Survival from Bladder Cancer in Shiraz, Southern Iran: A Hospital-Based Study

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Abstract: Bladder cancer is still one of the most widespread cancers of the urinary organ. Studies in Iran indicate a recent increase in the incidence of this disease. This study was undertaken to determine the survival from bladder cancer in Shiraz, Fars Province, Southern Iran. Data were collected from 515 patients with bladder cancer registered at Nemazee Hospital Cancer Registry Center affiliated to Shiraz University of Medical Sciences between 2001 and 2009. Patients were followed to record the outcome. The relationship between each variable and survival time was tested with the Kaplan-Meier and Cox regression method. Cumulative survival rate was 94.40% after 1 year, 68.38% after 3 years and 49.30% after 5 years. No significant relationship was seen between variables such as sex, occupation and education. The cumulative survival rate in our study population was less than other reports. Age higher than 60 years and treatment type were the most important predictors of survival time observed in our patients.

Key words: Bladder · Cancer · Survival Analysis · Iran

INTRODUCTION

Bladder cancer is the most prevalent cancer of urinary tract [1]. Its worldwide mortality rate was reported 132432 cases in 2000, ranking the 4th in United States [2]. In 2009, the incidence in United States was 71000 and with a mortality rate of 14000 [1]. Rate of mortality from disease shows a decreasing pattern in the Western Europe in the two past decades, whereas, an increasing trend was shown in some Eastern European countries [3]. Bladder cancer usually occurs in adults and the mean age at diagnosis of the disease in men and woman are usually 69 and 71 years, respectively [4, 5].

Although, the incidence is rare in children and young people, it may occur as a non-aggressive and low grade type [6]. The incidence rate in men was shown 4-5.2 times more than women [7-10]. Various studies were conducted to determine the survival rate of bladder cancer in the world. The rate of 5-year survival has increased from 75% to 81% during 1975-1996 [1, 2, 11]. Also, the rate of 5-year survival of aggressive cancers has been reported 60% and the rate of total survival, including aggressive and non-aggressive is reported 70% to 85%, this rate is usually higher in woman compared to men [12-16]. Additionally, the rate of 5-year survival in patients with urinary organ cancers is reported as 81% which also depends on the grade and stage of disease too [2].

Evaluations show that in spite of improvements in diagnostic and treatment methods and post cares, little recovery has occurred in patients' condition even after various chemotherapeutic measures [17]. Approximately, 50% of patients suffering from aggressive bladder cancers die during 3 to 4 years after chemotherapy [18]. Patient's survival are dependent on size of tumor, surgical area, number of affected lymph nodes and metastasis to lymphatic veins, out of which, the most important ones are the stage of tumor and lymph node involvement [10, 17-20]. When compared to the literature on other malignancies, information on quality of life in bladder cancer mostly denote to a decrease too [21].

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Based on guideline of non-communicable disease care system, this cancer has allocated the 5th position out of 13 common cancers in 2004-2008 [8]. Among men, it is the 2nd cancer in Markazi Province [15] and 3rd in Kurdistan Province and totally the 4th in Iran [10]. In Fars Province, Southern Iran; Farahmand *et al.* [22] have reported an increase in incidence of the disease in recent years.

Many risk factors are associated with bladder cancer such as urinary tract infections, diabetes, water contaminants, dietary factors, fluid intake, coffee consumption, selected drugs, occupational exposures and family history. Tobacco smoking and occupational exposure to aromatic amines were shown to be the identified risk factors for bladder cancer too [23, 24].

No hospital-based study has been conducted to determine the rate of survival among patients suffering from bladder cancer in Iran. So this study was carried out to determine the rate of survival of bladder cancer in Shiraz, Southern Iran.

MATERIALS AND METHODS

This is a survival analysis conducted on 514 patients suffering from bladder cancer registered at Fars Hospital-based Cancer Registry in Nemazee Hospital affiliated to Shiraz University of Medical Sciences in Shiraz, Southern Iran. The inclusion criterion was that the patients should have at least a complete follow up. The study population was all individuals who were the resident of Shiraz and suffered from bladder cancer and were under treatment in Nemazee Hospital. All registered patients in the cancer registry from 2001 to 2009 were included in the study.

Data collection was based on use of two questionnaires. The first one contained demographic variables of patients participating in the study such as age, sex, marital status, occupation, ethnicity, nationality, smoking habits, alcohol and narcotic consumption, blood groups, RH, disease grade and type of treatment. The second questionnaire consisted the contact time and patient's condition in the time of follow up. The collected data were analyzed using SPSS software (version 15, Chicago, IL, USA) after coding and entering in to computer. The Kaplan-Meier together with Log-Rank test and Cox multivariable analysis were used to analyze the data. Variables with significant level lower than 0.25 were included in the model as confounding ones. Significance level was considered as 0.05.

The monotonousness of the rate of mortality and improvement among the dead and followed up individuals in the study was determined.

RESULTS

Only one out of 574 of total individuals were Afghan (0.2%) and the others were Iranian. Religion of 99.9% is Islam. Among individuals, 434 (84.4%) were males and 462 were married (90%). Patients were divided into four groups in accordance with occupation, from whom, 134 individuals (26.75%) were farmers, 81 (16.1%) were housewives, 105 (20.9%) were clerks and 186 (36.3%) were workers. Surgery was done for 402 patients (78.8%) as TURB and radical cystectomy, 13 subjects (2.5%) were under chemotherapy, 7 (1.7%) were treated by radiotherapy and others were under treatment by a combination of all above-mentioned treatments. The mean and standard deviation of survival period in under taken population was 5.22±4.03 years and the mean of age, height and weight of patients were 63.69±13.9 years, 158.46±98.91 cm and 62.87±21 kg.

The rate 1, 3, 5 years survival time of patients suffering from bladder cancer was 0.944, 0.6838 and 0.4930 respectively. Figure 1 reveals patients' total survival time. As shown in Table 1, no significant relationship was seen between sex, marital status, education, ethnicity and BMI with survival using Kaplan- Mayer analysis ($p>0.05$). Regarding age, it showed a significant correlation ($p=0.001$). Table 2 shows the cancer grade, blood group, smoking and alcohol consumption without any significant difference ($p>0.05$), whereas RH and type of treatment showed a significant correlation with the survival rate ($p=0.001$). Ethnicity, blood group, RH, type of treatment and age variables were among those with a statistical significance of lower than 0.25 using Kaplan-Mayer test and were included in Cox Regression model.

Multivariable Analysis results (Table 3) showed that only two important variables remained in Cox regression model including age, type of treatment that played a major role in patients' survival in such a manner that people aged between 50 to 60 year-old had the risk of suffering from bladder cancer 2.7 times more, those aged 60-70 years about 4.7 times more and over 70-year-old, 4.5 times more risk compared to those under 50 years old. Chemotherapy and radio-therapy increased the probability of death 3 times more than a combined treatment method. Figure 2 shows the survival after controlling the remained confounding variables.
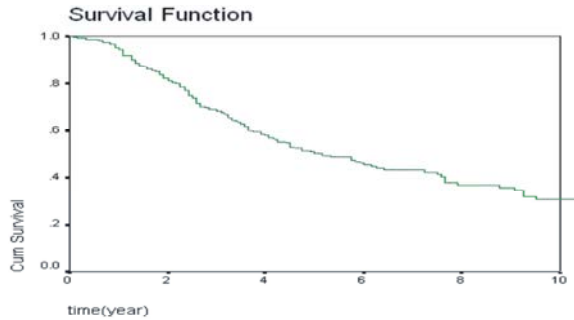
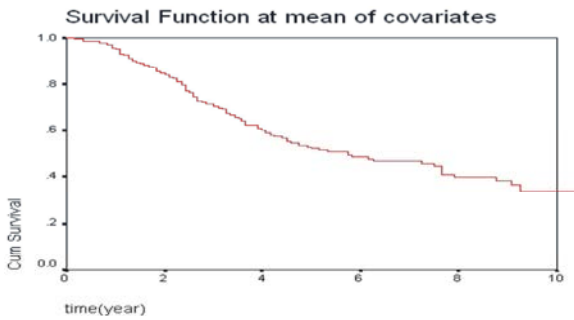Fig. 1: The cumulative survival function in patients with bladder cancer

Fig. 2: The cumulative survival function of the patients with bladder cancer after control of confounding factors

Table 1: The cumulative survival rates of Bladder cancer patients according to some variables.

Variables		1 year	3 years	5 years	P value
Sex	Female	0.9412	0.6869	0.4953	0.4345
	Male	0.9406	0.789	0.4990	
Marital status	Married	0.9456	0.6865	0.5107	0.5999
	Single	0.8914	0.6201	0.3887	
BMI	Thin:<18.49	0.9310	0.5660	0.2494	0.4630
	Normal:<18.5-24.99	0.9268	0.6787	0.5506	
	Over weight and obese:>25	0.9601	0.7146	0.4516	
Ethnicity	Farsi	0.9432	0.6548	0.4967	0.0758
	Non-Farsi	0.9434	0.7857	0.5003	
Education	High school	0.9511	0.6998	_	0.9373
	College	0.9286	0.7792	_	
Occupation	Farmer	0.9495	0.6925	0.5011	0.5101
	Housewife	0.96	0.6907	0.4755	
	Clerk	0.8814	0.7293	0.5519	
	Worker	0.9254	0.6447	0.4743	
Age (years)	<50	0.9714	0.8704	0.7266	<0.001
	50-60	0.9620	0.7114	0.5924	
	60-70	0.9554	0.6640	0.3946	
	>70	0.9138	0.6001	0.3978	

Table 2: The cumulative survival rates of Bladder cancer patients according to some variables.

Variables		1 year	3 years	5 years	P value
Blood group	A	0.888	0.709	0.473	0.199
	AB	0.90	0.70	0.40	
	B	0.952	0.761	0.648	
	O	0.957	0.710	0.473	
RH factor	Negative	0.903	0.834	0.758	0.029
	Positive	0.970	0.840	0.707	
Smoking	Addicted to morphine	0.862	0.646	0.503	0.451
	Smoker	0.944	0.725	0.544	
	Bubble smoker	0.942	0.594	0.426	
	Non-smoking	0.955	0.669	0.424	
Alcohol consumption	Yes	0.870	0.644	_	0.796
	No	0.945	0.684	0.509	
Type of treatment	Chemotherapy and radiotherapy	0.70	0.30	_	<0.001
	Surgery	0.945	0.705	0.532	
	Combined treatment	0.960	0.647	0.446	
Cancer grade	Zero	0.963	0.674	0.414	0.782
	One and over	0.861	0.575	_	

Table 3: COX multivariable analysis results in the survival of patients with bladder cancer.

Variables	Coefficient	SD*	P	HR**	Confidence interval (95%)
<50 years	-	-	-	1	-
50-60 years	1.02	0.451	0.024	2.76	1.14-6.68
60-70 years	1.54	0.445	0.001	4.67	1.95-11.17
>70 years	1.5	0.431	<0.001	4.49	1.93-10.46
Combined treatment	-	-	-	1	-
Chemotherapy and radiotherapy	1.10	0.435	0.011	3.0 13	1.29-7.06

*Standard deviation, **Hazard Ratio

DISCUSSION

It was shown that he average annual crude incidence rate and ASR for bladder cancer in Fars Province, Southern Iran in males was reported 1.56 and 2.63 while these figures in females were 0.25 and 0.42 and it ranked the 6th cancer in males in Fars Province, Southern Iran denoting to the importance of this cancer in the area [25]. In Fars Province, Southern Iran; Farahmand *et al.* (2009) reported an increase in incidence of bladder cancer in recent years. They demonstrated that the frequency increased with age and was higher in men while TCC was the most common type [22]. Ahmadi *et al.* [26] demonstrated that bladder cancer was more in the elderly and the males.

The mean age and BMI of our patients were 63.69 years and 23.8 kg/m². These figures were 66 years and 27 in one study undertaken by the Alberta Urology Institute Radical Cystectomy Database [27]. In a study in Esfahan, the age at diagnosis of disease was 64.4 years which is in agreement with our findings too [28]. The follow up period in our study was 5.22±4.03 years, which is in concordance with the findings of Brookfield *et al.* [29] in African women which was 5.2 years. In another study, this follow up was 6.7 years [16].

In our study, 1, 3 and 5 years survival time in patients suffering from bladder cancer were 0.9440, 0.6836 and 0.4930 respectively. Rezainzadeh *et al.* [30] in Fars Province, Southern Iran revealed that the overall survival rate of bladder cancer was less than other areas at the end of 1, 3, 5, 10 years which was equal to 0.8989, 0.7132, 0.5752 and 0.2459 respectively. The disease was noticed more in males. The mean and the standard deviation of variables of age, BMI and time of follow-up were obtained as 64.2 ± 12.9 years, 23.7 ± 4.7 kg/m² and 62.6 ± 48.4 months respectively. Another study showed that 5 year survival time in bladder cancer patients was 0.81, which was correlated to factors such as grade and stage of disease [3]. The 5 years survival time was 0.82.96 in another study [16].

In Rodriguez*et al.*'s study, male patients constituted 83.3% of the participants [16]. Findings of another study - in which females consisted 34.6% of the participants - revealed that the survival accumulation in males was more than females after five years [31]. Based on WHO reports, the survival accumulation at the end of five years in Thai females and males suffering from the bladder cancer was 39 and 61.5% respectively. The survival accumulation after five years in female and male patients from Madras, India was 15 and 25% respectively [32]. A multi ethnic study denoted to a higher survival rate among Asian males [33].

Manterola*et al.*'s study showed that the survival accumulation at the end of five years was 50% [34]. In another study, the survival accumulations at the end of five and ten years were 57 and 54% respectively [35]. In another multi ethnic study, the overall survival of bladder cancer was 66, 61, 59 and 52% in Japanese, Caucasian, Filipino and Hawaiian patients respectively [33]. In one study, the survival rates of the patients between 60-70 and those between 70-80 reduced respectively 1.3 and 1.2 times in comparison to the patients aging under 60 years old [36]. Comparing the rate of 1, 3 and 5 years survival time, no significant difference was noticed between both sexes of patients suffering from bladder cancer.

The 1 and 3 years survival rate in patients suffering from bladder cancer showed a significant difference regarding aged groups while survival decreased when the increase in age and in 60-70 years age group, the lowest survival was noticed. Two important variables of age and type of treatment play an important role in patients' survival in Cox reemission model as the patients in 50-60 years age group were more at the risk of bladder cancer (2.7 times more) and in 60-70 years age group (4.7 times more) and in older than 70 years old (4.5 times more) in comparison to those under 50 years old. Fairy showed that the survival rate reduces 1.3 times less in patients aged 60-70 years and 1.2 times less among those aged 70-80 years when compared with those less than 60 years [27]. The results of the present study showed a stronger relationship, but follows a similar model, as the most effect age group were 60-70 years age group whereas the severity reduced among those who were older than 70-years old.

Cox results showed that chemotherapy and radiotherapy increased themortality rate 3 times more in comparison to a combined treatment.

The results of Fairey's study is in contrary of our findings, as chemotherapy had no significant effect, whereas, surgery has caused a reduction in survival rate [27]. Another study showed that radiotherapy and chemotherapy were suitable measures in bladder cancers and a combined treatment was beneficial in cancers sized 5 cm or more [37].

In a study by Gulliford *et al.* the severity of the disease was the most influential factor on the patients' survival in that study.[38] Chemotherapy was shown to be a gold standard for patients suffering from cancer of bladder; however, half of patients suffering from invasive diseases died in spite of chemotherapy.[39] Removal of the bladder and pelvic tissues involved was demonstrated to be the standard treatment of these patients. Nevertheless, radiotherapy is still the only solution for patients who cannot receive the standard treatment due to their age, status and suffering from other diseases [40].

According to available data, the combination therapy is considered as the final treatment of choice [39]. Based on studies undertaken on the issue, a combination of radiotherapy, pharmaceutical supplements and operation was shown to be beneficial on the survival rate of the patients [40]. According to the study performed in England, the survival rate of cancer of bladder decreased from 1998 to 2004 [41] which denotes to a need of reform in early diagnosis of the disease, correct use of therapeutic measures, operation, radiotherapy and the combination of all methods.

It was shown that the delay in referring the patients to clinics to start the treatment is important in management of the disease decreasing the patients' survival rate [42]. So early diagnosis of the disease was emphasized as it leads to an increase in accumulation of the survival rate at the end of five years up to 100% [38]. Our results indicate that most cancers were diagnosed at advanced stages and radiotherapy, chemotherapy, surgery or a combined treatment were effective in treatment of the cancer patients.

In our study, the rate of survival of 1, 3 and 5 years among patients suffering from bladder cancer showed no significant difference in married subjects in comparison to single ones. In a study in Norway, no relationship was seen between marriage and survival too [43]. Also in a study in Esfahan [28], no correlation was noticed between marriage and disease which agrees with the our findings, but in the study of Data *et al.*[44] using cox regression model, married individuals showed a higher survival rate. In another study in USA, it was shown that married people had 20% higher survival rate than single subjects and 44% higher survival rate than widows [45].

In the present study, a histological grade of 73.3% was zero and no difference was seen among patients in accordance with Kaplan-Mayer test whereas, in another study [2], the grade or stage of disease was one of the affecting factors on the survival rate. The reason for such difference may be the small numbers of the subjects in this study who were in grade one or higher.

In the present study among the study population, no difference was seen between the survival rate and smoking. Similar results were noted in Tootoonchi *et al.* [28] in Esfahan in use of narcotics as a risk factor, but in another study, smoking had a correlation with bladder cancer, showing that 35-50% of patients suffered from bladder cancer [2]. In Brookfield *et al.* [29] the survival of smoking patients was not higher than survival of non-smoking ones. In another study, it was shown that the rate, period, times of consumption and the method of use of narcotics were higher in patients suffering from bladder cancer in comparison to control ones [46]. Regarding smoking, Erdurak *et al*. [47] showed that tobacco was the main risk factor for bladder cancer in Manisa which was responsible for 56% of cases; predominantly in rural population.

Some other studies have revealed that other diseases such as other cancers and hypertension can also affect on patients survival [43]. This factor was not considered in the present study which is one of limitations of the present study. Age over 60 years and type of treatment were the most important effective factors in survival of patients, as a increase in age led to a lower survival rate, whereas, in over 70 years old subjects, the severity reduced. Surgery or surgery together with chemotherapy and radiotherapy had a better effect on the survival of patients regarding the stage of disease. In relation to sex, 80 patients (15.6%) were females and 434 (84.4%) were males. A correlation between sex and hormones and occupation was previously reported too [22].

The cumulative survival rate in our study population was less than other reports. Since age older than 60 years and treatment type were the most important predictors of survival time observed in our patients, screening for early diagnosis and use of combination therapy seem necessary for older subjects.

ACKNOWLEDGEMENTS

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