Original Article
Middle East Journal of Cancer; October 2023; 14(4): 570-577

Prostate Cancer Survival Analysis of 872 Patients in Southern Iran: A Retrospective Cohort Study

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Please cite this article as: Sepahvand M, Salehi A, Omidvari A, Omidvari S, Mohammadianpanah M. Prostate cancer survival analysis of 872 patients in southern Iran: a retrospective cohort study. Middle East J Cancer. 2023;14(4):570-7. doi: 10.30476/mejc.2023.95281.1763.

Abstract

Background: Prostate cancer remains one of the most common and lethal cancers among men worldwide. This study aimed to investigate the characteristics, prognostic factors, and outcomes of patients with prostate cancer who were treated and followed up in Shiraz, southern Iran over the past 12 years.

Method: This retrospective medical chart review was performed on 872 patients with prostate cancer who were treated and followed up in the Radiation Oncology Department of Shiraz University of Medical Sciences. The survival analysis was conducted for the patients, and the receiver operating characteristic (ROC) curve analysis was performed for the prostate-specific antigen (PSA) level.

Results: The median age of the patients at presentation was 69 years (range 35-91 years). In terms of local treatments, 28% of the patients underwent prostatectomy, and 23% were treated with transurethral resection of the prostate. The remaining 49% of patients were treated with non-surgical therapies. Patients between 55 and 75 years had the longest survival duration. The shortest survival was observed in the third Gleason group and those over 75 years old, while the first Gleason group and patients younger than 55 years had the longest survival duration. Hypoalbuminemia had no effect on the survival duration. A PSA level of 33.8 ng/dl was the most suitable cut-off point to predict bone metastasis, and patients with a PSA level of more than 33.8 ng/dl had significantly less survival duration than the others.

Conclusion: More aggressive treatment and shorter follow-up intervals are recommended for patients with an initial PSA level of more than 33.8 and those younger than 55 years old.

Keywords: Prostatic neoplasms, Survival analysis, Prostate-specific antigen, Prognosis, ROC curve

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Introduction

Based on the global cancer report, prostate cancer is the third most common cancer and the fifth leading

Received: April 19, 2022; Accepted: April 02, 2023

cause of male mortality in recent years.[1] It is primarily a cancer of the elderly, with more than 75% of cases occurring in patients older than 65 years of age.[2] Typically, patients present with lower urinary tract symptoms that are not significant for this diagnosis. In fact, the European Association of Urology recommends screening men with at least 10 to 15 years of life expectancy in order to detect more localized disease.[3]

Prostate-specific antigen (PSA), a protein specific to prostate tissue, is measured as an indicator of prostate function. According to the latest report from the National Cancer Institute, the age-standardized incidence rate of prostate cancer has increased, while the mortality rate has decreased due to early tumor detection by checking PSA levels.[4] Another way to screen for prostate cancer is digital rectal exam (DRE). Regardless of the PSA level, patients with palpable nodularity or asymmetry of the prostate gland in DRE undergo transrectal ultrasonography (TRUS) and biopsy.[5-7]

Histologically, there are four types of prostate cancer: adenocarcinoma (the most common type), transitional cell carcinoma, small cell carcinoma, and sarcoma.[8] The Gleason score is the most widely accepted grading system for prostate cancer. In this scoring system, the PSA level and clinical staging are crucial for deciding on the proper treatment.[8, 9] Treatment options for these patients include prostatectomy, radiotherapy, hormone therapy, and orchiectomy. Recent studies have shown that overall survival in prostate cancer is affected by the site of metastasis and pre-operation albumin and PSA levels.[10-13] Early initiation of anti-androgenic medication along with fewer sites of metastasis is suggested as an effective factor for increasing prostate cancer survival.[14]

Prostate cancer is the sixth most common cancer in Iran, with a higher incidence compared with other Asian countries.[15, 16] Due to the lack of sufficient national evidence about the survival of prostate cancer in southern Iran, we conducted a study on overall survival and associated factors of prostate cancer during a 12-year survey at Shiraz University of Medical Science.

Materials and Methods

In this retrospective cohort study, we included 872 men with proven invasive prostate adenocarcinoma who referred to the Shiraz

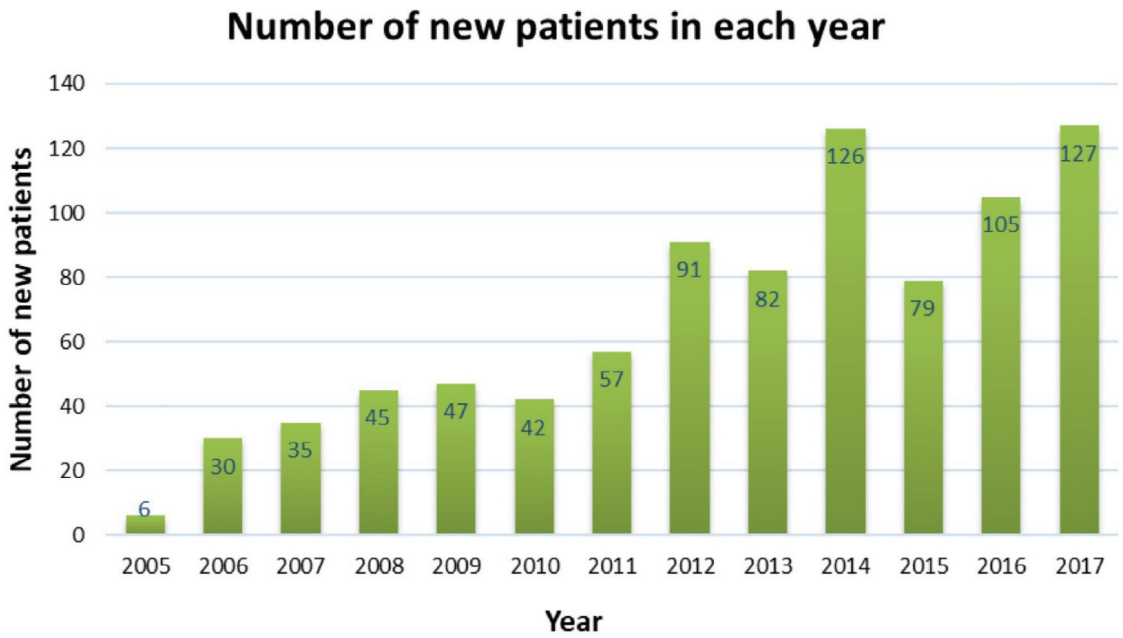

Figure 1. This figure shows the distribution of patients diagnosed during the study period.

Table 1. Multivariate analysis of prognostic factors for overall survival

Variables	Crude HR ^-1 (95% CI)	*P*-value	HR ^-1 adjusted (95% CI)	*P*-value
Age (years)				
<55	ref	< 0.001		0.647
55-75	0.512 (0.232 - 1.132)	0.098	0.000 (0.000-0.000)	0.989
>75	0.418 (0.291 - 0.601)	< 0.001	0.447 (0.082-2.427)	0.351
Grade Group				
1	ref	0.001		0.243
2	0.411 (0.240-0.701)	0.001	0.648 (0.078-5.348)	0.687
3	0.391 (0.213-0.719)	0.003	0.682 (0.065-7.185)	0.750
4	0.871 (0.436-1.740)	0.695	5.237(0.402-68.151)	0.206
5	0.438 (0.230-0.832	0.012	0.712 (0.061-8.240)	0.785
PSA (ng/ml)		0.001		0.019
<33.8	ref		ref	
≥33.8	0.164 (0.109-0.245)		0.191 (0.047-0.765)	
Surgery type				
No surgery	ref	0.001	ref	0.218
TURP	2.257 (1.466-3.474)	< 0.001	4.451 (0.798-24.813)	0.089
prostatectomy	2.369 (1.375-4.080)	0.002	1.294 (0.157-10.676)	0.811
Hormone therapy		0.002		0.034
No	ref		ref	
Yes	2.024 (1.302-3.145)		6.277 1.144-34.439)	
Orchiectomy		0.001		0.007
No	ref		ref	
Yes	0.301 (0.183-0.497)		0.145 (0.036-0.588)	
Albumin (g/dl)		0.838		0.501
<4	ref		ref	
≥4	0.895 (0.309-2.595)		1.938 (0.282-13.325)	
Radiotherapy		0.001		0.281
No	ref		ref	
Yes	0.895 (0.309-2.595)		2.849 (0.425-19.085)	
Chemotherapy regimen				
No chemotherapy		<0.001		
CTX + VCR	0.042 (0.009-0.188)	<0.001		
Docetaxel	0.309 (0.065-1.466)	0.139		0.079
CTX + VCR + Docetaxel	0.115 (0.010-1.280)			
Others	0.310 (0.063-1.532)	0.151		
Unknown	0.444 (0.090-2.190)	0.319		

CI: Confidence interval; PSA: Prostate-specific antigen; HR: Hazard ratio; TURP: Transurethral resection of the prostate; CTX: Cytoxan (cyclophosphamide); VCR: Vincristine

University of Medical Sciences Radiation Oncology department from January 2005 to December 2017. The study was approved by the Ethics Committee of Research of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1401.107), and all patients signed informed consent. Non-invasive prostate cancer, such as "carcinoma in situ," and pathologies other than adenocarcinoma, such as lymphoma and sarcoma, were excluded. A data gathering form was designed under the supervision of two Radiation Oncologists. The Radiation Oncology department was the only center for non-surgical treatments of prostate cancer in the Fars province during the study. These Radiation Oncologists taught two last-year medical students about the nature of the disease, its treatment, and how to retrieve data from clinical records. The medical students gathered the demographic and clinico-pathological information from the clinical records and wrote them down in the data sheet. Retrieved data was rechecked by Radiation Oncologists at the end.

The variables included in the study were age at incidence, Gleason sum and stage, histology, serum hemoglobin (Hb), albumin (Alb), and PSA, number and ratio of positive biopsies, type of surgery, chemotherapy regimen, medical or surgical (orchiectomy) hormone therapy, radiation dose, and metastasis. The time of the pathology

report proving prostate cancer was assumed as the disease presentation time. Patients were classified into three groups based on their age at presentation: under 55 years old (early prostate cancer), 55-75, and over 75 years old. Hypoalbuminemia was defined as an Alb level less than 4 g/dl. Hb under 14 g/dl was assumed as anemia, and Hb more than 18 g/dl was assumed as polycythemia. The chemotherapy agents used were cyclophosphamide (CTX), vincristine (VCR), and Docetaxel. In this study, and according to the pathologic report, the Gleason grade groups were applied for defining tumor grade and risk of tumor recurrence. The Gleason grade group scoring system included the scores of Gleason grade and Gleason pattern.

The data was analyzed using SPSS version 23. Each patient had its own specific ID, and the data was checked to omit any repeated cases. Before all parametrical tests, a Kolmogorov-Smirnoff normality test was done, and if the variable had no normal distribution, non-parametric tests were done instead. In all statistical tests, the maximum acceptable amount of type one error was assumed to be 0.05. To describe quantitative variables, mean and median were used as central tendency measures, and standard deviation (SD) was used as the dispersion index. T-tests were used to compare quantitative variables in different subgroups. Kaplan-Meier survival plots were drawn for categorized Alb and PSA levels, age, and grade groups. Tarone-Ware test was done to compare survival in the mentioned subgroups. Receiver operating characteristic (ROC) curve analysis was done to determine the most suitable PSA cut-off point to predict further

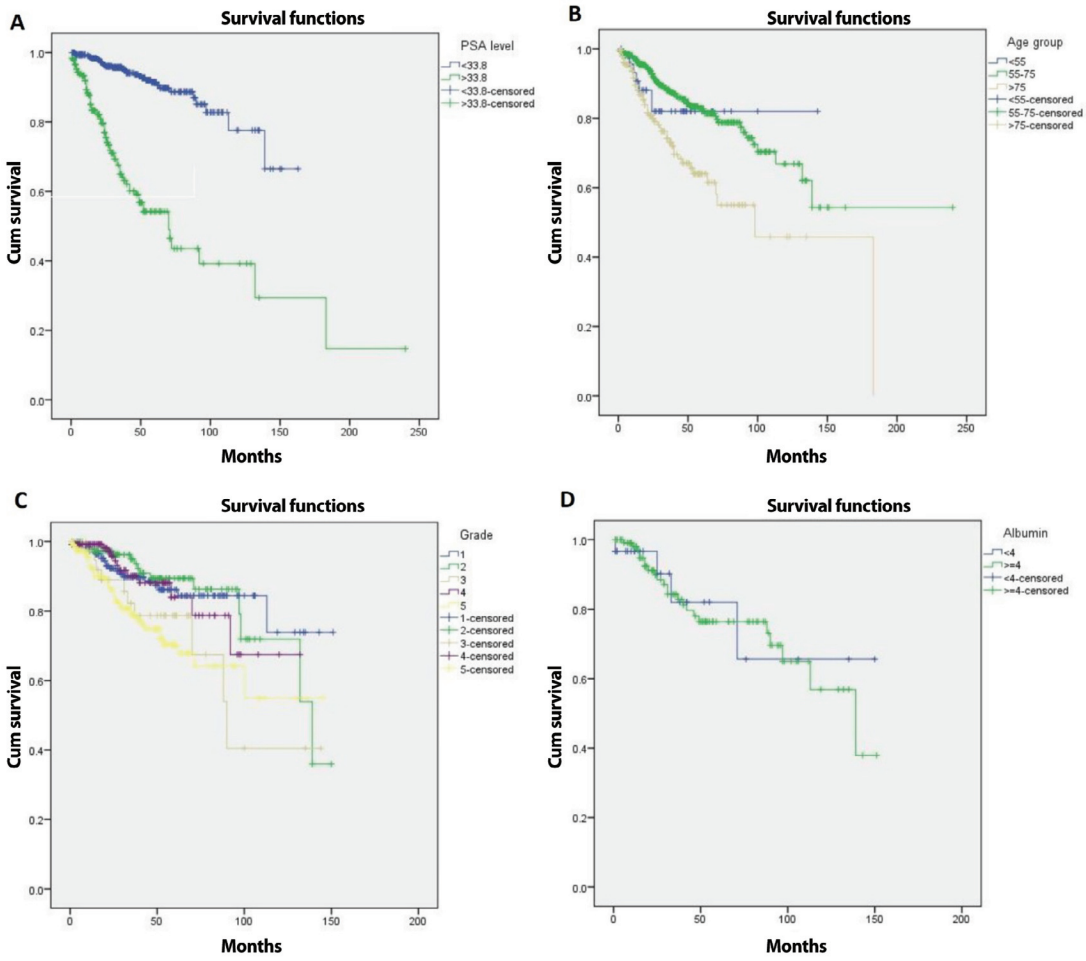

Figure 2. This figure shows the prognostic impact of the serum PSA level (A), age (B), tumor grade (C) and serum albumin level (D) on the overall survival rate of 872 patients with prostate cancer.
PSA: Prostate-specific antigen; Cum: Cumulative

bone metastasis. Finally, Cox regression analysis was used to determine the possible effect of age, grade group, PSA and Alb level, surgery type, hormone therapy and orchiectomy, radiotherapy, and chemotherapy regimen on patients' survival. Crude and adjusted hazard ratios were calculated for these factors.

Results

The total number of patients was 872, of whom 783 were eligible for survival analyses. The frequency of cases per year is shown in figure 1. The median age of the patients at presentation was 69 years (range 35-91 years). In terms of local treatments, 28% of the patients underwent prostatectomy, and 23% were treated with transurethral resection of the prostate (TURP). The remaining 49% of patients were treated with non-surgical therapies. Radiotherapy was prescribed for 756 patients during their treatment, with a mean radiation dose of 54 Gy. 708 patients received single-agent or multiple-agent hormone manipulation during the course of treatment. The differential frequency of each single agent was as follows: Bicalutamide for 9 patients, Zoladex for 152 patients, Cyprotroneacetate for 84 patients, Dipherline for 449 patients, Eligard for 70 patients, Flutamide for 200 patients, Decapeptyl for 203 patients. In addition, 56 patients underwent orchiectomy in their treatment course. Zoledronic acid was prescribed for 122 patients with skeletal metastasis. The most frequent Gleason grade groups were 5 and 1, and the least frequent grade group was 3.

The mean Hb level among all the patients was 12.3 g/dl, and 74.5% of patients were anemic, with less than one percent of them having polycythemia. The Hb level among our patients [12.3 (95% CI 1.43-1.94) g/dl] was significantly lower than 14 g/dl. The mean serum Alb level was 4.2 ± 0.46 g/dl. Hypoalbuminemia in these patients had no effect on the survival duration (Table 1). The mean PSA level was 94.7 and 21.7 in the positive and negative bone scan groups, respectively ($P < 0.001$). There was no difference between the two groups in Hb and Alb. Among the 872 patients, 386 patients had a positive bone scan during their follow-up. Patients with a positive bone scan had significantly higher numbers of positive prostate biopsies ($P < 0.001$). The Kaplan-Meier survival curves of the age group, grade group, PSA level, and serum Alb level are illustrated in figure 2.

In multivariate survival analysis, PSA level ($P = 0.019$), hormone therapy ($P = 0.034$), and orchiectomy ($P = 0.007$) were independent predictors of overall survival (Table 1). A ROC curve was applied for the PSA cut-off point to predict skeletal metastasis. The AUC (Area under the curve) for PSA level predicting bone metastasis was 0.709 (Figure 3).

Discussion

In our study of 872 cases of prostate cancer, the median age at presentation was 69 years. More than 80% of our patients underwent hormone therapy, and three-quarters of them were anemic. A higher PSA level was a strong predictor of lower survival but more bone metastasis. In multivariate analysis, PSA level, hormone therapy, and orchiectomy independently predicted the patients' survival.

The frequency of patients referred here from 2005 to 2017 had an increasing trend. There was an increasing incidence of prostate cancer in 15 countries all around the world in the last two decades of the past century.[17] This increasing trend could be due to both the increasing incidence of prostate cancer in our region, improvement of diagnostic methods, and higher clinical suspicion.

The median age of the patients referred to our clinic was 69 years. In Polyakov et al.'s study on 1564 patients with prostate cancer published in 2017, the median age at presentation of disease was 71 years.[18] These findings are relatively compatible with our study.

In the current study, 55 to 75-year-old patients had the longest overall survival. Age alone has no significant effect on survival in multivariate analysis; therefore, the observed survival difference in age groups may be attributable to other factors. In a Brazilian study, age was not an independent prognostic factor for prostate cancer when the effect of other variables was

omitted.[19]

In Grönberg et al.'s study, done on more than 6000 patients, there was no significant difference in survival between different age groups; however, a higher rate of high-grade disease in younger patients was observed.[11] Longer survival time in the 55-75 year age group may be due to more aggressive disease in younger patients and a higher rate of comorbid diseases in elders. Because of the shorter survival and higher rate of high-grade disease in younger patients, a more aggressive approach and more frequent follow-ups are recommended for them.

In the present study, the mean PSA level was significantly higher in patients with further bone metastasis, and those with PSA > 33.8 ng/dl had a lower survival rate. In a study on 1873 patients, PSA levels between 20 and 70 had a reverse correlation with survival duration; however, in PSA levels between 70 and 100, there was no relationship with survival.[12] As a matter of fact, in patients with higher initial PSA, a more aggressive approach to detect early bone metastases is needed.

Low Alb levels and patients' anemia had no significant effect on survival duration. The mean Hb level was significantly lower than the normal level. In Sejima et al.'s study published in 2013 on 179 patients, lower levels of Alb before surgery were significantly related to higher rates of disease recurrence.[13]

In a study in 2018, pretreatment Alb/globulin was an independent prognostic factor for progression-free survival.[20] In many studies, there is a relationship between cancer and anemia[21, 22] and anemia makes cancer patients' prognosis worse.[23] Further studies with larger sample sizes are needed to assess the effect of Alb level and Hb on survival.

The strengths of our study were the large sample size and long-term follow-up to determine prognostic factors of prostate cancer and define PSA level as a predictor of bone metastasis. The limitations of our study were retrospective design,

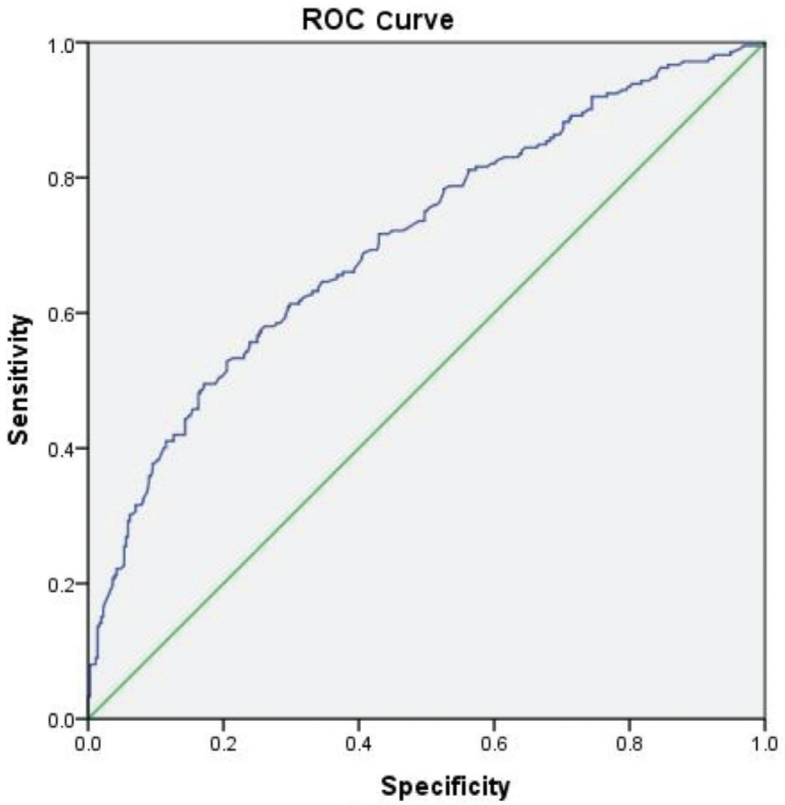

Figure 3. This figure shows the ROC curve for PSA cut-off point to predict skeletal metastasis.
ROC: Receiver operating characteristic; PSA: Prostate-specific antigen

lack of uniform pathological reports, and missing data.

Conclusion

Based on our findings, we observed higher levels of aggression in the behavior of the disease in patients who are under 55 years old, emphasizing the importance of early screening. However, larger prospective studies are needed in our society to determine the appropriate age for starting screening and the PSA level that predicts a clinically significant form of the disease.

Acknowledgements

This study was approved and supported by the Shiraz University of Medical Sciences. The study was conducted as the thesis for the MD-MPH degree by Mahsa Sepahvand.

Conflict of Interest

None declared.

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