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Survival Analysis and Prognostic Factors in Prostate Cancer Patients: A Single Center Experience in Eastern Anatolia

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Abstract

Objective: Prostate cancer (PC), one of the most common malignancies of the urogenital tract, is more common in older men and shows significant prognostic differences among individuals. In recent years, new grade groups and American Joint Committee on Cancer (AJCC) stage groups have been used to predict prognosis. However, there is limited information on the prognostic significance of this new system in PC patients in Turkey. In this study, we aimed to evaluate the follow-up results of patients with diagnosis of PC, and the clinical significance of the new prognostic staging system in this patient population in Eastern Anatolia Region.

Methods: Retrospectively, 141 PC patients being followed up in Erzurum Ataturk University of Medical Oncology Department were included in this study. The relationships between overall survival (OS) and progression free survival (PFS) and clinical-pathological parameters were analysed using Kaplan-Meier curves and compared with the log-rank test. Univariate and multivariate analysis were used to determine the prognostic significance of clinical and pathologic variables for PFS and OS.

Results: The median age of patients was 69 and the majority of them were stage IV patients (79.4%). The median value of prostate specific antigen (PSA) was 39 ng/mL and the median Gleason score was 8. The majority of the patients had PSA value of ≥ 20 ng / ml (61.7%) and Gleason grade group 5 (35.5%). The median PFS and OS values were 29 and 33 months, respectively. The 5-year survival rates were 50% for local-locoregional disease and 20% for metastatic disease. PFS and OS were longer in patients with good Eastern Cooperative Oncology Group (ECOG) performance status (0-1), early stage (I-II), undergone to surgery, having low PSA (< 10 ng / ml) and low Gleason group (1-2). According to the multivariate analysis; stage, PSA and Gleason grade group were independent prognostic factors for both PFS and OS.

Conclusion: The new grading system, PSA and AJCC staging system are independent prognostic factors in patients with PC. Considering that patients in our region have shorter life spans compared to the world, these prognostic factors should be used more effectively in daily practice in determination of treatment strategy.

Keywords: Gleason grade group, Prostate cancer, PSA

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Prostat Kanserli Hastalarda Sağkalım Analizi ve Prognostik Faktörler: Doğu Anadolu Tek Merkez Deneyimi

Öz

Amaç: Ürogenital traktın sık görülen malignitelerinden biri olan prostat kanseri (PK) özellikle ileri yaş erkeklerde daha yaygındır ve bireyler arasında önemli prognoz farklılıkları göstermektedir. Son yıllarda prognozu öngörmek için yeni grade grupları ve Amerikan Kanser Komitesi (AJCC) evre grupları kullanılmaya başlanmıştır. Ancak ülkemizde PK'lı hastalarda bu yeni sistemin prognostik önemini gösteren bilgiler sınırlıdır. Bizde bu çalışmada ülkemiz Doğu Anadolu Bölgesinde PK tanısıyla takip edilen hastaların hem takip sonuçlarını hem de yeni prognostik evreleme sisteminin klinik önemini ortaya koymayı amaçladık.

Yöntemler: Erzurum Atatürk Üniversitesi Tıp Fakültesi Tıbbi Onkoloji Bilim Dalı'nda PK tanısıyla takip edilen 141 hasta çalışmaya retrospektif olarak dahil edildi. Genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) ile klinik-patolojik parametreler arasındaki ilişkiler Kaplan-Meier eğrileri kullanılarak analiz edildi ve log-rank testi ile karşılaştırıldı. Tek ve çok değişkenli analiz klinik-patolojik değişkenlerin PFS ve OS için prognostik önemlerini belirlemekte kullanıldı.

Bulgular: Çalışmadaki hastaların medyan yaşı 69'du ve çoğunluğunu evre IV (%79,4) vakalar oluşturuyordu. Hastaların medyan prostat spesifik antijen (PSA) değeri 39 ng/mL, medyan Gleason skoru ise 8'di. Çalışmada PSA değeri ≥ 20 ng/mL (%61,7) olan ve Gleason grade grubu 5 (%35,5) olan hastalar çoğunluktaydı. Medyan PFS 29 ay ve medyan OS 33 aydı, 5 yıllık yaşam oranları lokal-lokorejyonel hastalık için %50, metastatik hastalık için %20 idi. ECOG performans durumu iyi olanların (0-1), cerrahi yapılanların, erken evrede (I-II) olanların, düşük PSA'sı (< 10 ng/mL) olanların ve Gleason grubu düşük olanların (1-2) PFS ve OS'si daha uzundu. Multivariate analizde evre, PSA ve Gleason grade grubu hem PFS hem de OS için bağımsız prognostik faktör olarak bulundu.

Sonuç: PK'lı hastalarda yeni grade sistemi, PSA ve AJCC evreleme sistemi bağımsız prognostik faktörlerdir. Bölgemizdeki hastaların dünya geneline göre daha kısa yaşam sürelerine sahip oldukları göz önünde bulundurulduğunda hastaların tedavi stratejisini belirlemede bu prognostik faktörler günlük pratikte daha etkin olarak kullanılmalıdırlar.

Anahtar kelimeler: Gleason grade grup, Prostat kanseri, PSA.

INTRODUCTION

Prostate cancer (PC) is one of the solid organ malignancies with increasing incidence in advanced age. PC is the second most common cancer in men, and constitutes an important fraction of cancer-related deaths[1]. Although the incidence varies between countries, it is known that there were 174650 new cases of PC cancer in the United States in 2019, and approximately 31620 patients died as a result of this malignancy[2]. In Far Eastern countries, e.g. Japan, PC incidence has increased over the years[3]. PC is the third most common cancer among all cancers in our country (8.2%)[4]. According to GLOBOCAN data, 17000 new cases of PC were diagnosed in Turkey in 2018. As stated by this data, PC has an annual death rate of 4.4%[4].

Although there is no single etiological factor of PC, many factors such as age, family history, genetic factors, diet, obesity and environmental factors have been associated with PC[5]. Curative treatment options for local / locoregional disease include radical prostatectomy (RP), external beam radiotherapy, and brachytherapy[5]. Androgen deprivation therapy (ADT) forms the basis of adjuvant therapy in high-risk patients[5]. Although good treatment response is obtained with ADT in a limited patient group in metastatic disease, the majority of PC patients become resistant to castration[6,7]. In addition to conventional cytotoxic chemotherapies such as docetaxel and cabazitaxel, new antihormonal drugs such as abiraterone, enzalutamide and immunotherapy agents such as pembrolizumab are among the treatment options[8-13]. The use of Sipuleucel-T is possible in asymptomatic or mildly symptomatic patients with chemotherapy naive metastatic castration resistant prostate cancer (mCRPC)[5]. Radium-223 is recommended for men with bone-predominant, symptomatic, and mCRPC without visceral metastases[5]. Despite these new treatment modalities emerged in recent years besides standard treatments, PC is

still a heterogeneous disease with significant prognostic and treatment response differences among individuals. Therefore, it is important to predict prognosis of the disease at the time of diagnosis. In many studies; advanced stage, increased tumor diameter, high Gleason score and high prostate specific antigen (PSA) values were found to be associated with poor prognosis and shorter survival[14]. Although some prognostic nomograms have been developed by including parameters of age, Eastern Cooperative Oncology Group (ECOG) performance score, visceral metastasis, hemoglobin, PSA, lactate dehydrogenase, alkaline phosphatase, and albumin[15,16], American Joint Committee on Cancer (AJCC) 8th edition, which is generally acknowledged in current guidelines, includes stage, PSA and Gleason grade as prognostic parameters[17,18]. There are limited number of studies showing the clinical importance of the new prognostic grouping system updated in 2017, for our country. In addition, there is no study demonstrating the follow-up results of PC patients in the Eastern Anatolia Region. Therefore, in this study we aimed to demonstrate both follow-up results and clinical significance of the new prognostic staging system in PC patients in our region.

METHODS

Total 141 patients have been followed up in Erzurum Atatürk University Medical Oncology Clinic between January 2013 and June 2019 were included in this study, retrospectively. Demographic, clinical and histopathological features such as age, ECOG performance status, stage, PSA value, Gleason pattern, metastasis status, treatment modality and treatment response, were obtained from archive file records and electronic recording system of our hospital. According to the International Society of Urological Pathology (ISUP) consensus report, patients were divided into grade 1 (≤ 3 + 3), grade 2 (3 + 4), grade 3 (4 + 3), grade 4 (4 + 4, 3 + 5, 5 + 3) and grade 5 (4 + 5, 5 + 4, 5 + 5) groups based on Gleason patterns[19]. In addition, patients were divided into three groups namely < 10, ≥ 10-20, and ≥ 20 ng / mL, according to PSA results[19]. Patients were staged according to AJCC 8th edition prognostic groups[17,18].

In this study, all procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics committee approval was obtained from the ethics committee of Erzurum Ataturk University (Approval number: 08/27-26.12.2019).

Statistics

Overall survival (OS) was calculated from the date of diagnosis to the date of death, and censored at the date of last follow-up for survivors. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of recurrence or death, and censored at the date of last follow-up for survivors without recurrence. Associations between clinical-demographical and histopathological parameters with PFS and OS were analyzed by using Kaplan–Meier curves and compared by the log-rank test. Univariate and multivariate cox-regression analyses were performed to determine effects of possible prognostic factors; including age, ECOG, surgery, AJCC TNM stage, PSA, Gleason grade group, metastasis and metastasis area, for both PFS and OS. Hazard ratios (HRs) estimated from the Cox analysis were reported as relative risks with corresponding 95% confidence intervals (CIs). All analyses were performed using the SPSS statistical software package (SPSS statistics 21.0). A p value of < 0.05 was considered as statistically significant.

Table I: Clinical and demographic characteristics of prostate cancer patients.

	n (%)
Age	
≤ 65	47 (33.3)
> 65	94 (66.7)
ECOG	
0-1	72 (51)
2	41 (29.1)
3	28 (19.9)
Surgery	
Yes	29 (20.6)
No	112 (79.4)
Palliative radiotherapy	
Yes	72 (51.1)
No	69 (48.9)
AJCC TNM stage	
I	8 (5.7)
II	11 (7.8)
III	10 (7.1)
IV	112 (79.4)
PSA	
< 10	38 (27)
≥ 10-20	16 (11.3)
≥ 20	87 (61.7)
Gleason grade group	
1	25 (17.7)
2	8 (5.7)
3	23 (16.3)
4	35 (24.8)
5	50 (35.5)
Metastasis	
Var	112 (79.4)
Yok	29 (20.6)
Metastasis region	
Bone	75 (67)
Lung	7 (6.3)
Liver	9 (8)
Other	21 (18.7)
Treatment regimens	
Dosetaksel	62 (43.8)
Abirateron	21 (14.9)
Enzalutamid	16 (11.3)
Kabazitaksel	5 (3.5)
Lu-177	5 (3.5)
Progression	
Yes	109 (77.3)
No	32 (22.7)
Status	
Alive	44 (31.2)
Death	97 (68.8)

ECOG: Eastern Cooperative Oncology Group Performance Status, AJCC: American Joint Committee on Cancer, PSA: Prostate Specific Antigen

At the time of analysis, the median PFS and OS values were 29 and 33 months, respectively (Table II). Patient groups with ECOG scores of 0-1, 2, and 3, had PFS durations of 41, 27, and 22 months and OS durations of 50, 28, and 22 months respectively. The difference between the groups was significant only for OS duration (p: 0.026), but not significant regarding PFS duration (p: 0.069).

Both PFS (37 vs 25 months, p: 0.004) and OS (82 vs 29 months, p: 0.001) were longer in patients who underwent RP. The differences between the stage groups (I vs II vs III vs IV) were statistically significant for both PFS (82 vs 79 vs 48 vs 24 months, p: 0.004) and OS (105 vs 83 vs 49 vs 29 months, p: 0.004). Differences between the groups with PSA values < 10 ng / mL, ≥ 10-20 ng / mL and ≥ 20 ng / mL were significant in terms of both PFS (79 vs 28 vs 21 months, p< 0.001) and OS (87 vs 39 vs 27 months, p< 0.001) (Figure 1). When the Gleason grade groups (1, 2, 3, 4 and 5) were compared, both PFS (81, 52, 32, 29 and 17 months, respectively) and OS durations (98, 64, 49, 39, and 20 months, respectively) were decreasing as the grade were increasing (p: 0.001, p: 0.013, respectively) (Figure 2). Patients with metastasis had shorter PFS and OS durations compared to patients without metastasis (PFS: 27 vs 79 months, p: 0.016, and OS: 32 vs 82 months, p: 0.018).

A Cox proportional hazards model was used to evaluate the potential predictors as seen in Table III. The univariate analysis revealed that PFS was significantly associated with ECOG, surgery, stage, PSA and Gleason grade group (p: 0.023, p: 0.004, p: 0.001, p< 0.001, p< 0.001, respectively). The univariate analysis revealed that OS was significantly associated with ECOG, surgery, stage, PSA and Gleason grade group (p: 0.008, p: 0.001, p: 0.001, p< 0.001, p: 0.002, respectively).

In multivariate analysis, for both PFS and OS, stage (p: 0.022 and p: 0.044, respectively), PSA (p: 0.015; and p: 0.021, respectively), Gleason grade group (p< 0.001 and p: 0.010, respectively) were found as independent prognostic factors.

Table II: The relationship of clinical-demographic characteristics with progression-free survival and overall survival

	Total (n)	Total (%)	PFS			OS		
			Mean	Median	p	Mean	Median	p
Age								
≤ 65	47	33.3	37.1	25	0.180	52	29	0.334
> 65	94	66.7	55.4	32		68	37	
ECOG								
0-1	72	51	52.1	41	0.069	67.8	50	**0.026**
2	41	29.1	50.6	27		60.1	28	
3	28	19.8	34.2	22		41	22	
Surgery								
Yes	29	20.6	66.6	37	**0.004**	89.7	82	**0.001**
No	112	79.4	33.3	25		41.2	29	
AJCC TNM stage								
I	8	5.7	124.7	82	**0.004**	157.7	105	**0.004**
II	11	7.8	64.9	79		75.1	83	
III	10	7.1	59.3	48		72.6	49	
IV	112	79.4	42.1	24		50.1	29	
PSA								
< 10	38	27	107.2	79	**< 0.001**	115.5	87	**< 0.001**
≥ 10-20	16	11.3	51.8	28		62.7	39	
≥ 20	87	61.7	35.2	21		46.4	27	
Gleason grade group								
1	25	17.7	69.3	81	**0.001**	71.1	98	**0.013**
2	8	5.7	60.5	52		66	64	
3	23	16.3	58.7	32		71.7	49	
4	35	24.8	45.4	29		63.3	39	
5	50	35.5	29.7	17		42.2	20	
Metastasis								
Yes	112	79.4	43.3	27	**0.016**	54	32	**0.018**
No	29	20.6	74.3	79		99.4	82	
Metastasis region								
Bone	75	67	49.2	29	0.191	61.5	33	0.079
Lung	7	6.3	28.2	2		32.7	13	
Liver	9	8	21.5	20		23	24	
Other	21	18.7	31.2	29		38.7	32	
Overall	141	100	50.3	29		64.8	33	

Statistically significant p values are in bold (p < 0.05) ECOG: Eastern Cooperative Oncology Group Performance Status, AJCC: American Joint Committee on Cancer, PSA: Prostate Specific Antigen

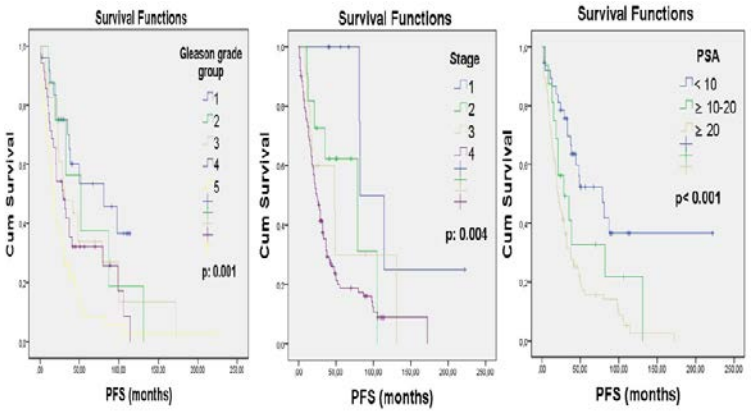

Figure 1: PFS times according to Gleason grade group, stage and PSA

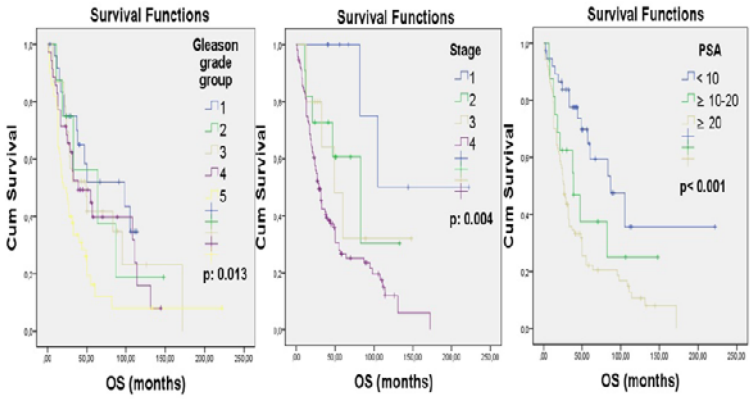

Figure 2: OS times according to Gleason grade group, stage and PSA

Table III: Univariate and multivariate analyses of parameters for progression-free survival and overall survival

Parameters	Univariate		Multivariate	
PFS	HR	p	HR	p
Age (≤ 65 vs > 65)	0.763 (0.510-1.140)	0.186	-	-
ECOG	1.310 (1.038-1.654)	**0.023**	1.218 (0.959-1.571)	0.106
Surgery (Yes vs No)	0.556 (0.371-0.833)	**0.004**	0.826 (0.531-1.283)	0.394
AJCC TNM stage	1.605 (1.225-2.103)	**0.001**	1.417 (1.052-1.908)	**0.022**
PSA (< 10 vs ≥ 10-20 vs ≥ 20)	1.658 (1.300-2.114)	**< 0.001**	1.365 (1.062-1.754)	**0.015**
Gleason grade group (1 vs 2 vs 3 vs 4 vs 5)	1.353 (1.169-1.565)	**< 0.001**	1.348 (1.155-1.573)	**< 0.001**
OS				
Age (≤ 65 vs > 65)	0.812 (0.529-1.247)	0.341	-	-
ECOG	1.387 (1.088-1.770)	**0.008**	1.246 (0.971-1.600)	0.084
Surgery (Yes vs No)	0.487 (0.317-0.749)	**0.001**	0.733 (0.462-1.161)	0.186
AJCC TNM stage	1.703 (1.246-2.328)	**0.001**	1.398 (0.994-1.968)	**0.044**
PSA (< 10 vs ≥ 10-20 vs ≥ 20)	1.696 (1.299-2.215)	**< 0.001**	1.383 (1.050-1.823)	**0.021**
Gleason grade group (1 vs 2 vs 3 vs 4 vs 5)	1.272 (1.090-1.484)	**0.002**	1.238 (1.053-1.456)	**0.010**

Statistically significant p values are in bold (p < 0.05)

ECOG: Eastern Cooperative Oncology Group, AJCC: American Joint Committee on Cancer, PSA: Prostate Specific Antigen

DISCUSSION

As one of the common malignancies of urogenital tract, PC continues to be an important cause of morbidity and mortality both nationally and globally, despite many new treatment approaches[1-4]. It is important to determine prognosis and predict the course of the disease, which has significant heterogeneity in treatment responses varying among individuals. Therefore, in this study, we aimed to demonstrate the clinical significance of the new prognostic staging system and follow-up results of our patients with PC diagnosis in Eastern Anatolia Region. According to our results, good ECOG performance score, surgical treatment, early stage, low PSA score and low Gleason grade group were associated with longer PFS and OS durations. According to multivariate analysis; stage, PSA score and Gleason grade group were found as independent prognostic factors.

As stated by Surveillance, Epidemiology, and End Results (SEER) data, PC is seen between the ages of 65 and 75 years and the median age is 66 years[20]. Of the patients, 77.2% have local disease at diagnosis[20]. In our study, the majority of patients were older than 65 (66.7%) years, and the median age was 69, which is consistent with the literature. Contrary to the literature, the majority of our patients were advanced-stage patients. This may be due to fact, that some of our patients were being followed up in other clinics prior to admission to our hospital and/or late admission of the patients to our clinic due to their individual concerns. According to 2009-2015 data, the expected 5-year survival rate of PC is 98%[20]. This rate is 100% for local disease and 30.5% for metastatic disease[20]. The 5-year survival rates of the patients in our study were lower in both patient

groups with local-locoregional disease (50%), and with metastatic stage (20%) compared to the world.

PC continues to be a major public health problem for men in 6-8. decades and therefore screening programs have been adopted in some countries. As a result of PSA screening, low-risk PC is diagnosed more frequently, and most patients do not develop progressive disease over the years[21]. However, it is important to differentiate indolent disease from progressive disease, which progresses to lethal form and requires treatment, in PC patients[21]. Some clinical and histopathological parameters were used to evaluate the risk status, the need for treatment and prognosis in patients with PC[15,16]. In a study executed on 50 patients investigating the prognostic significance of ECOG performance score, it was shown that patients with good ECOG score (0, 1) had longer OS duration compared to patients with poor ECOG scores (≥ 2). However, ECOG was not found as an independent prognostic factor. In the same study, no correlation was found between ECOG performance status and PFS[22]. Man et al. demonstrated in their study on 179 patients with PC, that ECOG was an independent prognostic factor for OS[23]. Lolli and colleagues in their study on 230 patients with mCRPC showed that ECOG performance is associated with prognosis[24]. Similar to previous studies, we could not find ECOG score as an independent prognostic factor for PFS/OS, although we demonstrated that patients with good ECOG performance status (0-1) had longer PFS and OS. We think that the discrepancies between the studies on showing the ECOG score as an independent prognostic factor may be due to subjective differences in ECOG evaluation.

As another clinical variable, prognostic value of age has been the subject of many studies. Takemura et al. divided patients with metastatic PC in patients into two age groups (under and over the age of 74), and concluded that there was no significant PFS difference between the groups. However, they showed that age was important for OS, but it was not an independent prognostic factor[22]. In another study, 70 years of age was selected as cut-off value for determination of age groups, but no significant OS difference was found between patients under and over 70 years of age[23]. In a study executed on patients with mCRPC treated with abiraterone, it was shown that age did not cause significant differences in OS[24]. In our study, we divided the patients into two groups as ≤ 65 and > 65 years, and we found that age is not an independent prognostic factor for PFS and OS, similar to previous studies.

The system, which was approved by ISUP in 2014 and included five different Gleason grade groups instead of the Gleason score, was added to the 8th edition of AJCC prognostic staging system[17-19]. Different from the previous one, in this version Gleason pattern was used, and 5 different prognostic grade groups were formed according to the scores[17,19]. The prognostic impact of these new Gleason grade groups has been discussed in some previous studies. Chen et al. investigated prognostic significance of the new grade and stage groups on 13798 PC patients from SEER database, and demonstrated that both the Gleason grade and the new AJCC stage groups were independent prognostic factors for OS and cancer-specific survival (CSS)[25]. Another study on 847 patients, who received definitive external beam radiation therapy, demonstrated that the new Gleason grade group was an independent prognostic factor for OS, biochemical recurrence-free survival (bRFS), distant metastases-free survival (DMFS), and prostate cancer-specific survival (PCSS)[26]. Leapman et al. found in their study on approximately 10000 PC patients undergoing biopsy and RP, that the new grading system had a significant association with the risk of metastasis and prostate cancer specific mortality[27]. According to another study on

110000 PC patients from SEER database, the staging was shown to be an independent prognostic factor for both OS and CSS[28]. In our study, we found that the new staging system and Gleason grade group system were as independent prognostic factors for both PFS and OS, similar to the previous studies in the literature.

PSA is another prognostic marker in the 2017 AJCC staging system. PSA is also widely used in the management of patients with diagnosed prostate cancer such as in surveillance

following diagnosis, monitoring response to therapy and in combination with both clinical and histological criteria in risk stratification for recurrence. One study performed on 50 PC patients showed that patients with high PSA (> 250 ng / ml) had shorter PFS and OS, and PSA was an independent prognostic factor[22]. By using E3805 Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) database, Lauren et al. divided 790 patients with metastatic and hormone-sensitive PC into three groups according to their PSA values (≤ 0.2, > 0.2 to 4, and > 4 ng/mL). In this study, low PSA (≤ 0.2) levels at 7. months were associated with longer OS[29]. Another study on 257 patients demonstrated that the PSA response at 6. months had prognostic importance[30]. In our study, we divided the patients into three groups by using PSA levels at diagnosis (< 10 ng / mL vs ≥ 10-20 ng / mL vs ≥ 20 ng / mL) according to the AJCC prognostic scoring in the NCCN guideline. We showed that low PSA group (< 10 ng / mL) had longer PFS/OS durations. In addition, we demonstrated that PSA is an independent prognostic factor for both PFS and OS. Our results were similar to previous studies.

Although our study was the first study in our country's Eastern Anatolia Region, that performed survival analysis on patients with PC, by using the new prognostic grouping system, it had some limitations. Our study was retrospective, and included relatively limited patients. Therefore, the multicentre, prospective studies with higher number of patients are needed to confirm our results.

CONCLUSION

Despite new treatment dynamics, PC is still common in men and has significant mortality rates. In our country and region, there is limited information on the survival duration of PC patients and the factors predicting these durations. Our study is the first study executed in our region, which shows a strong association of the new grading system, PSA and AJCC staging system with prognosis of patients with PC. Since our patients are detected at a more advanced stage and have a shorter life spans, treatment strategies should be reviewed and follow-up of the patients should be continued with increased meticulousness.

Ethics Committee Approval: Ethics committee approval was obtained from the ethics committee of Erzurum Ataturk University (Approval number: 08/27-26.12.2019).

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

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