Original Article
http://mjiri.iums.ac.ir
Medical Journal of the Islamic Republic of Iran (MJIRI)

Med J Islam Repub Iran. 2022 (18 Apr);36.37. https://doi.org/10.47176/mjiri.36.37

Estimating the Prevalence of Bladder Cancer by Stage in Iran as a Developing Country

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Received: 5 Jul 2021 Published: 18 Apr 2022

Abstract

Background: Bladder cancer is among the 10 most common cancers globally and in Iran. The prevalence rate is a crucial metric for both estimating disease burden and policymakers. On the other hand, bladder cancer is a heterogeneous disease with different stages, high recurrence, and progression rate. In planning treatment procedures, it is important to know the prevalence of bladder cancer by stages. In the current study, we aimed to estimate the 5-year prevalence of bladder cancer by stages using the Markov model.

Methods: This was a simulation study. To estimate the 5-year prevalence of bladder cancer by stages, we used the Markov model with a time horizon of 5 years following diagnosis. We simulated the natural history of bladder cancer using a literature review. We extracted survival rate, stage-specific recurrence, and progression rate using local and international publications and expert opinion. In addition, we used the Iranian life table and extracted probabilities of mortality due to other causes of death.

Results: Five-year prevalence of bladder cancer for the year 2018 was estimated at 21,807 patients. Non- muscle-invasive bladder cancer accounted for around 68% of all cases, with 42% in the Ta low-grade stage. About 32% of bladder cancer prevalent cases were muscle-invasive bladder cancer patients, from which about 8% had metastatic tumors.

Conclusion: Researchers and policymakers can utilize the findings of this study to conduct economic burden analyses and plan resource allocation.

Keywords: Markov Model, Bladder Cancer, Prevalence, Stage, Epidemiology, Iran

Conflicts of Interest: None declared
Funding: This work was supported by Kerman Neuroscience Research Center, Institute of Neuropharmacology (grant number: 9421).

Cite this article as: Rashidian H, Haghdoost AA, Daroudi R, Raadabadi M, Ebadzadeh MR, Zendehdel K. Estimating the Prevalence of Bladder Cancer by Stage in Iran as a Developing Country. *Med J Islam Repub Iran.* 2022 (18 Apr);36:37. https://doi.org/10.47176/mjiri.36.37

Introduction

Bladder cancer is the 10th most common cancer worldwide, with an incidence number of about 6 million annually. Bladder cancer ranks 13th in terms of death due to cancer. Worldwide, bladder cancer is the 6th most common cancer and the 9th most common cause of death due to cancer among men (1). There is a wide range of geographical variations in the bladder cancer incidence, with the highest variation in North Africa, Central and West Asia, and the lowest in Sub-Saharan Africa (1). Bladder cancer with an age-standardized rate of (ASR) of 10.1 is

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↑What is "already known" in this topic:
Bladder cancer is one of the most prevalent cancers among the male Iranian population. The transition between stages of this cancer is high because of the high recurrence and progression rate. However, statistics about the prevalence of this cancer by stage are not available.

→What this article adds:
In the current study, we used the Markov model to estimate bladder cancer prevalence by stage in the first 5 years of diagnosis. Researchers can use the findings of this study to evaluate economic studies, and policymakers can use them to distribute resources and prepare for cancer treatment needs.

[DOI: 10.47176/mjiri.36.37]

the 5th most common cancer in Iran among men, which is more than the world average (1).

The majority of bladder cancer cases have a good prognosis, however, the relatively high recurrence (30%-40%) and progression rate (15%) of bladder cancer (2) results in a high economic burden. On the other hand, the management of therapeutic procedures is a big issue for clinicians due to the high transition rate of patients' status and variations in treatment procedures based on different stages of bladder cancer that include Bacillus Calmette-Guerin therapy, radiotherapy, chemotherapy, and cystectomy (3). We necessarily need the estimation of bladder cancer prevalence by stages and states to provide appropriate treatment for patients. This information will enable researchers and policymakers to conduct economic studies (such as cost of illness and economic evaluation studies) and allocate resources more efficiently.

Dynamic models, such as the Markov model, are recommended here since they change over time and patients might progress through different phases of the disease (4). To the best of our knowledge, there are no statistics and studies available estimating the prevalence of bladder cancer cases by different stages in Iran; therefore, we designed the current study to provide mentioned statistics for the first time.

Methods

This was a simulation study and to estimate the 5-year prevalence of bladder cancer by stage we used a Markov model. In this model, we simulated the state of bladder cancer cases for the time horizon of 5-year following their diagnosis because most bladder cancer cases recover or die during the first 5 years following their diagnosis. All analyses were performed using Microsoft Excel 2016.

Markov Model

In this step, we simulated the natural history of bladder cancer using the Markov model. According to the American Joint Committee on Cancer classification, bladder cancer cases are divided into 2 major groups of non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) based on their spread to the thick layer of muscle in the bladder wall. NMIBC is divided into 3 minor groups, including Ta (confined to epithelium), CIS (Carcinoma in Situ), and T1 (confined to lamina propria). Also, some of Ta tumors are low grade and some are high grade. MIBC cases are divided into local muscle-invasive (invade to smooth muscle) and metastatic (invade to other organs) (Fig. 1).

We modeled the natural history of bladder cancer in 8 health states, including Ta low grade, Ta high grade, T1, Carcinoma in situ (CIS), locally advanced (T2, T3), metastatic, death from cancer, and death from other causes. We simulated a cohort in which bladder cancer cases can move between different states in the Markov model. A simplified Markov model of bladder cancer is depicted in Figure 2. Oval shapes in the figure are representative of health states of bladder cancer cases. In this model, every person can experience only 1 state at the same time. Arrows in the picture show the transition between health

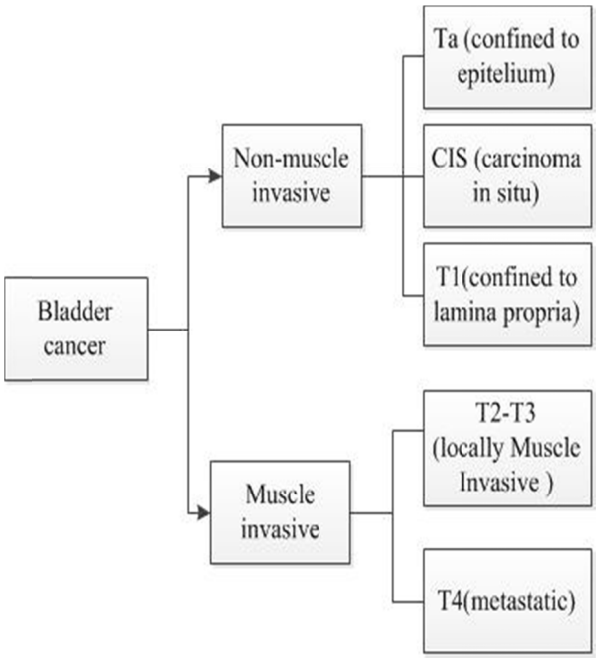

Fig. 1. Bladder cancer classification based on penetrance to muscle

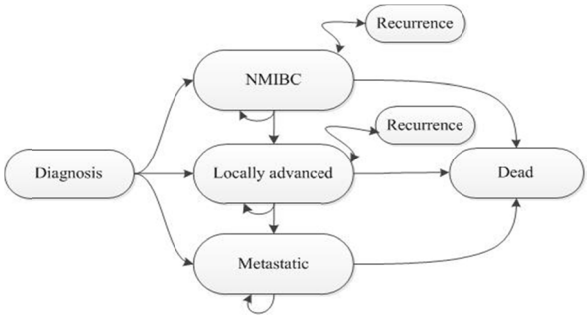

Fig. 2. Markov model for bladder cancer patients

states. Each cycle was equal to 1 year and each patient experience 1 health state in each cycle and the next cycle may remain in the same health state or transit to other states (Fig. 2).

In the first step, according to the stage distribution of incident bladder cancer cases, patients were assigned to health states. Bladder cancer patients after receiving the first treatment in the first cycle could experience several health states in other cycles of the model. NMIBC and locally advanced bladder cancer cases can recur after treatment or progress to the upper stages or die from cancer or other causes. Also, metastatic bladder cancer cases can die from cancer or other causes.

Model Parameters

To estimate the 5-year prevalence of bladder cancer for the year 2018, we extracted bladder cancer incidence statistics from Globocan and National Cancer Registry (1). We extracted the survival rate using the national literature. We extracted the stage distribution of bladder cancer cases reviewing the literature, However, statistics about stage-specific recurrence and progression rate were not available through the national literature, thus, we used the interna-

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Table 1. Probabilities of recurrence, progression and mortality of bladder cancer cases for the first five years of diagnosis

Probabilities of recurrence in NMIBC[a] and MIBC[b] (per year) (15-18)	First year	Second year	Third year	Forth year	Fifth year
Probabilities of recurrence in Ta low grade	26%	13%	6%	5%	3%
Probabilities of recurrence in Ta high grade	39%	11%	6%	2%	3%
Probabilities of recurrence in T1	39%	11%	6%	2%	3%
Probabilities of recurrence in CIS	45%	13%	7%	2%	3%
Probabilities of recurrence in locally advance after cystectomy	10%	4%	2%	1%	1%
Probabilities of progression in NMIBC[a] and MIBC[b] (per year) (15-20)					
Probabilities of progression in Ta low grade	4.0%	2.0%	2.0%	1.0%	1.0%
Probabilities of progression in Ta high grade	8%	5%	3%	2%	2%
Probabilities of progression in T1	15%	8%	5%	3%	3%
Probabilities of progression in CIS	15%	8%	5%	3%	3%
Probabilities of progression in locally advance after cystectomy	27%	15%	9%	5%	5%
Probabilities of mortality in NMIBC[a] and MIBC[b] (per year) (1, 10, 16, 18, 20)					
Probabilities of mortality in Ta low grade	2.0%	2.0%	2.0%	2.0%	2.0%
Probabilities of mortality in Ta high grade	5.0%	15.0%	15.0%	10.0%	10.0%
Probabilities of mortality in T1	5.0%	15.0%	15.0%	10.0%	10.0%
Probabilities of mortality in CIS	5.0%	15.0%	15.0%	10.0%	10.0%
Probabilities of mortality in locally advance after cystectomy	20.0%	18.0%	15.0%	15.0%	13.0%
Probabilities of mortality in metastases	60%	80%	60%	60%	60%
Probabilities of mortality from other causes	0.0115	0.0115	0.0115	0.0115	0.0115

[a]. Non-muscle invasive bladder cancer
[b]. Muscle invasive bladder cancer

Table 2. Stage distribution of bladder cancer cases (15-17, 19, 21)

NMIBC[a]	70%
Patients with tumors that are Ta at initial NMIBC diagnosis	70%
Ta tumors that are low grade at initial NMIBC diagnosis	63%
Ta tumors that are high grade at initial NMIBC diagnosis	37%
Patients with tumors that are T1 at initial NMIBC diagnosis	20%
Patients with tumors that are CIS at initial NMIBC diagnosis	10%
MIBC[b]	30%
Locally advance	65%
Metastases	35%

[a]. Non-muscle invasive bladder cancer
[b]. Muscle invasive bladder cancer

tional literature, then we modified statistics using an expert panel.

We used the survival rate of bladder cancer cases to estimate the number of death due to bladder cancer. To extract probabilities of mortality from other causes, we used the Iranian life table. According to evidence, the mean age of bladder cancer occurrence is about 62 years old, thus, we extracted death probability for the ages 60-65 years from the life table, which was equal to 0.0115 (Table 1).

We estimated the stage distribution of bladder cancer cases using the available literature and expert opinion. Considering the existing literature and reviewing the medical records of a referral hospital, we considered a percentage of 70% to NMIBC and 30% to MIBC (Table 2).

Prevalence Estimation

To estimate the 5-year prevalence of bladder cancer by stage, we assumed that new bladder cancer cases occur in the middle of each year, then we calculated the 5-year prevalence for the middle of the year 2018. We entered incidence cases of bladder cancer in the midpoint of the years 2014, 2015, 2016, 2017, and 2018, therefore, we had 5 patient groups in the model. The number of cycles for each patient group depends on the time of their disease diagnosis. For example, for incidence cases of the year 2014, we had 4 cycles and for 2015 incident cases we had 3 cycles, and so on (Fig. 3). In the end, we estimated a 5-year prevalence of bladder cancer cases counting survivor patients at the last cycle of each group by stage.

Ethical Considerations

The study protocol was approved by the Institutional Review Board (IRB) of Kerman University of Medical Sciences (IRB no. 9421). Informed consent was confirmed by the IRB.

Results

ASR of bladder cancer was 7.4 per 100,000 (n = 6041) for the year 2018 and about 70% of bladder cancer incidence cases (n = 4229) were non-muscle-invasive, and others were muscle-invasive (n = 1812). Moreover, about 40% of bladder cancer cases (n = 2368) were detected at the low-grade Ta stage and only about 12% of cases (n = 725) were metastatic (Table 3).

The prevalence of bladder cancer distribution by stage and incidence year is provided in Table 4. The 5-year

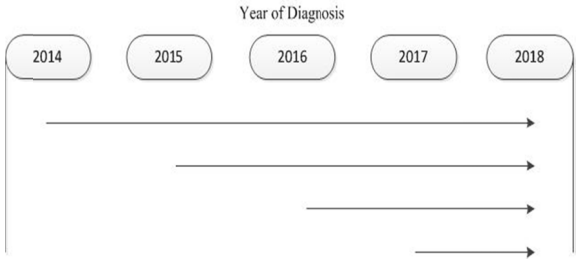

Fig. 3. Patient groups entered into Markov model and related cycles

[DOI: 10.47176/mjiri.36.37]

Table 3. Yearly incidence number of bladder cancer case by stage for the year 2014 to 2018

	2014	2015	2016	2017	2018
BC annual incidence (crude rate per 100000)	7.17	7.22	7.28	7.34	7.40
bladder cancer annual incidence (number)	5588	5703	5821	5952	6041
NMIBC[a]	3911	3992	4075	4166	4229
Patients with tumours that are Ta at initial NMIBC diagnosis	2738	2795	2852	2916	2960
Ta tumours that are low grade at initial NMIBC diagnosis	2190	2236	2282	2333	2368
Ta tumours that are high grade at initial NMIBC diagnosis	548	559	570	583	592
Patients with tumours that are T1 at initial NMIBC diagnosis	782	798	815	833	846
Patients with tumours that are CIS at initial NMIBC diagnosis	391	399	407	417	423
MIBC[b]	1676	1711	1746	1786	1812
Locally advance	1006	1027	1048	1071	1087
Metastases	671	684	699	714	725

[a]. Non-muscle invasive bladder cancer
[b]. Muscle invasive bladder cancer

Table 4. Prevalence of bladder cancer distribution by stage and incidence year

Years	2018	2017	2016	2015	2014	Total (number)	Total (percent)
Ta, low grade	2,368	1,560	1,734	1,750	1,663	9,075	0.42
Ta, low grade, recurrence	-	607	275	118	91	1,091	0.05
Ta, high grade	592	273	332	283	254	1,734	0.08
Ta, high grade , recurrence	-	227	54	23	6	310	0.01
T1	846	332	420	353	313	2,264	0.10
T1 , recurrence	-	325	71	29	7	432	0.02
CIS	423	142	205	174	156	1,100	0.05
CIS , recurrence	-	186	41	17	4	248	0.01
Locally advance	1,087	776	677	589	503	3,632	0.17
Locally advance , recurrence	-	107	31	14	4	156	0.01
Metastases	725	567	234	152	87	1,765	0.08
Total (number)	6,041	5,102	4,074	3,502	3,088	21,807	100.00
Total (percent)	0.28	0.23	0.19	0.16	0.14	100.00	

prevalence of bladder cancer for the year 2018 was estimated at 21,807 patients. About 68% of bladder cancer prevalent cases were NMIBC, with about 42% in Ta low grade, and about 32% of prevalent cases were MIBC with about 8% in the metastatic stage.

About 28% of bladder cancer prevalent cases were incidence cases in 2018 and the rest of them were incidence cases detected in previous years. Out of 5588 incidence cases in 2014, about 3088 were alive in 2018, which was equivalent to 55% of the 5-year survival rate. About 10% of bladder cancer cases were at recurrent state, about half of which were at low-grade Ta stage at the time of diagnosis. Out of 29105 incidence cases, 4349 (14.9%) patients died of cancer and about 352 (1%) died due to other causes.

Discussion

Bladder cancer is a heterogeneous disease with different stages, treatment procedures, and costs (3). Moreover, the recurrence and progression rates of bladder cancer are high and different based on disease stages. Although when estimating bladder cancer prevalence, we can use the incidence and the survival rate simply, to estimate bladder cancer prevalence cases by stage and time of diagnosis, we should use models such as the Markov model that assume future states depend only on the current state. Developing the Markov model, we used the incidence, recurrence, and progression rate of bladder cancer and also death due to bladder cancer and other causes. The 5-year prevalence of bladder cancer was estimated to be 21,807 for the year 2018 in Iran.

According to the results of the present study, the 5-year prevalence of bladder cancer was estimated to be 21,807 for the year 2018 in Iran. However, the Global Cancer Observatory (GLOBOCAN) 2018 estimated about 17,284 five-year prevalence cases of bladder cancer in Iran, which is lower than the current study results. The GlOBOCAN 2018 used the prevalence and incidence rates from Nordic countries (5) and the human development index statistics (6) to estimate country-specific prevalence numbers. However, in the present study, we used survival and incidence rate statistics to estimate the prevalence of bladder cancer. Therefore, the estimate provided in the GlOBOCAN 2018 underestimates the true prevalence of bladder cancer by about 20%.

In western countries most of the bladder cancer prevalent cases are NMIBC, which is approximately 75% (7), however, according to the current study results, lower percentages (68%) of bladder cancer prevalent cases were at lower stages (8). In developing countries, cancer cases are diagnosed at advanced stages (9).

The 5-year survival rate of bladder cancer prediction in our model was equal to 55%, which is consistent with the literature (10) and lower than what has been reported from western countries (75%) (7). The decreased survival percentage of bladder cancer cases in Iran could be attributable to earlier detection, inadequate treatment, or the difficulty of providing an optimal mix of surgery and radiotherapy for bladder cancer patients in Iran (9). The higher survival rate of bladder cancer cases in developed counties could be due to improvement in detection and treatment. If bladder cancer is detected early and treated appropriately, it has a moderate to good prognosis (9).

Nowadays, modeling tools such as the decision tree and the Markov model are widely used to assess disease burden (11, 12). In the year 2016, Leal et al used the Markov

[DOI: 10.47176/mjiri.36.37]

model to estimate the 10-year prevalence and economic burden of bladder cancer in European countries (13). However, The present study was the first to estimate the prevalence of bladder cancer by stage and years of incidence using the Markov model in Iran.

There was limited evidence about the natural history of bladder cancer in Iran, thus, we extracted some of them, including the recurrence and the progression rate, from the literature of other countries and adapted them according to urologists' opinion and the exiting literature.

Although studies have revealed that there may be a probable sex difference in urothelial cell carcinoma of the bladder with treatment implications (14), gender-specific transition probabilities were not accessible in the literature. However, most bladder cancer patients are men and sex differences may not be a big concern. Also, studies have shown that elderly people have poor prognosis than young people (2), but age-specific transition probabilities were not available in the literature, and bladder cancer cases mainly occur in the age above 65 years. Furthermore, we assumed that all bladder cancer patients received some form of treatment in our analyses; otherwise, the 5-year prevalence rate would have been underestimated. We propose conducting prospective studies to determine the rate of recurrence and advancement of bladder cancer cases by gender and age. Also, we suggest estimating the prevalence of bladder cancer directly using incidence data from cancer registries and follow-up for emigration or death. Moreover, developing a screening programs is suggested for high-risk populations, as the percentage of NMIBC cases was lower in Iran than in western countries and treatment costs are strongly related to the stage of disease at diagnosis.

Conclusion

For the first time in Iran, we utilized the Markov model to estimate the prevalence of bladder cancer by stages. The current study's findings can be used to estimate the economic burden of bladder cancer and to diagnose cases of bladder cancer. The method used in the current study can be used to assess the prevalence of bladder cancer in other developing nations.

Acknowledgment

This work was supported by Kerman Neuroscience Research Center, Institute of Neuropharmacology (grant number: 9421). The authors are thankful to Kerman Shahid Bahonar hospital staffs for their assistance to conduct the study.

Conflict of Interests

The authors declare that they have no competing interests.

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[DOI: 10.47176/mjiri.36.37]