

RESEARCH ARTICLE

Survival of Patients with Prostate Cancer in Yazd, Iran

Shokouh Taghipour Zahir^{1*}, Mohammad Reza Nazemian², Sanaz Zand², Samad Zare³

Abstract

Background: Prostate cancer is the second leading cause of cancer death in men worldwide. Several factors such as availability of screening tests, and dietary, other lifestyle, environmental and genetic influences contribute to worldwide disparities in prostate cancer incidence and mortality rates. Our aims were to investigate patient characteristics at the time of diagnosis, common treatment strategies employed and survival in an Iranian male population with prostate cancer. **Materials and Methods:** Archives of Pathology Departments of five referral centers affiliated with the School of Medicine of Shahid Sadoughi University in Yazd province were reviewed. Paraffin-embedded blocks were reviewed by two independent pathologists to confirm the diagnosis. The latest modification of the Gleason Scoring System was adopted to determine pathological grading. Following pathological evaluation, patients were contacted via telephone to acquire information regarding their current status. **Results:** Pathology blocks were available for 113 patients. However, upon phone contacts, we were unable to determine the survival status in 23 patients (response rate=83%). Therefore, 90 patients were enrolled in the final analysis. The median follow-up time was 6.0 years (ranging from 0.3 to 8.8 years). There were 30 death attributed to prostate cancer in the study group. Kaplan-Meier analysis revealed that patient age at the time of diagnosis was a significant predictor of survival. Another significant predictor of poorer survival was higher tumor grade. **Conclusions:** Our observations indicate that age and pathological grade can negatively affect survival of individuals with prostate cancer in Iran.

Keywords: Prostate cancer - survival - tumor grade - Gleason score

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Introduction

Prostate cancer is the second leading cause of death in men worldwide (Jemal et al., 2010, Siegel et al., 2013). In the United States, prostate cancer was estimated to account for 29% of new cases of cancer, and 9% of cancer-related mortality in adult male population in 2012 (Siegel et al., 2012). Over the past few decades, incident rates for prostate cancer have increased by epidemic proportions; owing primarily to the enhanced availability of medical surveillance and also advancements in screening strategies (Siegel et al., 2012a; 2012b). Hence, in countries such as the US, where the use of screening tests is common, an 80-fold higher incidence rate compared with China has been observed (Jemal et al., 2002).

There is general consensus that the use of screening tests is not the only cause of mentioned geographical differences (Jemal et al., 2010). Indeed, dietary, lifestyle, environmental, and genetic factors also play an important role in making such incidence diversities. For instance, African-Americans are at a disproportionately higher risk of both developing prostate cancer and having poorer survival in the US and Brazil cohorts (Bostwick et al.,

2004, Bouchardy et al., 1991, Platz et al., 2000). It is postulated that transition to a western dietary pattern is the primary reason for dramatic increase in the incidence of prostate cancer in Japanese men migrated to the US (Dunn, 1975). Furthermore, it has been proposed that polymorphisms in genes encoding enzymes involving in testosterone metabolism can also be responsible for observed discrepancies (Shibata and Whittemore, 1997, Watanabe et al., 2000). Mortality rates for prostate cancer also significantly vary between different geographic regions (Hsing et al., 2000, Quinn and Babb, 2002). Age-adjusted mortality rates among US blacks is reported to be roughly 10-times higher than that of the Asian populations living in Hong-Kong, Japan and Singapore (Hsing et al., 2000).

Given the worldwide disparities in prostate cancer incidence and mortality rates and sparsity of studies delineating survival of patients with prostate cancer in Iran, the present study was conducted. The aims were to investigate patients' characteristics at the time of diagnosis, common treatment strategies employed and survival rate of Iranian male population with prostate cancer.

¹Department of Pathology, Shahid Sadoughi Hospital, ²School of Medicine, ³Department of Urology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran *For correspondence: taghipour@ssu.ac.ir

Materials and Methods

This retrospective study was conducted in Yazd, Iran between January 2011 and 2013. Archives of pathology departments of five referral centers affiliated with school of medicine of Shahid Sadoughi University in Yazd province were reviewed. Patients' demographic information such as age at diagnosis, area of residence, treatment protocols and telephone number were extracted from the available data. It should be noted that, it is a general policy of Shahid Sadoughi University affiliated hospitals that all patients are asked to sign an informed consent form upon their freewill agreeing that their medical records be used for research purposes. Patients refusing to consent were not included in the present study. Study protocol was reviewed and approved by medical ethics committee at Shahid Sadoughi University.

Paraffin-embedded blocks were reviewed by two independent pathologists to confirm the diagnosis. Latest modification of Gleason Scoring System, a well-established predictor of prostate cancer prognosis, was adopted to determine pathological grading (Epstein, 2010). Gleason score can serve as an independent prognostic factor for prostate cancer (Andren et al., 2006). To calculate Gleason score of a specimen, based on microscopic appearance, the two most frequent tissue patterns are identified. Each pattern is then assigned an independent score of one to five, one indicating normal prostate tissue and five representing no recognizable gland. These two scores are summed to form a final score ranging from two to ten. Gleason scores 2-3 represent low grade disease, 4-6 moderate, 7 intermediate, and finally scores between 8 to 10 are representative of high grade prostate cancer.

Patients were categorized into two groups based on their cancer stage; those with stage I and II were considered as having local prostate cancer, while those with higher stages (III and IV) were considered as having regional and metastatic disease.

Following pathological evaluation, patients were contacted via telephone to acquire information regarding their current status. In case of death, condolences were expressed to patients' family members. Follow-up time was defined as the interval between diagnosis time and the time of death or last contact with the patient. Survival was defined as patient being alive upon the telephone contact.

Statistical analysis

Statistical analyses were performed using SPSS software version 21.0 for windows (IBM Inc., NY, US). Categorical variables are demonstrated as proportions and continuous variables as mean and standard deviation (SD). In all analyses, continuous variables with non-normal distribution are reported using median (interquartile range). Kaplan-Meier method was used to assess the impact of different categorical predictors on patients' survival. Difference in distribution of events between classes of categorical variables was evaluated using the log-rank test. Categorical variables showing significant association with patient survival were then placed in a multivariate Cox regression model in order to calculate

adjusted Hazard Ratios (HRs) along with their 95% confidence interval (95%CI). In all tests, a p value of less than 0.05 was considered as the threshold to reject the null hypothesis.

Results

Pathology blocks were available for 113 patients. However, upon phone contacts, we were unable to determine the survival status in 23 patients (response rate=83%). Therefore, 90 patients were enrolled in the final analysis. Baseline characteristics of study participants are presented in Table 1. Patients' age ranged from 40 to 90 years (mean: 67.37±9.82). Patients were more likely to be in the seventh and eighth decades of their life at the time of diagnosis (32.2% and 36.5%, respectively).

Patients frequently reported Lower Urinary Tract Symptoms (LUTS) such as frequency, nocturia and obstructive symptoms; overall 57 out of 90 (63.3%) patients reported at least one of these symptoms at the time of diagnosis. The second most frequent symptoms were complaints regarding sexual functioning (e.g. erectile dysfunction or painful ejaculation), which was observed in 40% of cases. Treatment strategies in order of frequency were surgery (67.8%), hormone therapy (34.4%) and radiotherapy (25.6%).

Median value of Prostate Specific Antigen (PSA) was 16.75 (8.52-48.00). Regarding disease severity, only 5 (5.5%) patients were categorized in low-grade group. On the contrary, 38(42.2%) patients were classified in intermediate-grade group (Gleason score=7).

The median follow-up time was 6.0 years (ranging from 0.3 to 8.8 years). There were 30 death attributed to

Table 1. Baseline Characteristics of Study Subjects (Total number=90)

	Number	%
Age		
<60	19	21.10%
60-69	29	32.20%
70-79	32	35.60%
80<	10	11.10%
Symptoms		
Lower urinary tract symptoms*	57	63.30%
Sexual dysfunction	36	40.00%
Hematuria	20	22.20%
Abdominopelvic pain	16	18.80%
Gastrointestinal symptoms	14	16.60%
Incontinency	12	14.30%
Weight loss	5	6.60%
Treatment protocol		
Surgery	61	67.80%
Hormone therapy	31	34.40%
Radiotherapy	23	25.60%
Stage		
Local (I, II)	80	88.90%
Regional + Metastatic (III, IV)	10	11.10%
Grade (Gleason score)		
Low (2-4)	5	5.60%
Moderate (5-6)	23	25.60%
Intermediate (7)	38	42.20%
High (8-10)	24	26.70%

*Including frequency, nocturia and obstructive symptoms

Table 2. Effects of Different Factors on Survival of Patients with Prostate Cancer

	Event/Total	p value
Age		<0.001
<60	19-Jan	
60-69	29-May	
70-79	14/32	
>80	10-Oct	
Grade (Gleason score)		0.001
Low (2-4)	5-Mar	
Moderate (5-6)	23-Mar	
Intermediate (7)	Oct-38	
High (8-10)	14/24	
Stage		0.789
Local (Stage I, II)	26/80	
Regional+Metastatic (Stage III, IV)	10-Apr	
Lower urinary tract symptoms*		0.613
Yes	20/57	
No	Oct-33	
Sexual dysfunction		0.079
Yes	Aug-36	
No	22/54	
Gastrointestinal symptoms		0.371
Yes	14-Jun	
No	24/76	
Weight loss		0.251
Yes	5-Mar	
No	27/85	
Incontinency		0.502
Yes	12-May	
No	25/78	
Hematuria		0.073
Yes	20-Oct	
No	20/70	
Abdominopelvic pain		0.834
Yes	16-Jun	
No	24/74	

* Including frequency, nocturia and obstructive symptoms

Table 3. Cox-proportional Regression Model for Factors that Showed Significant Predictive Role in Univariate Analysis

	Hazard Ratio	95% CI		p value
		Lower	Upper	
Age				
<60	1			Ref.
60-69	1.955	0.667	5.725	0.221
70-79	3.128	1.122	8.724	0.029
80<	7.113	2.506	20.189	<0.001
Tumor grade				
Low (2-4)	1			Ref.
Moderate (5-6)	0.989	0.592	1.651	0.968
Intermediate (7)	1.879	1.134	3.114	0.014
High (8-10)	2.384	1.14	4.985	0.021

prostate cancer in the study group. The results of Kaplan-Meier analysis are summarized in Table 2. Kaplan-Meier analysis revealed that patients' age at the time of diagnosis was a significant predictor of survival. Another significant predictor of poorer survival was tumor grade (p=0.001). Neither did the cancer stage anticipate patients' outcome nor did the initial presenting symptoms.

Consequently, age at the time of diagnosis and tumor grade were put in a multivariate Cox proportional hazard

model to calculate HRs (95%CI) and the results are presented in Table 3. Both age and tumor grade were significantly associated with poorer survival. Patients in higher age categories had higher risk of death. HR (95%CI) for patients in the oldest age category (>80 years) was 7.113 (2.506-20.189) as opposed to patients in the youngest group (< 60 years, reference category). On the other hand, high grade tumor was associated with a HR (95%CI) of 2.384 (1.140-4.985) compared with low grade tumor as the reference category (Table 3).

Discussion

We are reporting here, for the first time, survival of Iranian patients with prostate cancer in Yazd, Iran. The medical records along with histopathological evaluation of 90 patients were reviewed and their current survival status was determined via telephone interviews. The impact of several factors including age, tumor grade, disease stage, and patients' symptoms at the time of diagnosis on the survival was investigated in order to identify determinant variables. Among these, only patients' age and tumor grade were significantly and negatively linked to survival. Old age and high tumor grade were independent predictors of death in patients with prostate cancer.

Only a few reports are available regarding prostate cancer incidence in Iran. Data obtained from five provinces (Ardabil, Guilan, Mazandaran, Golestan and Kerman) showed that age-standardized incidence rate (ASR) of this cancer was 5.1 per 100,000 between 1996 and 2000 (Sadjadi et al., 2007). A report from population-based cancer registry of Tehran, the capital of Iran, revealed that the corresponding figure was 15.6 for the period of 1998-2001 (Mohagheghi et al., 2009). In recent years, establishing national registries in Iran has allowed estimating prevalence of prostate cancer across country more precisely. The first report representing national incidence of different cancers in Iran was published in 2009 and manifested that ASR of prostate cancer was 9.41 per 100,000 in 2005 (Mousavi et al., 2009).

Experts are unanimous on this issue that prostate cancer is a disease of old age (Jemal et al., 2011). In this regard, it is very rare to diagnose prostate cancer in males younger than 50 years old, as opposed to 63% of cases which are diagnosed in individuals older than 65 years (Crawford, 2009). While the risk of developing prostate cancer exponentially increases after the age of 50, it has been estimated that the lifetime risk is 16.7% (Crawford, 2003). This figure is likely to be an underestimation since many histological cases of malignant transformation do not advance to clinical disease. Autopsy evaluation of 320 men without apparent clinical history of prostate cancer, detected evidences of malignant transformations in 40% of cases older than 60 years (Zlotta et al., 2013). Our results are in accordance with previous reports that older patients who were diagnosed with prostate cancer have shorter survival probably due to comorbidities deteriorating health status (Holmberg et al., 2012).

The most common Gleason score in our study population was 7, with 42.2% of cases. The prognosis of patients with this score varies considerably based on the

most prevalent tumor pattern. Numerous studies have demonstrated that patients with score 4+3 have poorer survival than those with score 3+4 (Chan et al., 2000, Makarov et al., 2002, Rasiah et al., 2003) (as mentioned earlier the first number indicates the most common tumor pattern). Up to three-fold increase in the mortality of patients with score 4+3 has been reported compared to patients with Gleason score 3+4 (Stark et al., 2009). Due to our relatively small sample size we were not able to assess the impact of most prevalent tumor patterns on patient survival. There is a growing concern that use of finasteride can increase the number of patients diagnosed with high-grade tumor (Gleason score > 8) (Kramer et al., 2009, Theoret et al., 2011, Thompson et al., 2013). Food and Drug Administration (FDA) issued a change in safety information of the medication, adding the mentioned warning (Thompson et al., 2013). Nevertheless, it is well established that the incidence of low-grade cancer may reduce as a consequence of finasteride administration (Thompson et al., 2013).

Drawing a conclusion out of the put forward details it comes to this point that our observations indicate that age and pathological grade can negatively affect survival of individuals with prostate cancer.

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