Original Article
Özgün Araştırma

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Factors predicting biochemical recurrence following robot-assisted radical prostatectomy: single-center experience

Robot yardımlı radikal prostatektomi sonrasında biyokimyasal rekürrensi predikte eden faktörler: tek merkez deneyimi

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ÖZET

Amaç: Bu çalışmada uzun takip süresine sahip hastalarda Biyokimyasal Rekürrens (BCR) gelişimini predikte eden faktörleri araştırmayı hedefledik.

Gereç ve Yöntemler: Robot Yardımlı Radikal Prostatektomi (RARP) uygulanan 758 hastanın verileri geriye dönük olarak tarandı. Postoperatif dönemde prostat spesifik antijen (PSA) değerlerinin 0,2 ng/mL ve üzeri saptanması BCR olarak kabul edildi. BCR gelişmeyen grup Grup 1, BCR gelişen grup Grup 2 olarak sınıflandırıldı.

Bulgular: Ortalama yaş iki grup arasında benzerdi. BCR gelişen grupta PSA değerleri anlamlı oranda yüksek izlendi (p<0,001). BCR gelişen grupta biyopsi gleason skoru (GS), risk sınıflaması ve spesmene ait GS oranları anlamlı olarak yüksek izlendi (sırasıyla p=0,02, p<0,001, <0,001). BCR gelişen grupta pozitif cerrahi sınır (PSM), ekstra prostatik yayılım (EPE), seminal vezikül invazyonu (SVI) ve lenf nodu pozitifliği (LNI) oranları anlamlı olarak yüksek izlendi. Çok değişkenli analizlerde; PSA, risk sınıflaması, spesmene ait GS, PSM, SVI ve T evreleri anlamlı parametreler olarak izlendi.

Sonuç: BCR gelişimini predikte eden değerler PSA, risk sınıflaması, spesmene ait GS, PSM, SVI ve T evresidir. Bu konuda ortak kabul gören modellerin yaygınlaşması ile hasta yönetimi ve hasta beklentilerinin optimizasyonunun sağlanabileceği kanaatindeyiz.

Anahtar Kelimeler: *robot yardımlı radikal prostatektomi, biyokimyasal rekürrens, prostat kanseri, PSA*

ABSTRACT

Objective: In this study, we aimed to investigate factors predicting the development of biochemical recurrence (BCR) in our clinical experience with patients over a long follow-up.

Material and Methods: The data of 758 patients who underwent robot-assisted radical prostatectomy (RARP) were retrospectively reviewed. In the postoperative period, the prostate-specific antigen (PSA) value is measured as 0.2 ng/mL and above, regarded as biochemical recurrence (BCR). The non-BCR group was regarded as Group 1, and the BCR group as Group 2.

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This study was approved by the Ethics Committee of Health Science University, Ümraniye Training and Research Hospital (Approval Number: 233, Date: 23/06/2022). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

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Results: The mean age was similar between the two groups. The PSA values were significantly higher in the group that developed BCR (p<0.001). The biopsy Gleason score (GS), risk classification, and specimen GS were significantly higher in this group (p=0.02, p<0.001, and p<0.001, respectively). The BCR group also had statistically significantly higher positive surgical margin (PSM), extraprostatic extension (EPE), seminal vesicle invasion (SVI), and lymph node invasion rates. According to the multivariate analyses, PSA, risk classification, specimen GS, PSM, SVI, and T stage were significant parameters in the prediction of BCR.
Conclusion: The parameters that predict the development were determined as the PSA value, risk classification, specimen GS, PSM, SVI, and T stage. The widespread adoption of commonly accepted methods will help achieve better patient management and optimize patient expectations.

Keywords: *robot-assisted radical prostatectomy, biochemical recurrence, prostate cancer, PSA*

INTRODUCTION

Prostate cancer (PCa) is the most common non-cutaneous cancer. It is the most common cause of cancer-related death in male patients (1). Biochemical recurrence (BCR) is relevant to metastasis and mortality and is observed at rates reaching 27% after radical prostatectomy (RP) (2–4). Although surgery is a good option, 4-25% of these cases progress to metastatic disease within 15 years (5). Therefore, identifying patients at high risk due to PCa and their early treatment may lead to better oncological outcomes. In addition, identifying cases at low risk of BCR will prevent unnecessary additional treatments (6, 7).

Many studies have been conducted, and models such as CAPRA score and Kattan nomograms have been established based on data obtained from large series to predict BCR (3, 8–11). The search for more predictive models has increasingly continued with the multiparametric magnetic resonance imaging (mp-MRI) technique and better identification of lesions, coupled with developments in nuclear medicine (9, 10) . In this study, we aimed to investigate factors predicting the development of BCR in our clinical experience with patients over a long follow-up period.

MATERIAL AND METHODS

Patient Selection

After receiving approval from the local ethics committee (2022/233), the data of 758 patients who underwent robot-assisted RP (RARP) for PCa at Umraniye Training and Research Hospital between January 2016 and December 2020 were reviewed. Patients who performed preoperative radiotherapy or hormone therapy for PCa, and those with detected or suspected metastases during staging were not included in the study. Further excluded from the study were patients with a follow-up of less than 1 year, those with unavailable postoperative follow-up data, and those referred to adjuvant radiotherapy.

Preoperatively, a whole-body bone scan and cross-sectional abdominopelvic computed tomography were performed to evaluate the presence of metastasis among the patients determined to be moderate and high risk according to the risk classification. All the operations were undertaken using the da Vinci XI surgical systems® (Intuitive Surgical Inc., Sunnyvale, California, USA) and the Frankfurt technique described by Wolfram et al (12). Pneumoperitoneum was created with a Veress needle. A total of 5 ports were placed, one for the camera port, one for the assistant port, and three for the robot arms. All surgeries were performed transperitoneally. The operative stages were defined as; patient positioning, trocar placement, and robot docking. After these steps, dissection of the seminal vesicles and entering the extraperitoneal space were performed. Incision of the bladder neck was performed after ligating the dorsal venous complex. Finally, prostatic pedicles, neurovascular bundle preservation, and anastomosis were performed. Bilateral nerve-sparing surgery was performed in cases with preoperative potency and no suspicion of extraprostatic extension (EPE). According to the Partin nomogram, pelvic lymph node dissection was performed in cases with a risk of nodal metastasis greater than 5%.

The follow-up was performed in the first postoperative month, followed by every three months for two years and every six months after that. Whether they developed BCR, two groups were divided.

Data Collection

All the specimens were evaluated clinically and pathologically as stated as to the 2009 TNM classification of the "American Joint Committee on Cancer, seventh edition" (13). The patients were divided into classes low, moderate, and high-risk (14). A positive surgical margin (PSM) was defined as the presence of a tumor in the inked margins. The prostate specific antigen (PSA) value measured as 0.2 ng/mL and above in two consecutive measurements in the postoperative period was accepted as BCR. Any increase in the Gleason score (GS) from the biopsy result to the RP specimen result was considered a GS upgrade. In addition, the patients with a GS of 3+4 in biopsy and 4+3 in the RP specimen were accepted to have a GS upgrade.

Statistical Analysis

Numbers and percentages were used to show the categorical data. The mean and standard deviation values were used to show numerical data. The normality tests of numerical data were performed by using the Shapiro-Wilk test. Numerical data normally distributed were compared with the Student's t-test, and the Mann-Whitney U test was used to compare non-normally distributed numerical data. The categorical data were compared with the Pearson chi-square test. A p-value was regarded as significant at the <0.05 level. The univariate and multivariate binary logistic regression analyses were used to analyze factors predicting BCR development. Statistical analyses were done with the Statistical Package for the Social Sciences version 21 (IBM SPSS Statistics; IBM Corp., Armonk, NY).

RESULTS

Patient Characteristics

A total of 758 patients were included. Table 1 presents the demographic, preoperative, and postoperative data of the 98 (12.9%) patients that developed BCR and 660 (87%) patients that did not develop BCR. The mean age, body mass index, and American Society of Anesthesiologists score were similar. In the BCR group, the PSA values were significantly higher ($p < 0.001$). This group had significantly higher biopsy GS, risk classification, and specimen GS values. The PSM, EPE, the rate of the invasion of seminal vesicle (SVI), and lymph node (LNI) rates were different between groups. The mean follow-up duration of all the patients and the time to BCR in those that developed recurrence were calculated as 33.2 ± 14.3 months and 11.3 ± 10 months, respectively.

Univariate and Multivariate Analyses

In the univariate analysis, PSA, biopsy GS, risk classification, specimen GS, PSM, EPE, SVI, LNI, and T stage were determined to be significant parameters. In multivariate analysis, PSA, risk classification, specimen GS, PSM, SVI, and T stage were significant parameters predicting BCR (Table 2).

Table 1: Demographic and clinical data

	Total (n)	Non-BCR, n (%)	BCR, n (%)	p
Number of patients (mean ± SD)	758	660 (87)	98 (12.9)	
Age (years)	63.3 ± 6	63.1 ± 4	64 ± 7.3	0.233
BMI (kg/m^2)	27.4 ± 2.3	27.3 ± 3.4	27.6 ± 3.7	0.633
PSA (ng/dL)	8.4 ± 7	8.1 ± 5.1	12.3 ± 4.2	**<0.001**
PV (cc)	52 ± 18.3	51.3 ± 7.8	54 ± 3.2	0.323
Biopsy GS				**0.02**
3+3	469 (61.8)	446 (67.5)	23 (23.4)	
3+4	159 (20.9)	139 (21)	20 (20.4)	
4+3	75 (9.8)	53 (8)	22 (22.4)	
4+4	48 (6.3)	20 (3)	28 (28.5)	
4+5	7 (0.9)	2 (0.3)	5 (5.1)	

Risk				**<0.001**
	Low	576 (75.9)	535 (81)	41 (41.8)	
	Moderate	110 (14.5)	82 (12.4)	28 (28.5)	
	High	72 (9.4)	43 (6.5)	29 (29.5)	
Blood loss (cc)		170 ± 120	169.2 ± 110.3	173.4 ± 130 ± 2	0.745
Upgrade, n (%)		303 (39.9)	255 (38.6)	48 (48.9)	**0.037**
Specimen results, n (%)					**<0.001**
	GS				
	3+3	298 (38.6)	289 (43.7)	9 (9.1)	
	3+4	323 (42.6)	300 (45.4)	23 (23.4)	
	4+3	93 (12.2)	60 (9)	33 (33.6)	
	4+4	22 (2.9)	7 (1)	15 (15.3)	
	4+5	22 (2.9)	4 (0.6)	18 (18.3)	
	PNI	668 (88.1)	587 (87.5)	90 (91.8)	0.121
	PSM	121 (15.9)	63 (9.5)	58 (59.1)	**<0.001**
	EPE	233 (30.7)	172 (26)	61 (62.2)	**<0.001**
	SVI	82 (10.8)	37 (5.6)	45 (45.9)	**<0.001**
T stage					**<0.01**
	2	454 (59.8)	412 (62.4)	42 (42.8)	
	3	289 (38.1)	255 (38.6)	34 (34.6)	
	4	15 (1.9)	3 (0.4)	12 (12.2)	
	LNI	22 (2.9)	27 (3.5)	16 (16.3)	**0.02**
Follow-up duration (month)		33.2 ± 14.3	33 ± 17.2	35.2 ± 11.5	n/a
Time to BCR (month)		11.3 ± 10	11.4 ± 9.2	11 ± 10.3	n/a

***SD:** Standard deviation, **BCR:** Biochemical recurrence, **BMI:** Body mass index, **PV:** Prostate volume, **GS:** Gleason score, **PNI:** Perineural invasion, **PSM:** Positive surgical margin, **EPE:** Extraprostatic extension, **SVI:** Seminal vesicle invasion, **LNI:** Lymph node invasion*

Table 2: Results of the univariate and multivariate analyses

	Univariate			Multivariate		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
PSA	1.233	1.103-1.444	**0.03**	1.502	1.470-1.602	**0.037**
Biopsy GS	2.112	1.077-4.322	**0.04**			
Risk	7.553	4.143-11.162	**<0.001**	4.278	2.165-6.244	**0.025**
Specimen results						
GS	2.774	1.278-4.322	**0.01**	1.322	1.032-3.228	**0.041**
PSM	9.997	7.163-13.554	**<0.001**	14.554	8.563-18.224	**<0.001**
EPE	6.554	5.322-8.133	**0.012**			
SVI	9.199	7.888-11.203	**0.02**	4.322	2.655-6.433	**0.047**
LNI	3.444	2.056-7.544	**0.039**			
T stage	3.555	2.465-6.233	**0.01**	4.588	3.988-6.122	**0.048**

***HR:** Hazards ratio, **CI:** Confidence interval, **GS:** Gleason score, **PSM:** Positive surgical margin, **EPE:** Extraprostatic extension, **SVI:** Seminal vesicle invasion, **LNI:** Lymph node invasion*

DISCUSSION

The cancer control indicators following RP include pathologically organ-confined disease with negative margins, BCR, local invasion, metastases, and overall and cancer-specific survival (5). BCR is often the earliest marker of tumor recurrence after RP (15). The development of BCR after RP may be relevant to higher rates of metastasis and mortality (16). The rate of the BCR was 27% in a study with a 10-year follow-up after RP (17). Therefore, it is important to establish preoperative predictive models and risk classification systems for BCR.

After RP, the interval between BCR and metastasis development has been reported as 8 years, from metastatic disease to mortality as 5 years (15). BCR is one of the most important markers of mortality. For this reason, it is important to manage alternatives such as close follow-up and early intervention (18). In the last few decades, more recent models, e.g., the CAPRA score, have been developed to replace older methods, such as the Kattan nomograms and Han tables (8, 16, 19, 20). Researchers have also attempted to strengthen such models by integrating the findings from the developing mpMRI technology and molecular evaluations (10, 21–23).

Wald et al. revealed a correlation between early BCR, preoperative serum PSA levels, and specimen GS, PSM, EPE, SVI, and LNI (24). Another study on BCR showed that GS detected in the specimen and the pathological stage was closely related to BCR (25). Similarly, Tağcı et al. reported a relationship between LNI and early BCR (26) another study by Ekşi et al., risk classification, mpMRI findings, PSM, SVI, and T stage were noted as significant parameters predicting BCR (11). In our study, the multivariate analysis revealed PSA, risk classification, specimen GS, PSM, SVI, and T stage to be the predictive parameters of BCR. In addition to the nomograms established for this purpose, more advanced algorithms can be created by integrating artificial intelligence and machine learning methods into hospital information systems (5, 11). We consider that as the external validation of such created models is undertaken and current knowledge increases, there will be more common and widely accepted models that can predict BCR.

The large scope of our patient selection criteria and the relatively adequate follow-up period in terms of BCR development are the main advantages. The retrospective nature is the main limitation of our study.

CONCLUSION

The parameters that predicted the development of BCR in the postoperative period in the patients who underwent RARP for PCa were determined as PSA, risk classification, specimen GS, PSM, SVI, and T stage. The widespread use of commonly accepted methods will help achieve better patient management and optimize patient expectations.

Conflict of Interest: The authors declare to have no conflicts of interest.

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Ethical Approval: The study was approved by the Ethic Committee of Health Science University, Ümraniye Training and Research Hospital (Approval Number: 233, Date: 23/06/2022). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

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