The relationship between the CAPRA-S and the time of biochemical recurrence following radical prostatectomy

CAPRA-S ile radikal prostatektomi sonrası biyokimyasal rekürrens zamanı arasındaki ilişki

Süleyman Tağcı[1], Cüneyt Özden[1], Yalçın Kızılkan[1], Samet Şenel[1], Doruk Demirel[1], Binhan Kağan Aktaş[1], Cevdet Serkan Gökkaya[1], Süleyman Bulut[1]

1 University of Health Sciences, Ankara Numune Health Research Center, Department of Urology, Ankara, Turkey

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Yazışma / Correspondence
Samet Şenel
Hacettepe, Ülkü Mah. Talatpaşa Blv. No: 44, 06230, Altındağ
Ankara / Turkey
Email: samet_senel_umt@hotmail.com
Phone:+90 537 880 22 85

ORCID

S.T.	0000-0002-5763-8916
C.Ö.	0000-0003-0101-6904
Y.K.	0000-0002-4729-0100
S.Ş.	0000-0003-2280-4192
D.D.	0000-0002-7670-9003
B.K.A.	0000-0003-0707-9308
C.S.G.	0000-0002-1466-6490
S.B.	0000-0002-7607-129X

Özet

Amaç: Radikal prostatektomi (RP) sonrası biyokimyasal nüks süresi ile "ameliyat sonrası prostat risk değerlendirme" skoru (CAPRA-S) arasındaki ilişkiyi değerlendirmek.

Gereç ve Yöntemler: Klinik lokalize prostat kanseri tanısı nedeniyle RP uygulanan 328 hastanın verileri retrospektif olarak değerlendirildi. Hastalar preoperatif PSA düzeyine ve RP spesmeninin patolojik özellikleri ve RP sonrası biyokimyasal nükse kadar geçen süre ile belirlenen CAPRA-S skoruna göre gruplara ayrıldı.

Bulgular: Ortalama takip süresi 76.9 ± 34.5 aydı. Biyokimyasal nüks, olguların % 23,2'sinde (n: 69) saptandı. Bunların % 71'inde (n: 49) erken, % 29'unda (n: 20) geç nüks saptandı. CAPRA-S skoruna göre 186 (% 62,4) hasta düşük riskli, 66 (% 22,1) orta riskli ve 46 (% 15) hasta yüksek riskli olarak sınıflandırıldı. Tüm hastaların 3 ve 5 yıllık biyokimyasal nükssüz sağkalım oranları sırasıyla % 88,9 ve % 81,8 olarak belirlendi. Düşük CAPRA-S skoruna sahip hastaların, orta ve yüksek gruptaki hastalara göre istatistiksel olarak anlamlı derecede daha yüksek 3 ve 5 yıllık biyokimyasal nükssüz sağkalım oranına sahip olduğu belirlendi. RP sonrası erken biyokimyasal rekürrensin sadece lenf nodu tutulumu ile istatistiksel olarak anlamlı korelasyon gösterdiği belirlendi (OR: 2.42, % 95 CI: 1.07-5.47, p = 0.03).

Sonuç: Bu çalışmanın sonuçları, RP sonrası biyokimyasal rekürrens riskini tahmin etmede etkili olan CAPRA-S skorunun RP sonrası biyokimyasal rekürrens zamanını tahmin etmede etkili olmadığını göstermiştir.

Anahtar Kelimeler: Biyokimyasal nüks, CAPRA-S skoru, prostat kanseri, radikal prostatektomi

Abstract

Objective: In this study, we aimed to evaluate the relationship between biochemical recurrence time and the "cancer of the prostate risk assessment post-surgery" score (CAPRA-S) after radical prostatectomy (RP).

Material and Methods: Retrospective evaluation was made of the records of 328 patients applied with RP for a diagnosis of clinically localized prostate cancer. The patients were separated into groups according to the CAPRA-S score determined according to the preoperative PSA level and pathological characteristics of the RP specimen and the biochemical recurrence time after RP.

Results: The mean follow-up period was 76.9±34.5 months. Biochemical recurrence was determined in 23.2% (n:69) of the cases, as early recurrence in 71% (n:49) and late in 29% (n:20). According to the CAPRA-S score, 186 (62.4%) patients were classified as low risk, 66 (22.1%) as moderate risk, and 46 (15%) as high risk. The 3 and 5-year BRFS rates of all the patients were 88.9% and 81.8% respectively. Patients with a low CAPRA-S score were determined to have a statistically significantly higher 3 and 5-year BRFS rate than patients in the moderate and high groups. Early biochemical recurrence after RP was statistically significantly correlated only with lymph node involvement (OR: 2.42, 95% CI: 1.07-5.47, p=0.03).

Conclusion: This study showed that the CAPRA-S score, which is effective in predicting the risk of biochemical recurrence after RP, was not effective in predicting the time of biochemical recurrence after RP.

Keywords: Biochemical recurrence, CAPRA-S score, prostate cancer, radical prostatectomy

This study was approved by the Clinical Research Ethics Committee of Ankara Numune Training and Research Hospital (Approval number: E16-757. Date: Feb 4,2016). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Prostate cancer is the most common cancer in males and the second most common, leading to death after lung cancer. The lifetime risk of having prostate cancer is high at 14% (1). The treatment method selected for clinically local stage prostate cancer is radical prostatectomy (RP) operation for patients with a suitable general condition and life expectancy (2). Local recurrence-free follow-up rates have been reported 83.9% for five years and 75.6% for ten years in patients with localized prostate cancer treated with RP (3). Biochemical recurrence (BR) develops in a third of patients applied with RP, and the time of BR is just as important as the risk of development (4). BR in the early stage after RP has been associated with an increased mortality risk specific to prostate cancer (5). Therefore, knowing the factors related to early BR after RP is important in determining treatment and follow-up protocols for the patients.

The "cancer of the prostate risk assessment post-surgery" score (CAPRA-S), which was defined to predict the risk of BR development after RP, is calculated using the six postoperative parameters. Those are prostate-specific antigen (PSA), the Gleason score (GS) in the RP specimen, surgical margin positivity (SMP), seminal vesicle invasion (SVI), extracapsular involvement (ECI) and regional lymph node involvement (LNI) (6). In recent years, the CAPRA-S score has become more widely used predictig of the development of BR after RP (7,8). However, there is no clear information in the literature about the relationship between the CAPRA-S score and the time of BR after RP.

It is known that "the cancer of the prostate risk assessment post-surgery" score can predict the risk of BR, but no data about BR time. So, this study aimed to examine the relationship between the CAPRA-S score and the time of BR following RP surgery applied to patients because of prostate cancer.

MATERIAL AND METHODS

This study was performed following the principles of the Helsinki Declaration and was approved by the Clinical Research Ethics Committee of Ankara Numune Training and Research Hospital on February 04, 2016 (Approval no: E-16-757).

This retrospective study included 328 patients who underwent RP to diagnose localized prostate cancer in our clinic between January 2000 and May 2014. A total of 30 patients were excluded as postoperative adjuvant radiotherapy was applied to 12 patients and, 18 patients did not attend postoperative follow-up appointments. The clinical and pathological data of the remaining 298 patients were examined retrospectively. Four different surgeons performed the operations. All surgeons had 10-15 years of experience. Extended lymph node dissection was performed in all cases. The 2002 TNM grading system was used in clinical and pathological grading. Clinical grading of the patients was made with the digital rectal examination, serum PSA value, pulmonary radiograph, whole-body bone scintigraphy and, pelvic radiological imaging. The indication for surgical treatment was made for patients evaluated as prostate cancer limited to the organ in the clinical grading.

There were no findings of metastasis in the clinical and radiological examinations of the patients. No patient was receiving hormonal treatment or radiotherapy preoperatively. RP and pelvic lymphadenectomy were applied to patients with localized prostate cancer with a life expectancy of >10 years and who had no comorbid disease that would hinder the operation. Surgical material was evaluated in respect of GS, ECI, SVI, and SMP. In the pathology examination of the surgical material, those with tumor cells seen within the surgical border were reported as SMP, overflow from the prostate capsule as ECI, infiltration of the muscular wall by seminal vesicles as SVI, and patients with no prostate capsule involvement as organ-restricted.

The CAPRA-S scores were calculated for the patients. Three groups were formed as patients with a CAPRA-S score of <3 as mild, those with a score of 3-5 as moderate and, those with a score >5 as high risk. Postoperatively, the patients were called for follow-up examinations, once every three months in the first year, at six-month intervals for five years, and annually after that. BR was accepted as a serum PSA level of ≥0.2ng/mL in two consecutive measurements (at an interval of at least one month) after RP. The patients were separated into two groups according to the time of BR; Group 1 included patients with BR time <24 months and Group 2, patients with BR time ≥24 months.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS for Windows 18.0 software. The Chi-square test was applied to categorical data and the Mann Whitney U-test to numerical data in the comparisons between the groups. In the evaluation of factors affecting BR, univariate and multivariate Cox Regression analyses were applied. The relative risk and the 95% confidence interval were calculated for each independent variable. Kaplan Meier and Log Rank analysis were used for the evaluation of BR-free survival (BRFS). A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The clinical and pathological parameters of all the patients are shown in Table 1. The distribution of points according to the levels of the six parameters that form the CAPRA-S score of the patients is shown in Table 2. According to the CAPRA-S scores, 62.4% (n:186) formed the low-risk group, 22.1% (n:66) the moderate-risk group, and 15% (n:46) the high-risk group. The mean follow-up period was 76.9±34.5 months. Throughout this follow-up period, BR was determined in 23.2% (n:69) of the patients. Of these, BR was seen early (<24 months) in 71% (n:49), and late (≥ 24 months) in 29% (n:20). No statistically significant difference was determined between the early and late BR patients regarding mean age, prostate volume, biopsy GS, PSA level, GS in the RP specimen, pathological grade, ECI, SVI, LNI, SMP, and CAPRA-S score (Table 3).

The three and five-year BRFS rates of all the patients were 88.9% and 81.8%, respectively. The mean BRFS was determined as 115.9±3.4 months (95% CI:109.4-122.6). The three and five-year BRFS rates of patients with a low CAPRA-S score were determined to be statistically significantly higher than those of patients in the groups with moderate and high CAPRA-S scores (p=0.0001, Kaplan Meier) (Table 4, Figure 1).

In the univariate Cox regression analysis, early BR was statistically significantly correlated only with LNI (OR:2.42, 95% CI:1.07-5.47, p=0.03). Early BR time after RP was not correlated with the preoperative PSA level, ECI, SVI, SMP, GS in the RP specimen, and the CAPRA-S score risk group (Table 5).

Table 1. The Clinical and Pathological Features of Patients

	Average ±SD
Age (year)	62.7 ± 6.3
PSA (ng/ml)	10.4 ± 6.5
Prostate Volume (mL)	46.2 ± 22.4
GS in the Biopsy	5.74±1.33
GS in the RP Specimen	6.1±1.4
Clinical Stage	**n (%)**
cT1a	14 (4.7)
cT1b	28 (9.4)
cT1c	130 (43.6)
cT2a	71 (23.8)
cT2b	39 (13.1)
cT2c	16 (5.4)
Pathological Stage	
pT0	2 (0.7)
pT2a	90 (30.2)
pT2b	55 (18.5)
pT2c	64 (21.5)
pT3a	59 (19.8)
pT3b+T4	28 (9.4)
SMP	61 (20.5)
LNI	10 (3.4)

***PSA:** Prostate Spesific Antigen, **RP:** Radical Prostatectomy,*
***GS:** Gleason Score, **SMP:** Surgical Margin Positivity, **LNI:** Lymph Node Involvement*

Table 2. Distribution of the Patients According to the Level of CAPRA-S Score Parameters

Parameters	Level	Points	n (%)
Prostate Spesific Antigen (ng/ml)	0-6	0	83 (27.9)
	6.01-10	1	94 (31.5)
	10.01-20	2	92 (30.9)
	>20	3	29 (9.7)
Gleason Score in the Radical Prostatecomy Specimen	≤6	0	217 (72.8)
	3+4	1	22 (7.4)
	4+3	2	27 (9.1)
	≥8	3	32 (10.7)
Surgical Margin Positivity	Negative	0	237 (79.5)
	Positive	2	61 (20.5)
Extracapsular Involvement	Negative	0	222 (74.5)
	Positive	1	76 (25.5)
Seminale Vesicle Invasion	Negative	0	270 (90.6)
	Positive	2	28 (9.4)
Lymph Node Involvement	Negative	0	288 (96.6)
	Positive	1	10 (3.4)

Table 3. The Datas of the Patients with Early and Late Biochemical Recurrence

	Early BR (n=49)	Late BR (n=20)	p
Age (year)	64.41±5.80	61.70±5.6	0.83*
PSA (ng/ml)	12.50±7.54	13.81±6.55	0.50*
Prostate Volume (mL)	43.27±19.86	35.79±11.52	0.12 *
GS in the biopsy	6.57±1.39	6.20±1.61	0.34 *
PSA Level (ng/ml)			
<10	24 (49%)	7 (35%)	
10-20	16 (32.7%)	10 (50%)	
>20	9 (18.4%)	3 (15%)	0.39**
GS in the RP Specimen			
GS≤6	19 (38.8%)	5 (25%)	
GS=7 (3+4)	10 (20.4%)	4 (20%)	
GS=7 (4+3)	3 (6.1%)	2 (10%)	
GS≥8	17 (34.7%)	9 (45%)	0.69**
Pathological Stage			
pT2a	3 (6.1%)	2 (10%)	
pT2b	7 (14.3%)	2 (10%)	
pT2c	7 (14.3%)	3 (15%)	
pT3a	15 (30.6%)	7 (35%)	
pT3b+T4	17 (34.7%)	6 (30%)	0.95**
ECI	28 (57.1%)	10 (50%)	0.59**
SVI	17 (34.7%)	6 (30%)	0.71**
LNI	7 (14.3%)	1 (5%)	0.27**
SMP	29 (59.2%)	11 (55%)	0.75**
CAPRA-S Score			
Low	9 (18.4%)	2 (10%)	
Modarate	16 (32.7%)	8 (40%)	
High	24 (49%)	10 (50%)	0.66**

Mann-Whitney U test* ***Chi-Square test* ***PSA:* *Prostate Spesific Antigen,*
RP: *Radical Prostatectomy,* ***GS:*** *Gleason Score,* ***SMP:*** *Surgical Margin Positivity,* ***LNI:*** *Lymph Node Involvement* ***ECI:*** *Extracapsular Involvement,* ***SVI:*** *Seminal Vesicle Invasion,* ***LNI:*** *Lymph Node Involvement,* ***SMP:*** *Surgical Margin*

Positivity

Table 4: BRFS Times and Rates of the Patients According to the CAPRA-S Score Groups

CAPRA-Score Groups	BRFS rates (3 years) (%)	BRFS rates (5 years) (%)	Average BRFS time (month)	%95 CI (Min-Max)
Low	94.6	94.6	139.6±2.5	134.8-144.5
Modarate	65.3	62.7	88.03±7.1	74.0-102.0
High	39.0	30.4	44.5±7.3	30.1-58.9

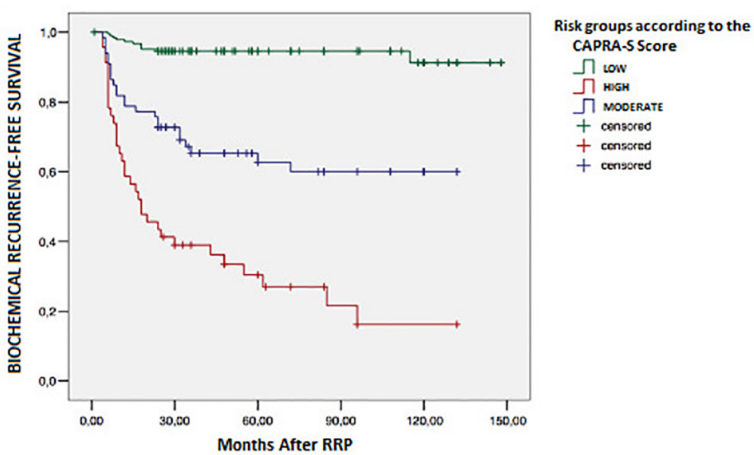
BRFS: *Biochemical Recurrence-free Survival*

Table 5: Univariate Cox regression analysis of factors associated with early BR time after RP

	OR	p	%95 CI (Min-Max)
PSA (ng/ml)		0.58	
<10	1	-	-
10-20	0.72	0.32	1.36
>20	0.99	0.98	2.13
ECI	1.25	0.43	2.21
SVI	1.19	0.55	2.15
LNI	2.42	**0.03**	**5.47**
SMP	0.86	0.60	1.5
GS in RP specimen		0.96	
GS≤6	1	-	-
GS=7 (3+4)	0.91	0.81	1.9
GS=7 (4+3)	0.84	0.77	2.8
GS≥ 8	0.85	0.61	1.6
CAPRA-S risk gropus		0.98	
Low	1	-	-
Modarate	0.95	0.91	2.17
High	1.0	0.99	2.16

PSA: *Prostate Spesific Antigen,* ***RP:*** *Radical Prostatectomy,* ***OR:*** *Odds Ratio,* ***GS:*** *Gleason Score,* ***SMP:*** *Surgical Margin Positivity,* ***LNI:*** *Lymph Node Involvement,* ***ECI:*** *Extracapsular Involvement,* ***SVI:*** *Seminal Vesicle Invasion,* ***LNI:*** *Lymph Node Involvement,* ***SMP:*** *Surgical Margin Positivity*

Figure 1. Biochemical ı ?RA-S scores.



RRP: Retropubic Radical Prostatectomy

DISCUSSION

Radical prostatectomy is the treatment method most frequently applied to patients who have prostate cancer clinically restricted to the organ and have a life expectancy of >10 years (9). In the follow-up period following RP, BR develops in 20%-30% of patients with increased PSA without any clinical or radiological findings of metastasis (10,11). BR develops in the early period, within the first two years after RP, in approximately two-thirds of patients (12,13). Consistent with the findings in the literature, BR was determined in 23.2% of the current study patients after RP, and of these patients, early BR was seen in 71% (n:49).

If early diagnosis and treatment are not applied, and thus no curative treatment, to patients who develop BR after RP, the metastatic disease can develop. Knowledge of the factors associated with early BR after RP is important in respect of follow-up of the patients and the determination of treatment protocols. Patients at risk of BR development after the primary treatment of localized prostate cancer have been identified using some clinical and pathological parameters (14,15). The CAPRA-S score has become more widely used in recent years to predict the risk of development of BR following RP. With extensive, multicentric, comparative studies, the CAPRA-S score has been externally validated, and the score's predictive power for BR after RP has been confirmed (7,8). A recent study of CAPRA-S score low, moderate, and high-risk groups reported the five-year BRFS rates to be 92.5%, 72.6%, and 32.8%, respectively (16). Similarly, in the current study, the 5-year BRFS rates of the low, moderate, and high-risk groups were 94.6%, 62.7%, and 30.4%, respectively.

The time of BR after RP is just as important as the risk of developing BR. The development of BR in the early period after RP is associated with an increased mortality risk specific to prostate cancer. However, no study in the literature has evaluated the relationship between the CAPRA-S score and the time of BR after RP. Freedland et al. reported that the 15-year survival rate specific to prostate cancer was 41% in patients with BR development <3 years after RP, and 87% in those with BR seen at >3 years after RP. According to the univariate analysis of that study, it was reported that the prostate cancer-specific mortality risk decreased by 24% with each year of delay in the development of BR after RP (5). Pound et al. showed that there was 20% more progression to metastatic disease in patients with BR at <2years after RP than those who developed BR at >5 years (17).

In recent years, studies have been conducted to determine factors related to aggressive (<9-12 months) BR after RP, early (<2 years), and late (>2 years) BR. Shahabi et al. determined GS =7 (3+4) in the RP specimen of 41% of patients seen with early BR (<2.9 years) and GS≤6 in 40% of patients with late BR (>2.9 years). According to the multivariate analysis, GS ≥ 7, SMP, and pathological T3a grades were associated with early BR (18). In the current study, GS≤6 in the RP specimen was determined in 38% of the patients seen with early BR, and GS≥8 in 45% of the patients with late BR.

In a study by Wald et al. there was determined to be a significant relationship between early BR (for both < 1 year and < 2 years) and preoperative serum PSA level, GS in the RP specimen, SMP, ECI, SVI, and LNI (19). Sundi et al. determined that a pattern of 4 from 4 or 5 cords of the primary pattern of GS in the biopsy was an independent risk factor associated with early BR (< 1 year) (20). Marius et al. reported that preoperative serum PSA level of >10 ng/ml, pathological grade pT3, GS >7 in the RP specimen, and SMP were independent risk factors related to early BR (<1 year) (21). In a study by Joseph et al., the GS in the RP specimen and pathological grade were related to BR time after RP (median 6.7 months) (22). In the current study, no statistically significant difference was determined between patients seen with early or late BR after RP in respect of mean age, serum PSA level prostate volume, biopsy GS, clinical grade, GS in the RP specimen, pathological grade, ECI, SVI, LNI, SMP, and the CAPRA-S score. In the univariate analysis of the factors related to early BR after RP, a statistically significant relationship was only determined between BR development and LNI.

There are some limitations to our study. Our study was conducted retrospectively. It is a handicap that a single surgeon performs not all operations. Another problem is that not all patients have the same follow-up period. However, we still think that this study will contribute to the literature in this way.

CONCLUSION

In conclusion, the results of this study showed that the CAPRA-S score, which is effective in predicting the risk of biochemical recurrence after RP, was not effective in predicting the time of biochemical recurrence after RP. BRFS in patients with low CAPRA-S was significantly higher than in the intermediate and high groups. In addition, a positive correlation was found between early BR time and LNI.

Conflict of Interest

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by the Non-invasive Clinical Research Ethics Committee of Ankara Numune Training and Research Hospital (Approval number: E-16-757. Date: Feb 4, 2016) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; ST, CÖ, Data acquisition; ST, BKA, Data analysis and interpretation; CÖ, DD, CSG, SB, Drafting the manuscript; ST, YK, Critical revision of the manuscript for scientific and factual content; CÖ, SŞ, BKA, CSG, Statistical analysis; DD, Supervision; SŞ, DD.

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