original article

Bladder cancer in Saudi Arabia: a registry-based nationwide descriptive epidemiological and survival analysis

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BACKGROUND: Our understanding of the risk factors, prevalence, incidence rate, and age distribution of bladder cancer (BC) in Saudi Arabia is insufficient due to limited data.

OBJECTIVES: Describe the epidemiology and analyze factors associated with survival in patients with BC in Saudi Arabia.

DESIGN: Retrospective medical record review.

SETTINGS: Registry-based nationwide study.

PATIENTS AND METHODS: The study included all records in the Saudi Cancer Registry of patients diagnosed with a primary BC from 1 January 2008 to 31 December 2017. Collected data included year of diagnosis, gender, age, marital status, region and nationality, tumor site of origin, tumor histological subtype, tumor behavior, tumor grade, tumor extent, tumor laterality, the basis of the diagnosis, and survival status. Factors predicting survival were tested by a Kaplan-Meier and Cox proportional hazards regression analysis.

MAIN OUTCOME MEASURE: Mortality status on last contact.

SAMPLE SIZE: 3750 patients.

RESULTS: The overall incidence of BC was 1.4 per 100 000 persons. Significant differences in the distribution of survival were observed by age, gender, nationality, place of residency, tumor morphology, tumor grade and extension. The adjusted predictors of decreased survival were age, squamous cell carcinoma, Grade III and IV bladder tumors, regional direct extension, regional lymph node extension, combined regional lymph node and direct extension, and distant metastasis. Male gender and being widowed were predictors of improved survival in the unadjusted analysis.

CONCLUSION: This study provides further understanding of BC in a region with a high prevalence of risk factorsuch as smoking. Highlighting these factors, specifically in Saudi Arabia, improves evidence-based practice in this region and may facilitate appropriate care to optimize outcomes.

LIMITATIONS: Retrospective study and underreporting.

CONFLICT OF INTEREST: None.

Bladder cancer (BC), which occurs in the lining of the bladder, has the highest recurrence rate of all malignancies. Globally, BC is considered the 6th most prevalent type of cancer in men and the 17th in women.[1] In 2018, there were 549 393 new cases and 199 922 patients died due to BC, according to the international database, GLOBOCAN. BC is a malignant proliferation which frequently arises from the urothelial cells that line the inside of the bladder. A mutation causes the cells to grow and divide more rapidly than the normal cells, which results in the irritation of the bladder wall and, in some cases, invasion of the muscular layer resulting in a more severe manifestation of BC. In time, it metastasizes to distant organs, such as the lymph nodes, bones, lungs, and liver. BC bladder cancer is categorized as non-muscle-invasive BC, also known as superficial BC, and muscle-invasive BC.[2] According to the National Cancer Institute, BC constituted 4.5% of all new cancer cases in the United States (US) in 2020, with an estimated 81 400 new cases and 17 980 deaths, constituting 3.0% of all cancer-related deaths in the US.[3] BC becomes more frequent with age, with a prevalence in men with a rate of 34.9 per 100 000 cases compared to women at 8.6 per 100 000 cases. The median age for diagnosis is 74 years; however 1.6% of BC patients are younger than 44 years.[3] In Europe, 151 198 cases of BC were diagnosed in 2012, 4.4% of all new cancer cases. In the same year, 52 374 Europeans died due to BC, also 3% of all cancer deaths. Men had a higher incidence than women with 26.9 and 5.3 cases per 100 000, respectively. The literature indicates that the highest incidence rate of BC in Europe occurs in Belgium and Malta, at 26.5 and 23.4 per 100 000 persons, respectively.[4] Several other European countries, including Belarus and Moldova, have lower incidence rates of 9.5 and 9.3 per 100 000, respectively. The lowest incidence rates occur in South American and Asian countries.[5] In the Middle East, according to the latest data of the World Cancer Research Fund International (2018), Lebanon has the second highest age-standardized incidence rate of BC globally in men with 40.4 cases per 100 000 and the highest for both genders with 25.0 cases per 100 000.[6] Locally, according to the 2013 Cancer Incidence Report in Saudi Arabia, there were 280 new cases of urinary BC, 4.3% and 0.8% of all newly diagnosed cases of cancer in men and women, respectively. It is ranked the 8th most frequent cancer in males and the 20th in females. Of the 280 cases, 227 were male (81%) and 53 female (19%). The overall age-standardized incidence rate was 3.8 per 100 000, in males and 1 per 100 000 in females. The median age at diagnosis was 63 years for males and 64 years in females.[7] The only local study reporting the characteristics of BC investigated patients younger than 40 years old, from 1994 and 2017, with a sample size of 38 cases. The majority (n=27, 71.1%) were male. The median age at diagnosis was 33 years, ranging from 1 to 40 years. Almost half (n=17, 45%) smoked. Macroscopic hematuria was present in 57.8% (n=22). The most frequent histopathology was papillary urothelial carcinoma (n=18, 58%). Of all the malignancies, 63.2% (n=24) and 44.7% (n=17) were low stage and low grade, respectively. For the majority (n=31, 81.6%), a transurethral resection of the bladder tumor was performed. Distant metastasis was reported in 5.3% (n=2) and 8% (n=3) died during follow-up.[8]

Our understanding of the risk factors, prevalence, incidence rate, and age distribution of BC in Saudi Arabia is limited; to the best of our knowledge, no local studies have been done. The aim of this study was to present a nationwide description of the epidemiology and an analysis of survival analysis for BC in Saudi Arabia. The incidence of tumors in a particular geographic area can expose the influence of the environment, race, and culture on the prevalence of cancer.

PATIENTS AND METHODS

This retrospective chart review included all the patients diagnosed with a primary bladder tumor from 1 January 2008, to 31 December 2017. Patients who were diagnosed with metastatic bladder tumors were excluded from the study. The data was collected from the Saudi Cancer Registry, which collects tumor data from all private, military, and Health Ministry hospitals in Saudi Arabia through five regional offices. Data analysis and periodic reporting are performed at the main office in Riyadh. All the eligible patients were enrolled. The variables were grouped according to year of diagnosis, gender, age, marital status, region and nationality, tumor site of origin, tumor histological subtype, tumor behavior, tumor grade, tumor extent, tumor laterality, the basis of the diagnosis, and the survival status.

Data analysis was performed with the IBM SPSS version 23.0 (IBM Corporation, NY, USA). Frequency and percentage were used to display the categorical variables and a mean and standard deviation for the continuous variables. A chi-square was used to test associations between the categorical variables and an ANOVA to compare the means of each group. The ANOVA was followed by a Tukey post-hoc test to determine the exact difference between groups. A Kaplan–Meier survival analysis was done to test the factors affecting survival and to generate survival curves for the different factors. A Cox proportional hazards regression analysis

was used to determine the factors predicting survival in BC patients. The model included several factors as predictors, including age, gender, nationality, place of residency, marital status, location of tumor, morphology of tumor, grade of tumor, and extension. The level of significance was set at 0.05.

The incidence rate was calculated for each type of tumor per 100 000 for each year separately and then the average over all years was calculated and reported. An accumulative average for bladder tumor incidence per 100 000 for each year was also calculated. The country's population size for calculation of the incidence rate for each year was acquired from the General Authority for Statistics. The study was approved by the Institutional Review Board of King Abdullah International Medical Research Center, Ministry of National Guard-Health Affairs, Riyadh, Kingdom of Saudi Arabia (approval number NRC21R/085/03). Patient confidentiality was ensured. Data were collected and used by the research team only. Serial numbers were used instead of medical record numbers to ensure anonymity. Due to the retrospective nature of the study, and the use of anonymized patient data, the requirement for informed consent was waived.

RESULTS

The registry contained 3750 patients with BC (**Table 1**). The mean age was 62.3 (15.0) years and the majority (58.6%, n 2196) were 60 years or older, males (n=3083, 82.2%) and Saudi (n=2672, 71.3%). Most were married (77.8%, n=2918). Almost a third (n=1123, 29.9%) resided in the central region. Most of the tumors were multifocal (85.6%) and urothelial carcinoma (89.9%) of various grades (**Table 2**). The overall pattern of BC incidence was similar for all the years with slight fluctuations. The highest incidence of the overall BC (1.4 per 100 000) was observed in 2010 and 2013, with the lowest incidence (1.1 per 100 000) in 2008. For the urothelial carcinoma, the fluctuating pattern of incidence was almost identical to the overall BC incidence, which was expected as it constituted 89.9% of all the BC types. The squamous cell and adenocarcinoma fluctuated throughout the study period. The squamous cell carcinoma incidence ranged from 0.05 to 0.09 per 100 000, and the adenocarcinoma from 0.02 to 0.06 per 100 000. The majority (n=3128, 83.4%) were alive at last contact. The mortality rate was 16.3% (n=610, with 12 unknowns). Of the deceased group, 579 (94.92%) died due to the cancer. The mean interval in years from diagnosis to death for the deceased group due to cancer was 0.92 (0.90) years.

Although both genders presented with multifocal tumors as the most frequent location, the gender difference was statistically significant for the distribution of the tumor location (*P*=.043) (**Table 3**). There was also a significant difference between the morphology of the tumor and gender (*P*<.001) the female group had a higher rate of adenocarcinoma and squamous cell carcinoma compared to males. A significant difference was also observed in terms of the extension of the tumor by gender (*P*=.002). The male group had a higher rate of localized tumors compared to the female group, and the female group had a higher rate of regional extension. A significant difference was found between the location of the tumor and age (*P*=.006).

Table 1. Sociodemographic profile of the study population (n=3750).

Profile	
Age group (years)	
≤18	24 (0.6)
19-39	216 (5.8)
40-59	1308 (34.9)
≥60	2196 (58.6)
Unknown	6 (0.2)
Gender	
Male	3083 (82.2)
Female	667 (17.8)
Nationality	
Saudi	2672 (71.3)
Non-Saudi	1078 (28.7)
Marital status	
Single	208 (5.5)
Married	2918 (77.8)
Divorced	16 (0.4)
Widowed	84 (2.2)
Unknown	524 (14.0)
Place of residency	
Central region	1123 (29.9)
Eastern region	615 (16.4)
Northern region	186 (5.0)
Western region	1309 (34.9)
Southern region	491 (13.1)
Unknown	26 (0.7)

Data are number (%)

Table 2. Tumor profiles.

Profile	
Location	
Trigone of urinary bladder	47 (1.3)
Dome of urinary bladder	36 (1)
Lateral wall of urinary bladder	231 (6.2)
Anterior wall of urinary bladder	54 (1.4)
Posterior wall of urinary bladder	102 (2.7)
Bladder neck	38 (1)
Ureteric orifice	31 (0.8)
Multifocal	3211 (85.6)
Morphology	
Adenocarcinoma	106 (2.8)
Squamous cell carcinoma	208 (5.5)
Urothelial carcinoma	3371 (89.9)
Other	65 (1.7)
Grade	
Grade I (well differentiated)	406 (10.8)
Grade II (moderately differentiated)	796 (21.2)
Grade III (poorly differentiated)	1053 (28.1)
Grade IV (undifferentiated anaplastic)	845 (22.5)
Unknown	650 (17.3)
Extension	
In situ	12 (0.3)
Localized	2380 (63.5)
Regional: direct extension	360 (9.6)
Regional: lymph node	71 (1.9)
Regional: lymph node and direct extension	114 (3)
Regional: not otherwise specified	2 (0.1)
Distant metastasis	448 (11.9)
Unknown	363 (9.7)

Table 2 (cont). Tumor profiles.

Profile	
Lateralization	
Not paired (unknown)	3747 (99.92)
Right	1 (0.03)
Left	2 (0.05)
Basis of diagnosis	
Death certificate	55 (1.5)
Clinical	10 (0.3)
Medical imaging	22 (0.6)
Cytology/ hematological	119 (3.2)
Histology of metastases	34 (0.9)
Histology of primary	3496 (93.2)
Autopsy	2 (0.1)
Unknown	12 (0.3)
Year of diagnosis	
2008	287 (7.65)
2009	331 (8.83)
2010	387 (10.32)
2011	352 (9.39)
2012	365 (9.73)
2013	421 (11.23)
2014	401 (10.69)
2015	366 (9.76)
2016	416 (11.09)
2017	424 (11.31)

Data are number (%).

The Tukey post-hoc test revealed a significantly lower age ($P<.05$) when comparing the group with tumors localized in the ureteric orifice to the groups with tumors localized in the posterior bladder wall or in the neck of the bladder. A significant difference was also found between age and the different morphologies ($P=.044$), the group with urothelial carcinoma had the highest age and the group with adenocarcinoma the lowest age. A significant association was found between age and grade ($P<.001$). The Tukey post-hoc test indicated that the groups with grades III and IV had a significantly higher mean age compared to the groups with Grade I and II ($P<.05$). In addition, a significant association ex-

isted between age and extension (*P*=.001). The group with a distant metastasis had a significantly higher age compared to the group with a localized tumor (*P*<.05).

A significant difference was found between the grade of the tumor and marital status (*P*=.044) (**Table 4**). The single group had the lowest rate of Grade IV tumors (21%), and the groups who were widowed or divorced had a notably higher rate of Grade IV tumors. A significant difference was found between the extension of the tumor and marital status (*P*=.026), the single group had the lowest rate of distant metastasis, and the groups who were widowed or divorced had a notably higher rate of distant metastasis. A significant difference was found between the grade of the tumor and the morphology (*P*<.001) (**Table 5**). Urothelial carcinoma had a notably higher rate of Grade IV tumors compared to adenocarcinoma and squamous cell carcinoma. A significant difference in the distribution of the tumor extension was also observed in terms of the morphology (*P*<.001), both adenocarcinoma and squamous cell carcinoma had a notably higher rate of distant metastasis compared to urothelial carcinoma.

A significant difference in survival was observed by age group (*P*<.001), the group with the longest mean survival was the 19 to 39 years age group, and the shortest was in the older and younger groups (mean of 6.75 years in ≥60 years group vs 1.99 years in the ≤18 years group. There was a significant difference in survival between genders (*P*<.001); the male group had a higher mean survival compared to the female group (5.49 years vs 4.99 years) (**Figure 1**). Saudis had longer mean survival years compared with the non-Saudis (5.33 years vs 3.98, respectively, *P*<.001) (**Figure 2**). The highest mean survival years occurred in the western region, and the lowest in the southern region (5.81 years compared to 4.71 years, respectively, *P*=.015). The location of the tumor was also significantly associated with longer survival (*P*=.014); the location with the highest mean survival was the lateral wall of the urinary bladder, and the lowest the anterior wall (6.54 years vs 2.36 years) (**Figure 3**). Mean survival for urothelial carcinoma was higher than for the groups with adenocarcinoma and squamous cell carcinoma (5.51 years vs 3.59 and 3.64 years, respectively, (*P*<.001) (**Figure 4**). Grade I and II tumors had a notably higher mean survival compared to the groups with Grade III and IV tumors (*P*<.001).The longest mean survival occurred in patients who had localized tumors; the lowest in the group with distant metastasis (6.46 years vs 2.26 years, respectively, (*P*<.001).

In the Cox proportional hazards regression analysis, the factors significantly associated with decreased

Table 3. Tumor characteristics by sex.

	Male	Female	*P* value
Location			
Trigone of urinary bladder	37 (1.2)	9 (1.4)	
Dome of urinary bladder	27 (0.9)	8 (1.2)	
Lateral wall of urinary bladder	193 (6.4)	32 (4.9)	
Anterior wall of urinary bladder	49 (1.6)	3 (0.5)	**.035**
Posterior wall of urinary bladder	73 (2.4)	27 (4.1)	
Bladder neck	34 (1.1)	4 (0.6)	
Ureteric orifice	26 (0.9)	5 (0.8)	
Multifocal	2591 (85.5)	567 (86.6)	
Morphology			
Adenocarcinoma	75 (2.5)	31 (4.7)	
Squamous cell carcinoma	134 (4.4)	74 (11.3)	**<.001**
Urothelial carcinoma	2821 (93.1)	550 (84)	
Grade			
Grade I (well differentiated)	344 (13.6)	58 (10.8)	
Grade II (moderately differentiated)	661 (26.1)	131 (24.5)	
Grade III (poorly differentiated)	842 (33.2)	195 (36.4)	.211
Grade IV (undifferentiated anaplastic)	687 (27.1)	151 (28.2)	
Extension			
In situ	11 (0.4)	1 (0.2)	
Localized	1971 (72)	379 (64.3)	
Regional: direct extension	281 (10.3)	67 (11.4)	
Regional: lymph node	55 (2)	15 (2.5)	**.002**
Regional: lymph node and direct extension	82 (3)	29 (4.9)	
Distant metastasis	336 (12.3)	98 (16.6)	

Data are number (%)

Table 4. Tumor characteristics by marital status.

	Single (n=208)	Married (n=2918)	Divorced` (n=16)	Widowed (n=84)	*P* value
Location					
Trigone of urinary bladder	1 (0.5)	35 (1.2)	0 (0)	1 (1.2)	
Dome of urinary bladder	2 (1)	25 (0.9)	0 (0)	1 (1.2)	
Lateral wall of urinary bladder	8 (4.1)	176 (6.1)	1 (6.3)	8 (9.6)	
Anterior wall of urinary bladder	5 (2.6)	42 (1.5)	0 (0)	1 (1.2)	.906
Posterior wall of urinary bladder	4 (2.1)	82 (2.9)	0 (0)	4 (4.8)	
Bladder neck	0 (0)	32 (1.1)	0 (0)	2 (2.4)	
Ureteric orifice	1 (0.5)	23 (0.8)	0 (0)	1 (1.2)	
Multifocal	172 (89.1)	2461 (85.6)	15 (93.8)	65 (87.3)	
Morphology					
Adeno-carcinoma	5 (2.6)	80 (2.8)	0 (0)	4 (4.8)	
Squamous cell carcinoma	12 (6.2)	165 (5.7)	2 (12.5)	6 (7.2)	.756
Urothelial carcinoma	176 (91.2)	2631 (91.5)	14 (87.5)	73 (88)	
Grade					
Grade I (well differentiated)	22 (13.6)	300 (12.3)	1 (6.7)	5 (7)	
Grade II (moderately differentiated)	53 (32.7)	618 (25.4)	2 (13.3)	11 (15.5)	
Grade III (poorly differentiated)	53 (32.7)	829 (34.1)	6 (40)	26 (36.6)	**.044**
Grade IV (undifferentiated anaplastic)	34 (21)	687 (28.2)	6 (40)	29 (40.8)	
Extension					
In situ	0 (0)	6 (0.2)	0 (0)	0 (0)	
Localized	134 (76.1)	1846 (69.8)	7 (50)	39 (52)	
Regional: direct extension	17 (9.7)	286 (10.8)	3 (21.4)	8 (10.7)	
Regional: lymph node	3 (1.7)	60 (2.3)	0 (0)	2 (2.7)	**.026**
Regional: lymph node and direct extension	2 (1.1)	96 (3.6)	1 (7.1)	7 (9.3)	
Distant metastasis	20 (11.4)	352 (13.3)	3 (21.4)	19 (25.3)	

Data are number (%). Marital status unknown for 521 patients.

survival were age, squamous cell carcinoma, Grade III, Grade IV, regional: direct extension, regional: lymph node extension, regional: lymph node and direct extension, and distant metastasis (**Table 6**). Male sex and being widowed were significantly associated with increased survival.

DISCUSSION

Patient demographics

The demographic characteristics of the population included in this study corresponded to that in similar descriptive studies in other countries. Arrizabalaga et al9 reported the descriptive epidemiology of BC in Madrid, noting a mean patient age of 65.9 years, similar to 62.3 years in the current study, with the majority (83.5%) male, similar to 82.2% in the current study. The same study also reported a tumor profile similar to our study, with 77% of the tumors primarily superficial and 23% infiltrating. In the current study, the age category most affected was 55 years and older with 90% of the BC diagnoses, compared with 8% of the diagnoses in the US in the age group 65 years and older.[10] Our findings are consistent with these national averages. Regarding tumor morphology, the current study indicated urothelial carcinoma as the most prevalent presentation. This correlates with an observational study conducted by Andreassen et al that investigated the incidence of this morphology over a 33-year period, between 1981 and 2014. The findings indicated that the incidence of urothelial carcinoma is higher, compared to other BC morphologies, with an incidence of 21.1 cases per 100 000 in men and 6.2 cases per 100 000 in women.[11]

Incidence rate of bladder carcinoma

Our study had findings consistent with national and international demographic information and tumor profiles. The only exception was the incidence of BC, which was lower at 1.4 cases per 100 000. An epidemiological study of the incidence of urinary bladder cancer in Europe demonstrated an incidence two-fold higher than the current study in certain countries.[12] Hungary, for example, reported an incidence of 3.9 cases per 100 000 in men and 7.4 cases per 100 000 in women.[12] These findings, however, were contradicted in a review by Saginala et al, who reported a four-fold increase in the incidence of BC in men compared with women, with a respective incidence of 9.6 cases per 100 000 in men and 2.4 cases per 100 000 in women globally. Despite the discrepancies, current reports indicate a higher incidence rate of BC compared with

Table 5. Tumor characteristics by morphology.

	Adeno-carcinoma	Squamous cell carcinoma	Urothelial carcinoma	*P* value
Location				
Trigone of urinary bladder	2 (1.9)	1 (0.5)	43 (1.3)	
Dome of urinary bladder	4 (3.8)	3 (1.4)	28 (0.8)	
Lateral wall of urinary bladder	3 (2.8)	10 (4.8)	212 (6.3)	
Anterior wall of urinary bladder	3 (2.8)	4 (1.9)	45 (1.3)	**.094**
Posterior wall of urinary bladder	2 (1.9)	4 (1.9)	94 (2.8)	
Bladder neck	2 (1.9)	4 (1.9)	32 (0.9)	
Ureteric orifice	1 (0.9)	0 (0)	30 (0.9)	
Multifocal	89 (84)	182 (87.5)	2887 (85.6)	
Grade				
Grade I (well differentiated)	15 (18.5)	18 (10.5)	369 (13.1)	
Grade II (moderately differentiated)	31 (38.3)	106 (61.6)	655 (23.3)	
Grade III (poorly differentiated)	29 (35.8)	39 (22.7)	969 (34.4)	**<.001**
Grade IV (undifferentiated anaplastic)	6 (7.4)	9 (5.2)	823 (29.2)	
Extension				
In situ	0 (0)	0 (0)	12 (0.4)	
Localized	44 (47.8)	88 (46.3)	2218 (72.9)	
Regional: direct extension	10 (10.9)	45 (23.7)	293 (9.6)	
Regional: lymph node	7 (7.6)	4 (2.1)	59 (1.9)	**<.001**
Regional: direct extension	4 (4.3)	12 (6.3)	95 (3.1)	
Distant metastasis	27 (29.3)	41 (21.6)	366 (12)	

Data are number (%)

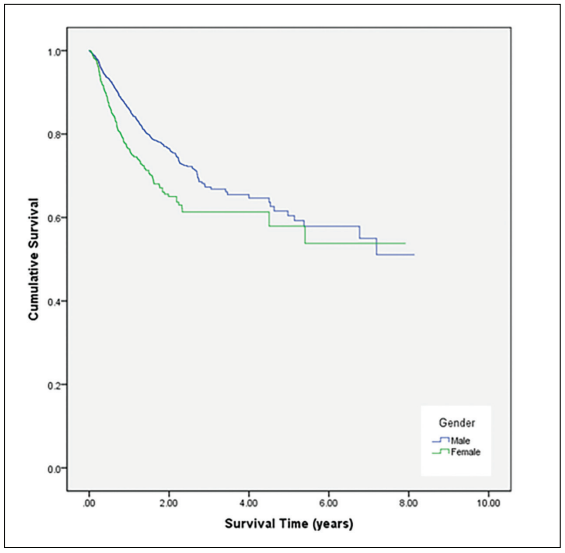

Figure 1. Kaplan-Meier survival analysis by gender.

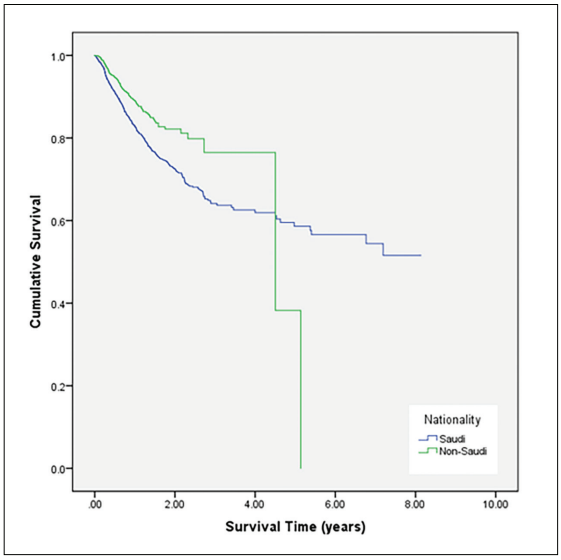

Figure 2. Kaplan-Meier survival by nationality

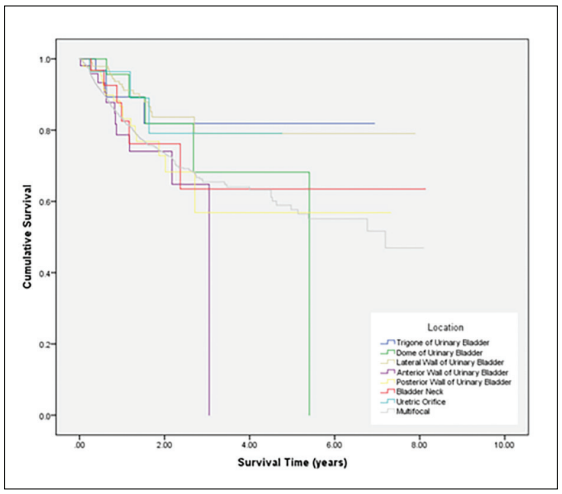

Figure 3. Kaplan-Meier survival by tumor location.

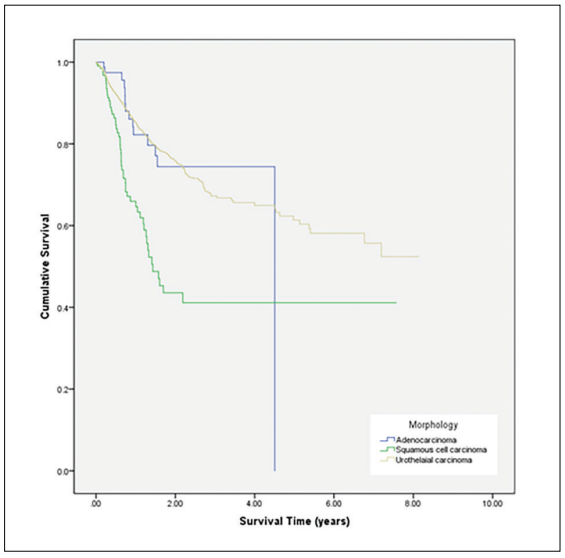

Figure 4. Kaplan-Meier survival by tumor morphology.

the current study.[13] The study by Andreassen et al also highlighted an increased incidence rate of BC, specifically urothelial carcinoma, compared to our study.[11]

Mortality rate

The mortality rate was 16.3% in our study, with 94.4% (n=579) of the deaths due to the cancer. The mean diagnosis-to-death interval was 0.92 years. The average five-year survival rate is 77% in patients diagnosed with BC in the US, a significant difference in the diagnosis-to-death interval compared with the current study.13 However, the mortality rate is similar to most other reports in the literature. Noon et al reported the BC-specific mortality rate and other-cause mortality rate for patients with newly diagnosed BC. The study, conducted over 15 years, reported that 5 years after the diagnosis, 40% had died, 19% directly as a result of BC, similar to the rate in our study (16.3%).[14] Evidence for this mortality is provided by Al-Husseini et al who reported an incidence-based mortality rate of 18.68% in patients with transitional cell carcinoma. The authors also noted that the mortality was increased in male patients, whites, and patients older than 84 years.[15]

Discrepancies in tumor characteristics

In the current study, differences in tumor characteristics were related to gender, tumor location, tumor morphology, and the extension of the tumor. The literature supports these findings, with several studies highlighting an exacerbated disease progression in women.[16] However, Horstmann et al found no difference in tumor histology based on gender, though they reported that muscle-invasive tumors were more frequent in men. In addition, primary tumors presented as more aggressive, and recurrence of the tumor was also more invasive in men. Horstmann et al reported that tumors were more prevalent in the urethra, trigonum and bladder dome or vault in men and were more prevalent in men than in women,[17] a finding consistent with our study. Literature on the differences in tumor characteristics in age categories is limited so our finding of an increased incidence of BC in the age group older than 60 years, with a mean age 62.3 years, is of interest. Our findings suggest that age significantly impacts the location of tumors, tumor morphology, disease grade and extension; however, additional research is required to substantiate this evidence.

The analysis of the tumor characteristics by marital status indicates enhanced survival in widowed patients. However, these findings contradict the findings of Niu et al, who conducted an observational study to assess the impact of marital status on the survival of patients with bladder urothelial carcinoma. In the Niu study, widowed patients had the worst cause-specific survival compared to patients with a different marital status. The 5-year survival of widowed patients compared with married patients indicated that widowed patients had a significantly higher risk of bladder-cancer-specific mortality.[18] Despite these discrepancies, our findings do corroborate the conclusion that marital status is relevant in improving cause-specific survival in patients with BC, based on several significant findings. For example, single patients had the lowest rate of Grade IV tumors and distant metastasis. The tumor characteristics also influence the tumor morphology in patients. Different histological variants of urothelial cancer constitute 25% of BC cases and significantly impact patient outcomes. The literature suggests that histological variants of this carcinoma are suggestive of a more aggressive disease presentation.[19] This is reflected in our findings as both adenocarcinoma and squamous cell carcinoma had a notably higher rate of distant metastasis, compared to urothelial cancer.

Table 6. Cox proportional hazards regression analysis.

Factor	Odds ratio	95% Confidence interval		*P* value
Age	1.023	1.015	1.032	**<.001**
Gender (male vs females)	0.717	0.549	0.937	.015
Marital status (single is the referent)				
Married	0.658	0.422	1.026	.065
Divorced	0.763	0.280	2.076	.596
Widowed	0.360	0.169	0.763	**.008**
Nationality (Saudi vs non-Saudi)	1.002	0.731	1.374	.99
Place of residency (central region is the referent)				
Eastern region	0.940	0.683	1.295	.706
Northern region	0.855	0.540	1.356	.506
Western region	0.828	0.642	1.067	.144
Southern region	0.727	0.521	1.015	.061
Location (trigone of urinary bladder is the referent)				
Dome of urinary bladder	0.922	0.151	5.644	.93
Lateral wall of urinary bladder	1.011	0.230	4.443	.989
Anterior wall of urinary bladder	3.128	0.657	14.893	.152
Posterior wall of urinary bladder	2.143	0.482	9.521	.316
Bladder neck	1.898	0.364	9.905	.447
Ureteric orifice	3.994	0.539	29.593	.175
Multifocal	2.203	0.545	8.914	.268

Table 6 (cont). Cox proportional hazards regression analysis.

Factor	Odds ratio	95% Confidence interval		*P* value
Morphology (Adenocarcinoma is the referent)				
Squamous cell carcinoma	3.653	1.780	7.496	**<.001**
Urothelial carcinoma	1.374	0.713	2.650	.342
Grade (Grade I [well differentiated] is the referent)				
Grade II (moderately differentiated)	1.270	0.718	2.246	.411
Grade III (poorly differentiated)	3.249	1.927	5.479	**<.001**
Grade IV (undifferentiated anaplastic)	2.470	1.444	4.225	**<.001**
Extension (localized is the referent)				
Regional: direct extension	1.563	1.117	2.187	**.009**
Regional: lymph node	2.947	1.761	4.934	**<.001**
Regional: lymph node and direct extension	3.625	2.479	5.301	**<.001**
Distant metastasis	6.291	4.925	8.035	**<.001**

*Significant at level .05

Factors associated with mortality and survival

Age is an accepted risk factor for disease progression and mortality in patients with BC, as reflected in the Kaplan-Meier survival analysis conducted in the current study. Reports of age as the major single risk factor are true for not only developing urothelial carcinoma, but also the incidence of death once diagnosed. It is estimated that the group older than 65 years are 11-fold more likely to develop urothelial carcinoma, and the mortality rate is 15-times higher than in patients younger than 65 years.[20] This is similar to our findings demonstrating the highest mean survival in the 19-39 years age group. The incidence and disease severity varies between genders, and several studies reported that the difference is due to varying carcinogenic exposure.[21] The literature also substantiates our finding that there is a higher mean survival in men compared to women, with women often presenting with a worse prognosis.[22] In addition to patient demographic information as a risk factor for BC and its associated morbidity and mortality, several risk factors have been identified regarding tumor characteristics. First, the current findings are indicative of tumor location influencing patient outcomes, with the highest mean survival in patients with a lateral wall tumor. The most likely rationale for these findings is the high success rate of tumor resection in this location.[23] Secondly, patients presenting with urothelial carcinoma are significantly more likely to survive than those with either adenocarcinoma or squamous cell carcinoma. These findings were also reported by Processali et al, who highlighted a significant increase in aggressive disease presentation in these morphologies, with an increased rate of mortality and decreased incidence of overall survival.[19] Grade and tumor extension were also associated with discrepancies in mortality and survival. The cancer grading system has been in use for many decades, and patients presenting with Grade III and IV carcinomas have a poorer prognosis. Arnold et al investigated patient survival and mortality in a cohort study conducted from 1995 to 2014, and confirmed an increased incidence in mortality in the group with Grade III and IV carcinomas.[24] Patients with localized tumors had the highest mean survival when compared to the group with distant metastasis. The group presenting with metastatic BC often survive only a few months after diagnosis.[25] This is validated by our findings, with an almost three-fold decrease in survival time, compared with the group with localized tumors.

Based on the current study, Saudi nationals had a higher mean survival in years than the non-Saudi group. This could be indicative of disparities in the healthcare provided to the non-Saudi group. These findings were replicated in several other studies investigating similar hypotheses. Nielsen et al compared the quality of cancer care in foreign-born versus US-born patients with lung or colorectal cancer, and reported that foreign-born patients were less likely than the US-born patients to report excellent quality of care.[26] Shavers et al highlighted the alarming statistic that racial and ethnic minorities, especially African Americans, have a 33% higher risk of mortality due to cancer than white patients; however, the underlying genetic factors could be another prominent reason.[27] These disparities are also present in immigrants, who

face challenges like the language barrier and a lack of knowledge about health and disease.[28]

The Cox proportional hazards regression analysis confirmed the evidence provided in the Kaplan-Meier survival analysis and identified several factors associated with both decreased and increased survival. The predictors identified as risk factors for decreased survival were age, squamous cell carcinoma, Grade III and Grade IV disease, lymph node and direct extension, and distant metastasis. Being male and being widowed were identified as predictors of increased survival. All the factors were corroborated by the literature, except being widowed as a predictor of increased survival. The recommendation for additional investigations related to the impact of marital status on the mortality and survival of BC patients is justified.

In conclusion, this study reports a nationwide descriptive epidemiological study and a survival analysis of BC in a region with a high prevalence of risk factors such as smoking. The findings are substantiated by the literature, with the only notable discrepancy being the enhanced survival of widowed patients diagnosed with BC. Saudi nationals had a higher mean survival in years than the non-Saudi group. This could be indicative of inequality in healthcare provision to the non-Saudis. Highlighting the detected risk factors, specifically in Saudi Arabia, improves evidence-based practice in this region and may aid in determining the appropriate care for these patients to optimize disease outcomes. This study could also facilitate the development of selective screening protocols, treatment strategies and surveillance treatment pathways. Future studies are recommended to explore the factors that contribute to the growing incidence rate of BC in the region over the years.

The primary limitation of studies reporting BC epidemiology in the literature is the incidence of underreporting to tumor registries. This variable may reduce the external validity of our findings and literature; it is defined as a source of systematic error in cancer research.[29] However, it is also suggested that the inclusion of prevalent cancers from death certificates in the initial years of the registration may compensate for the underreporting of patients.[30] To mitigate this issue, medical reporting should be deemed an essential requirement, with the accuracy of the responses validated by various methods of verification. In addition, the reviewed registry did not include the full TNM classification of each tumor which adds an additional limitation to our study. Also, the management done for each patient, which could possibly play a role in altering the individual survival chances of the patients, was not included. Finally important patient history components, such as smoking status, occupation, and previous radiotherapy or chemotherapy were not present in the reviewed registry. Registries are recommended to include these important parameters in their future collection rather than being only focused on the tumor related information.

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