a 4-fold risk of BCR after surgery, followed by cases with positive SM with a 2,5-fold risk of BCR.

A multivariable analysis was performed in the group of patients with no positive margins, excluding the non-

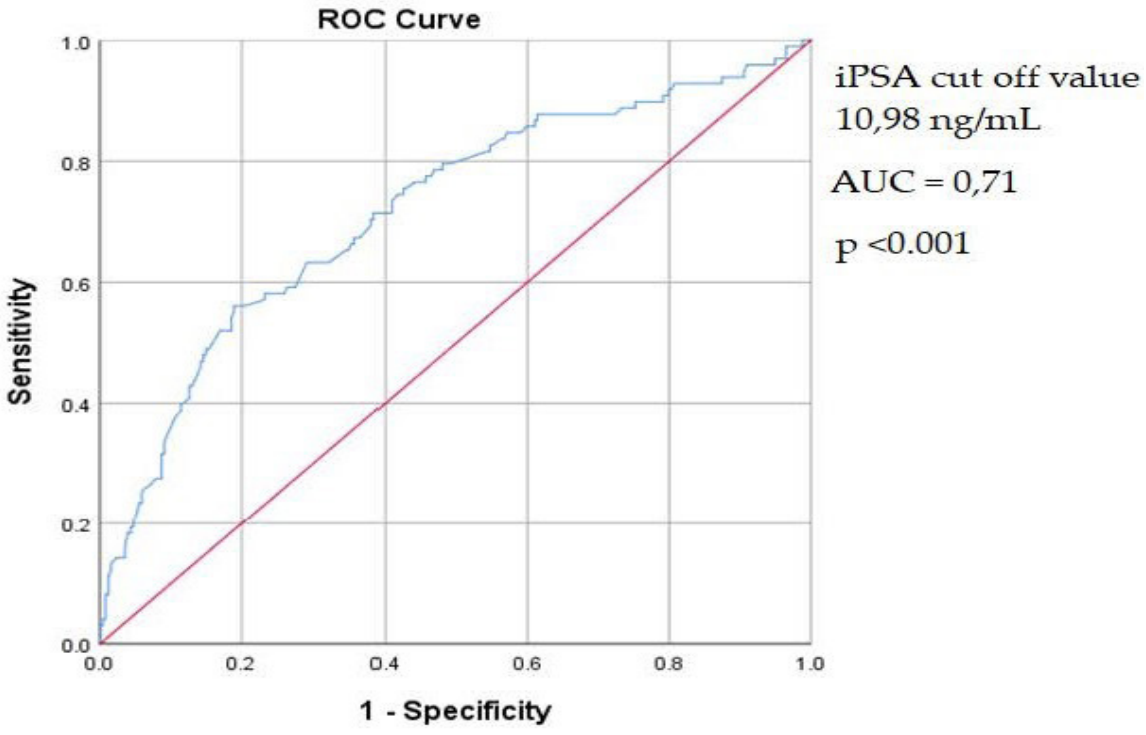

Figure 1. ROC curve for initial PSA.

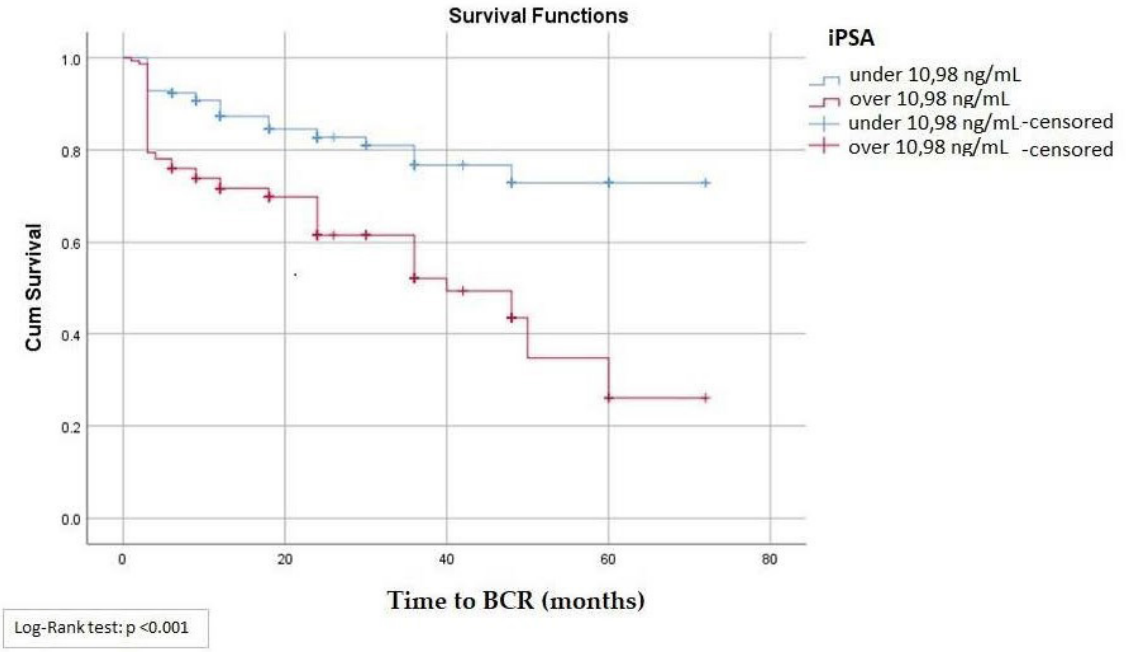

Figure 2. Cox Proportional Hazard Regression model with relative risk for time to BCR (months) in correlation with iPSA (BCR=biochemical recurrence).

biological factor that affected the BCR. **Table 3** summarizes the results obtained in the analysis. Accounting for multivariable analysis, 3 of the parameters were statistically significant: iPSA above 10,98 g/mL (95% CI : 1.11-6.02, OR = 2.58, *P* = .027); lymph node involvement (95% CI : 1.24–27.83, OR = 5.88, *P* = .026); Gleason score (95% CI: 1.006 – 3.09, OR = 1.76, *P* = .047). In patients with no positive margins, biological factors that has the greatest impact on biochemical recurrence were lymph node involvement with almost 6 times higher risk of recurrence, followed by iPSA with a 2,5-fold higher risk of recurrence.

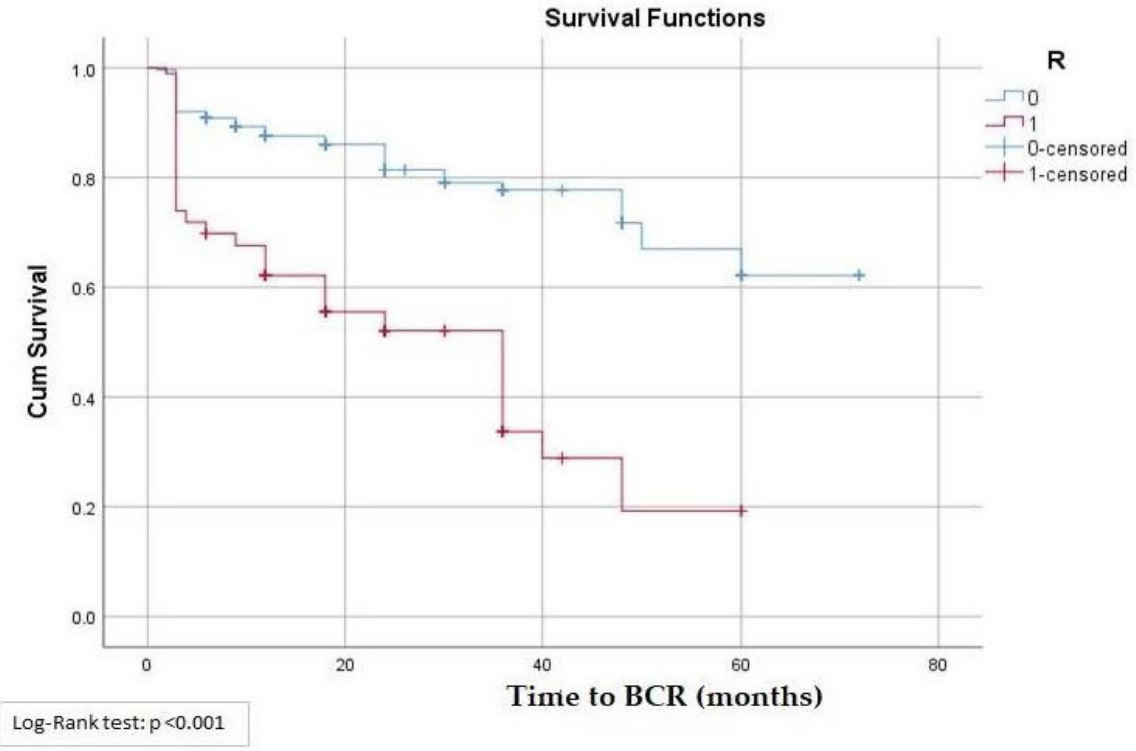

Figure 3. Cox Proportional Hazard Regression model with relative risk for time to BCR (months) in correlation with surgical margin status (BCR=biochemical recurrence).

To better understand the influence on time to BCR, multivariable Cox regression was performed underlining the most impactful factors significantly influencing time to BCR. The regression represented in Figure 3 showed that positive margins after radical prostatectomy independently increases the risk of biochemical recurrence by almost 1,7 times (OR = 1.640, P = .047) and the iPSA having a significant impact on the time to BCR, shown in **Figure 2** (OR = 1.014, P = .006). Thus 82,7% of patients with iPSA under the cutoff value were BCR free. 81,0% of patients with negative surgical margins at the histopathological examination were BCR free, while for the patients with positive surgical margins, only 46,9% were BCR free at follow-up, marking the impact of surgical margins. Out of the whole cohort, 27,3% of patients had BCR at one point at follow-up.

DISCUSSION

In summary of our results, vascular involvement and positive surgical margins were found to be the most impactful independent predictive factors for BCR after RP in all patients, results also described in literature in different published papers[10,16–18]. Furthermore, initial PSA and Gleason score at the final specimen examination were also statistically significant factors that influenced BCR. Studies analyzing the correlation between Gleason score and biochemical failure found similar results[19,20]. Pathological T stage (pT) did not have a significant impact in patients after RP in the multivariable analysis (P = .25) but there was a significant difference in patients with pT3 and pT4 regarding the risk of BCR compared to patients with pT2. In SM-negative patients, iPSA still represented an impactful factor in the risk of BCR, with Gleason score and lymph node involvement being also risk factors in these patients.

Only a limited number of studies have delved into the examination of factors impacting BCR specificity among patients with negative SM. Consequently, a comprehensive multivariate analysis was conducted within this specific patient subgroup to identify and emphasize the significant risk factors. Similar to the broader cohort, iPSA and Gleason score emerged as factors exerting influence on the oncological outcomes. Notably, while lymph node involvement did not show statistical significance in its influence on BCR within the overall cohort, it exhibited the most substantial impact among patients with negative SM, with an Odds Ratio of 5.88 and a significance level of P = .026.

Even though a high risk of BCR was observed in patients with vascular involvement and positive SM stretched over the whole follow-up, Cox regression showed the two as the most impactful factors regarding time to BCR. Thereby, patients who presented positive SM and high initial PSA had the fastest biochemical failures. EAU does not recommend a specific approach for RP, with results regarding the risk of positive SM being heterogenous in the literature, experience surgeons being encouraged to perform the surgical approach they feel most confident about.

In the literature, various studies have studied the significance of specific factors impacting BCR in patients who have undergone radical prostatectomy. Notable among these factors are positive surgical margins[15,17], lymphovascular involvement[21,22], perineural invasion[23–26] and Gleason score[27]. However, only a limited number of studies have taken a more comprehensive approach, encompassing a broader spectrum of factors and subjecting them to multivariable analysis. This research paper's statistical value lies in its extensive analysis of perioperative factors, which includes initial PSA levels and all histopathological findings. By considering this wider range of variables, we aim to provide a more holistic understanding of the complex interplay of factors influencing BCR post-radical prostatectomy.

D'Amico's classification system categorizes patients with prostate cancer into risk classes based on their likelihood of experiencing BCR and highlights the key factors that significantly influence treatment outcomes. Among these, the most pivotal factors are the biopsy Gleason score, iPSA level, and the clinical TNM classification[28]. These findings closely align with our own research results.[28,18,21-26]

The guidelines established by the EAU advise a follow-up schedule for patients who have undergone RP, which includes assessments at the 6-month mark for the first 3 years post-surgery, followed by annual check-ups. A comprehensive evaluation of risk factors should be done for each RP patient, with the aim of tailoring a personalized follow-up plan, depending on the number of present risk factors.

CONCLUSIONS

Perioperative factors such as initial PSA, Gleason score from the prostatectomy pathological examination, vascular involvement and positive SM were found to be the most impactful factors that affect the risk of biochemical recurrence in patients with localized PCa that underwent surgical treatment. Initial PSA and positive SM were factors that had the shortest time to BCR, thereby the most aggressive in the appearance of BCR. In patients with negative SM, iPSA, lymph node involvement and Gleason score had the greatest impact in the risk of BCR.

Prostate cancer represents a complex pathology that has an increasing incidence worldwide with an impactful effect on the male population, being the 5th most common death cause due to malignancy. Perioperative factors need to be carefully analyzed and a detailed follow-up needs to be conducted in order to assess the risk of biochemical and clinical recurrence, resulting in the optimal time for adjuvant treatment implementation.

More factors such as specific prostate proteins, micro-ARN and prostate molecules need to be analyzed and corelated to the BCR to better understand the bio-molecular action of the prostate cancer and find the ideal time for adjuvant treatment in patients with biochemical and clinical recurrence.

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Ethical Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Oncology Insitute "Prof. Dr. Ion Chiricuta" Cluj Napoca (approval code 138.1/10.07.2019).

CONFLICT OF INTEREST

The authors report no conflict of interest.

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