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RESEARCH ARTICLE

BLADDER CANCER: DIFFERENTIATION OF TYPES, AGE, SEX DISTRIBUTION AND ASSOCIATED VARIANTS WITH GRADATIONAmin Abdulkarem Okbah¹ , Azhar Azher Mohammed Al-Ankoshy⁴ ,
Hassan Abdulwahab Al-Shamahy^{2,3} ¹Departement of Histopathology, Faculty of Medicine and Health Sciences, Sana'a University, Republic of Yemen.²Medical Microbiology and Clinical Immunology Department, Faculty of Medicine and Health Sciences, Sana'a University.³Medical Microbiology department, Faculty of Medicine, Genius University for Sciences and Technology, Dhamar city.⁴Jabir Ibn Hayyan Medical University, Faculty of medicine, Department of Physiology, An-Najaf, Iraq.**ABSTRACT****Background:** Urinary bladder cancer (UBC) is the ninth most common cancer in the world, and the third most common cancer among men in West Asian countries, including Arab countries. Despite the increasing prevalence of UBC in developing countries, many places, including Yemen, do not have representative studies showing the true impact of these tumors on the population.**Aims:** To describe the different types of bladder cancers, and their distributions with age, and sex and to correlated different types with gradation, invasion muscles; and schistosomiasis in the last ten years in a single Yemini institute.**Materials and methods:** An observational descriptive study was performed on UBC patients who were subsequently diagnosed selectively by histopathological study in the Department of Pathology at the National Center for Public Health Laboratories (NCPHL) Sana'a, Yemen, over a period of about 10 years from January 1, 2012 to October 31, 2021. The study variables were cancer histological type, sex, grades and age. Types, grading and histological diagnoses were formed in line with the World Health Organization classification of bladder cancer.**Results:** Most of the cases were in the age group 60-69 years (32%), followed by 70 years (22.3%), and 50-59 years (20%). The most common UBCs were urothelial neoplasms (UNs) (71.5%), followed by squamous neoplasms (SNs) (24.4%) while other types were less frequent. There was a cytologically high grade with a significance rate (64.2%) with UNs. There was a significance rate of: schistosomiasis (43.8%) with SNs as $OR=19.5$ ($p<0.001$), and invasion of muscle fibers (66.4%) with SNs as $OR=3.3$, UNs (37.1%) as $OR=11.2$ ($p < 0.001$). Also there was a significance rate of GII grade (46.1%) with SNs as $OR=64.1$ ($p<0.001$) and GNs (33.3%) as $OR=3.8$ ($p=0.02$).**Conclusion:** The present study verification data congruence with those in the international literature and reports of neighboring countries, with some minor differences. This study documents a high incidence of urothelial neoplasms, with a male predominance and a peak incidence in the sixth decade of life. Imminent studies are needed to identify risk factors that increase cystitis in more detail and to study genetic susceptibility to inflammation and inflammatory markers before cancer is diagnosed.**Keywords:** cytologically grade, prevalence, schistosomiasis, Urinary bladder cancer, Yemen.**Article Info:** Received 1 November 2021; Revised 17 December; Accepted 31 December, Available online 15 January 2022**Cite this article-**

Okbah AA, Al-Ankoshy AAM, Al-Shamahy HA. Bladder cancer: Bladder cancer: differentiation of types, age, sex distribution and associated variants with gradation. Universal Journal of Pharmaceutical Research 2021; 6(6):57-64.

DOI: <https://doi.org/10.22270/ujpr.v6i6.701>**Address for Correspondence:****Prof. Hassan A. Al-Shamahy**, Medical Microbiology and Clinical Immunology Department, Faculty of Medicine and Health Sciences, Sana'a University. Medical Microbiology department, Faculty of Medicine, Genius University for Sciences and Technology, Dhamar city. Tel- +967-1-239551; E-mail: shmahe@yemen.net.ye**INTRODUCTION**

In Yemen as in the greater part of Arabic countries, there are only some particular epidemiological studies devoted to malignancies¹⁻⁷, and for this reason it is imperative to promote, update, build and continue to provide studies on the compartments of tumors with the aim of achieving greater impact on public health, early diagnosis and appropriate treatment always will

enhancing survival and minimizing subsequent potential consequences. Bladder cancer is a heterogeneous group of tumors and is the sixth most common cancer international and the next most frequent tumor of the genitourinary system subsequent to prostate cancer. The natural description of bladder cancers is their reappearance and progression to higher grades and stages⁸. Urothelial (transitional cell) carcinoma is the most common type of bladder cancer⁹.

Bladder tumors are more common in industrial areas and their incidence increases with exposure to cigarette smoking and arylamine¹⁰. *Schistosoma haematobium* is considering being pathologically associated with squamous neoplasms (SNs) plus transitional cell carcinoma of the bladder. This corresponds to the high prevalence of this type of cancer in the regions of the world infected with *S. haematobium*¹¹. The clinical consequence of bladder cancers depends on their differentiation, histological grade and most significantly, the depth of invasion of these lesions. Tumor grade and stage of urothelial carcinoma are closely related to progression, recurrence, and survival rates of patients⁹. Currently there is no standardized grading system for bladder cancer. The most commonly used regimens depend on the degree of metastasis¹². The World Health Organization and the International Society of Urology (WHO/ISUP) in 1998 made a decision to categorize many of these tumors as urothelial neoplasms¹².

Internationally, in 2020, bladder cancer was responsible in 172,000 deaths, down 12% (by age) from 2017, with 550,000 new cases annually¹³. In 2018, the age-adjusted rates of new bladder cancer cases were 6 per 100,000 people, and the age-adjusted mortality rate was 2 deaths per 100,000 people. It was found that Greece and Lebanon had the highest rate of new cases. In Lebanon, this high risk is connected to petrochemical air pollution and the high number of smokers. As for Yemen, according to the latest data of the World Health Organization published in 2018, bladder cancer deaths in Yemen amounted to 146, or 0.09% of the total deaths. The age-adjusted mortality rate is 1.48 per 100,000 inhabitants and Yemen ranks 133 in the world¹⁴. Occupational exposure and smoking are prospective risk factors for bladder cancer in Western Asia and Western countries^{15,16}. Persistent infections, for instance schistosomiasis, account for 50% of urinary bladder cancer cases in a number of developing countries¹⁵. Significant mortality and morbidity caused by schistosomiasis worldwide. It is expected that about 600 million inhabits in the tropics are at risk of infection and 200 million are infected¹⁷. *S. haematobium*, an agent of urinary schistosomiasis, is most regularly established in the Middle East including Yemen and sub-Saharan Africa. The hit the highest point prevalence and severity of early infection occurs among the ages of 10 and 20 years and decreases at the age of 65 years¹⁸. Histological studies are utilized as a criterion for the diagnosis of urinary bladder cancer and one of the most vital predictive factors in clinical practice¹⁹. Studies have revealed that most of the cancers associated with schistosomiasis are squamous neoplasms (SNs), while the smoking-related bladder cancer is transitional cell carcinoma (TCC)¹⁵. Principally, *S. haematemesis* was regard as a latent risk factor in the incident of bladder cancer, however at present, the most widespread type of UBC in Egypt is TCC. Histological studies on clinical specimens showed that the lesions were changed by squamous types, and suggested transforms in the cause or etiology of bladder cancer over the past 26 years. Available polymorphisms in the glutathione-S-

transferase genes are also connected with an increased risk of UBCs²⁰.

The Republic of Yemen is a considerable country with diverse topographic, climatic and environmental conditions. The population has reached 28 million people according to estimates in 2018^{21,22} with 46% of the population under 15 years old and only 2.7% over 65 years old^{23,24} by the year 2050, it is estimated that the population will increase to about 60 million²⁵ due to the high fertility rate in Yemen, which is 4.45 children per woman and this is among the top 30 in the world²⁶. Sana'a's population has grown rapidly, from about 55,000 in 1978²⁷ to nearly 4 million in the early 2020s. To date, this country lacks a National Cancer Registry Center (NCRC), and therefore there is a lack of cancer information and reliable data. For that reason, this study aimed to describe the different types of bladder cancer, the age and sex distribution of the cancer, the determination of the different types of it and its association with the gradation and invasion of the bladder muscles; and its association with schistosomiasis, in the past ten years.

SUBJECTS AND METHODS

Study designed: Retrospective descriptive study. The study was conducted using formal guidelines to find out the problem and find solutions to it.

Study site: The Department of Pathology at the National Center for Public Health Laboratories (NCPHL) in Sana'a city which serves the major government hospitals and private hospitals in the city of Sana'a and acts as a reference laboratory for the entire country.

Study population: Study was conducted on UBC patients (Patients are usually referred from hospitals for histological diagnosis) who were subsequently diagnosed selectively by histopathological study in the Department of Pathology at the National Center for Public Health Laboratories (NCPHL) Sana'a, Yemen, over a period of about 10 years from January 1, 2012 to October 31, 2021.

Study variables and cancer classification: Study variables were cancer histological type, sex, grades and age. Types, grading and histological diagnoses were formed in line with the World Health Organization and the International Society of Urology (WHO/ISUP 1998)²⁸. According to the WHO classification, patients were divided into 5 groups: urothelial neoplasms (UNs), squamous neoplasms (SNs), glandular neoplasms (GNs), neuroendocrine neoplasms (NENs) and mesenchymal neoplasms (MNs). Subgroups were then classified according to morphological diversity²⁸.

Inclusion criteria: Inclusion criteria for patients included the following: Complete UBC histopathological findings. Patients of any age and gender. Availability of clinical data, and histological slides that confirm the diagnosis of bladder cancer.

Exclusion criteria: Exclusion criteria included patients with no histopathological slides and insufficient clinical data in our record.

Statistical analysis

Data were reported using appropriate descriptive statistics (including frequency, mean, standard deviation, *OR*, *CI*, X^2 and *p*-value). First data were entered using the SPSS software to minimize errors. All statistical analyzes of the data were performed using the Statistical Package for Social Sciences (SPSS) version 24 and Excel 2007.

Ethical approval

From the Medical Research and Ethics Committee at the Faculty of Medicine and Health Sciences at Sana'a University, (reference number 421 on 12 October

2021), the ethical approval was obtained. Also, all data, including patient identification, have been kept confidential.

RESULTS

For age and gender distribution: Most of the cases were in age group 60-69 years (32%), followed ≥ 70 years (22.3%), and 50-59 years (20%), while only 2.5% in 20-29 years group. The mean age \pm SD of total was 57.1 ± 13.4 years, for male was 58.2 ± 13.6 years while for female was lower 53.9 ± 12 years (Table 1).

Table 1: Sex and age distribution of bladder cancer patients in Sana'a, Yemen.

Age groups Years	Male		Female		Total	
	No	(%)	No	(%)	No	(%)
20-29	10	(2.6)	3	(2.2)	13	(2.5)
30-39	24	(6.2)	10	(7.4)	34	(6.5)
40-49	60	(15.6)	27	(20)	87	(16.7)
50-59	63	(16.4)	41	(30.4)	104	(20)
60-69	129	(33.5)	37	(27.4)	166	(32)
≥ 70	99	(25.7)	17	(12.6)	116	(22.3)
Total	385	74	135	26	520	100
Mean age	58.2 years		53.9 years		57.1 years	
SD	13.6 years		12 years		13.4 years	
Min	20 years		21 years		20 years	
Max	99 years		80 years		99 years	
Mode	60 years		50 years		60 years	
Median	60 years		54 years		60 years	

Table 2: Distribution of urinary bladder cancers (UBC) with age parameters for 520 patients.

Types of UBC	No (%)	M:F ratio	Mean age \pm SD years	Age Mode	Age Median	<i>p</i> value
Urothelial neoplasms (UNs)	372(71.5)	3.5:1	59 ± 13.5	60	60	0.03
Squamous neoplasms (SNs)	128(24.6)	1.7:1	51.5 ± 11.5	60	50	<0.0001
Glandular neoplasms (GNs)	12(2.3)	5:1	48.1 ± 11.4	38	44	<0.0001
Neuroendocrine neoplasms (NENs)	3(0.6)	3:0	70 ± 0	70	70	Non available
Mesenchymal neoplasms (MNs)	5(0.96)	2:3	53 ± 12	40	50	0.49
Total	520(100)	2.9:1	57.1 ± 13.4	60	60	Reference

M:F ratio-male female ratio

Distribution of urinary bladder cancers (UBC) with age parameters: Of the 520 UBCs: 372 (71.5%) were urothelial neoplasms (UNs), 128 (24.4%) were squamous neoplasms (SNs), 12 (2.3%) were glandular neoplasms (GNs), 3 (0.6%) were neuroendocrine neoplasms (NENs), and 5 (0.96%) were mesenchymal neoplasms (MNs). When the mean age \pm SD for different types of UBC was considered: the largest mean age \pm SD with urothelial tumors (UNs) was (59 ± 13.5 years), while with squamous neoplasms (SNs) it was lower (51.5 ± 11.5 years), and it was much lower with glandular neoplasms (GNs) (48.1 ± 11.4 years).

Given male to female ratio: UBC was predominant in males and the sum was 2.9 to 1, for urothelial tumors it was 3.5 to 1, for squamous tumors it was 1.7 to 1, for glandular neoplasms it was 5 to 1, for neuroendocrine

tumors it was 3 to 0, and for mesenchymal neoplasms it was 2 to 3.

The association between cytologically high grade with type of bladder neoplasms: Consider the association between the high cytologically grade and the type of bladder tumors (UBC). There was a cytologically high grade with significance rate (64.2%) with UNs as *OR* 51.3, *CI* =20.5-128.5 while there is no significant association between the high cytologically grade with the remaining types of UBCs (Table 3).

The association between schistosomiasis with type of bladder neoplasms: Considering the association between schistosomiasis and the type of bladder tumors (UBC). There was a significance rate of schistosomiasis (43.8%) with SNs as *OR*=19.5, *CI* =10.4-36.4, $X^2=130$, *p*<0.001 while there is no association of schistosomiasis with the remaining types of UBCs (Table 4).

The association between invasion of muscle fibers with type of bladder neoplasms: When considering the association between invasion of muscle fibers and the type of bladder tumors (UBC), there was a significance rate of invasion of muscle fibers equal to 66.4% with SNs as $OR=3.3$, $CI=2.2-5.1$ followed by UNs (37.1%) with UNs as $OR=11.2$, $CI=7.2-17.6$, while there is no association of invasion of muscle fibers with the remaining types of UBCs (Table 5).

The association between low grade with type of bladder neoplasms: Consider the association between the low cytologically grade and the type of bladder tumors (UBC). There was a cytologically low grade with significance rate (35.8%) with UNs as $OR=6.7$, $CI=3.6-12.6$, also there was a significant association between the low cytologically grade and MNs as $OR=10.6$, $CI=1.2-95.7$, while there is no significant association between the low cytologically grade with the remaining types of UBCs (Table 6).

Table 3: The association between cytologically high grade with type of bladder neoplasms (UBC) for 520 patients.

Types of UBC	High Grade	OR	CI 95%	X^2	p
	No (%)				
Urothelial neoplasms (UNs) n=372	239(64.2)	51.3	20.5-128.5	157	<0.001
Squamous neoplasms (SNs) n=128	0(0)	0.0	0-0.014	150	<0.001
Glandular neoplasms (GNs) n=12	3(25)	0.36	0.09-1.3	2.3	0.12
Neuroendocrine neoplasms (NENs) n=3	1(33.3)	0.56	0.05-6.2	0.22	0.63
Mesenchymal neoplasms (MNs) n=5	1(20)	0.27	0.03-2.5	1.4	0.22
Total n=520	244(46.9)				

OR=odd's ratio, CI 95%=confidence interval 95%, X^2 =Chi square, p =p value

The association between GI grade with type of bladder neoplasms: When considering the association between histologically grade I and the type of bladder tumors (UBC). There was a significance rate of GI grade (87.04%) with SNs as $X^2=234$, $p<0.001$ while there is no occurrence of GI with the remaining types of UBCs (Table 7).

The association between GII grade with type of bladder neoplasms: When considering the association between histologically grade II (GII) and the type of bladder tumors (UBCs), there was a significance rate of GII grade (46.1%) with SNs as $OR=64.1$, $CI=124.8-165$ followed by GNs (33.3%) as $OR=3.8$, $CI=1.1-13$, while there is no occurrence of GII with the remaining types of UBCs (Table 8).

Table 4: The association between schistosomiasis with type of bladder neoplasm (UBC) for 520 patients.

Types of UBC	Schistosomiasis	OR	CI 95%	X^2	p
	No (%)				
Urothelial neoplasms (UNs) n=372	14(3.8)	0.062	0.03-0.11	108	<0.001
Squamous neoplasms (SNs) n=128	56(43.8)	19.5	10.4-36.4	130	<0.001
Glandular neoplasms (GNs) n=12	0(0)	0.0	0.0-1.7	1.9	0.63
Neuroendocrine neoplasms (NENs) n=3	0(0)	0.0	0.0-10.9	0.47	0.48
Mesenchymal neoplasms (MNs) n=5	0(0)	0.0	0-5.2	0.7	0.37
Total n=520	71(13.7)				

OR=odd's ratio, CI 95%=confidence interval 95%, X^2 =Chi square, p =p value

Table 5: The association between invasions of muscle fibers with type of bladder neoplasms (UBC) for 520 patients.

Types of UBC	Invasion of muscle fibers	OR	CI 95%	X^2	p
	No (%)				
Urothelial neoplasms (UNs) n=372	138(37.1)	11.2	7.2-17.6	135	<0.001
Squamous neoplasms (SNs) n=128	85(66.4)	3.3	2.2-5.1	33.8	<0.001
Glandular neoplasms (GNs) n=12	5(41.7)	0.89	0.28-2.9	0.03	0.85
Neuroendocrine neoplasms (NENs) n=3	0(0)	0.0	0.0-2.1	2.3	0.12
Mesenchymal neoplasms (MNs) n=5	2(40)	0	0-1.0	4	0.04
Total n=520	230(44.2)				

OR=odd's ratio, CI 95%=confidence interval 95%, X^2 =Chi square, p =p value

Table 6: The association between low grade with type of bladder neoplasms (UBC) for 520 patients.

Types of UBC	Low Grade	OR	CI 95%	X ²	p
	No (%)				
Urothelial neoplasms (UNs) n=372	133(35.8)	6.7	3.6-12.6	44.2	<0.001
Squamous neoplasms (SNs) n=128	2(1.6)	0.028	0.007-0.1	56	<0.001
Glandular neoplasms (GNs) n=12	6(50)	2.65	0.8-8.3	2.9	0.08
Neuroendocrine neoplasms (NENs) n=3	0(0)	0	0-4.4	1.1	0.2
Mesenchymal neoplasms (MNs) n=5	4(80)	10.6	1.2-95.7	6.8	0.009
Total n=520	145(27.9)				

OR=odd's ratio, CI 95%=confidence interval 95%, X²=Chi square, p=p value

Table 7: The association between GI grade with type of bladder neoplasms (UBC) for 520 patients.

Types of UBC	GI Grade	OR	CI 95%	X ²	p
	No (%)				
Urothelial neoplasms (UNs) n=372	0(0)	0	0-0.01	196	<0.001
Squamous neoplasms (SNs) n=128	68(87.04)	Undefined		234	<0.001
Glandular neoplasms (GNs) n=12	0(0)	0	0-1.8	1.8	0.17
Neuroendocrine neoplasms (NENs) n=3	0(0)	0	0-11.4	0.4	0.5
Mesenchymal neoplasms (MNs) n=5	0(0)	0	0-5.4	0.75	0.38
Total n=520	68(13.1)				

OR=odd's ratio, CI 95%=confidence interval 95%, X²=Chi square, p=p value

DISCUSSION

Bladder cancer is the sixth most common type of cancer globally, the second most common cancer of the genitourinary system after prostate cancer, and represents a heterogeneous group of tumors⁸. Urinary bladder cancer is rarely researched in Middle East countries, and notably in Yemen. 71.5% of bladder cancers in this study were urothelial neoplasms (UNs), followed by squamous neoplasms which accounted for

24.4%. The observed number of urothelial tumors was remarkably similar to the number previously reported from Yemen by Al-Samawi and Aulqi in 2013²⁹ and from neighboring Saudi Arabia (77%)³⁰. However, lower numbers have been reported in Africa; Nigeria (42%)³¹ and Tanzania (28%)³². In developed countries, over 90% of bladder cancer cases are urothelial neoplasms (UNs), and rare types of bladder cancer make up the remaining 10%³³.

Table 8: The association between GII grade with type of bladder neoplasms (UBC) for 520 patients.

Types of UBC	GII Grade	OR	CI 95%	X ²	p
	No (%)				
Urothelial neoplasms (UNs) n=372	0(0)	0	0-0.01	180	<0.001
Squamous neoplasms (SNs) n=128	59(46.1)	64.1	24.8-165	175.7	<0.001
Glandular neoplasms (GNs) n=12	4(33.3)	3.8	1.1-13	5.2	0.02
Neuroendocrine neoplasms (NENs) n=3	0(0)	0	0-12.5	0.4	0.51
Mesenchymal neoplasms (MNs) n=5	0(0)	0.0	0.0-5.9	0.69	0.4
Total n=520	63(11.9)				

OR=odd's ratio, CI 95%=confidence interval 95%, X²=Chi square, p=p value

In the USA, a high frequency of urothelial neoplasms (98%) was reported by Schned *et al.*⁹. The decline of urothelial neoplasms can be explained in Africa, consisting largely of countries below average in the Human Development Index (HDI), possibly due to lower exposure to industrial chemicals and limited access to tobacco. This is in contrast to USA, where the incidence of urothelial neoplasms is positively

correlated with a high HDI and a high GDP (Gross Domestic Product) per capita due to the more consuming and using of products with potentially carcinogenic preservatives; cosmetics etc. and more exposure to industrial chemicals³⁴. In the current study, Squamous neoplasms (SNs) accounted for 24.4%. However, significant variability in the prevalence of SNS in the bladder has been observed in

different parts of the world. It accounts for only 1% of bladder cancers in England³⁵ and 7% in the United States³⁶, but up to 75% in Egypt³⁷. The low incidence of SNs in the USA and England can be explained by the absent of *S. haematobium* infections in these areas. Approximately 43.8% of SNs in this study were associated with chronic infection with *S. haematobium*. A previous study conducted in Egypt illustrated that about 80% of SNs were accompanied by persistent infection with *S. haematobium*³⁷. Infection with *S. haematobium* may cause bladder cancer, in particular the squamous cell type³⁸. Schistosoma eggs cause a chronic inflammatory condition in the bladder wall that leads to tissue fibrosis^{39,40}. Glandular neoplasms (GNs) also accounted for 2.3% of malignant bladder tumors in this study which is similar to what was previously reported from Yemen by Al-Samawi and Aulqi in 2013 (3%)²⁹; and Rosai in the USA where its prevalence was 3%⁴¹. In general, it can be said that when comparing the frequency of histological subtypes in the current study with other studies, a clear difference was observed. This difference may be explained by the combined effects of environmental and genetic factors. It is known that mutations in the FGFR3, TP53, PIK3CA, KDM6A, ARID1A, KMT2D, HRAS, TERT, KRAS, CREBBP, RB1 and TSC1 genes may be associated with some cases of bladder cancer. Deletion of parts or all of chromosome 9 is also common for bladder cancer⁴³. In addition, it is believed that tobacco use is similarly prevalent worldwide and may explain the overall increase in urothelial neoplasms (UNs) in the current study patients³⁴. Furthermore in this study, men were 2.9 times more likely to develop bladder cancer than women. Worldwide, the male to female ratio varies between 1:3 and 1:5^{29,43,44}. On the other hand, a higher proportion was documented by Matalka *et al.*, in Jordan; 1:9⁴⁵. Androgen replacement therapy (ART), often referred to as testosterone replacement therapy (TRT) or hormone replacement therapy (HRT), is a form of hormone therapy in which androgen, often testosterone, is supplemented or exogenously replaced. Although there are no data on androgen use in our study patients, prescribing androgens to adult males is common in Yemen. So one other reason for male predominant is that androgen receptors, which are more active in men than in women, may compete a role in the occurrence of cancer⁴⁶. This hypothesis is also supported by the fact that men undergoing treatment with androgen suppression for an unrelated reason appear to have a lower risk of developing bladder cancer⁴⁷. In Africa, men are more likely to do fieldwork and to develop schistosomiasis, and this may explain to some extent the gap in squamous cell carcinoma in regions where bladder cancer is endemic⁴⁸. Nevertheless, females develop more aggressive disease and have worse outcomes than males⁴¹. This dissimilarity in result is interrelated to many factors such as difference in exposure to carcinogens, genetics, social, and quality of care⁴⁹. A common sign of bladder cancer is hematuria and it is often misdiagnosed as a urinary tract infection in women, delaying diagnosis. Furthermore, as revealed previously, the PSCA gene

may take part in a role in aggressive neoplasia in female patients⁵⁰. In the current study, patients' ages ranged from 20 to 99 years with a mean total age \pm SD was 57.1 \pm 13.4 years, for males 58.2 \pm 13.6 years while for females it was less than 53.9 \pm 12 years, most cases of UBC (74.3%) were present in patients over 50 years of age and in about 25.7% of younger adults no pediatric case occurred (Table 1). The frequency of UBC in Yemen increases with age, and a significant difference between age groups is observed. These results are consistent with those reported in other investigations where about 60 years was the mean age for males and 58 years for females, and the peak incidence of disease was observed between 60 and 70 years^{29,51,52}.

According to WHO classification (1973) bladder cancers are histologically graded into:⁵³, G1 (well differentiated), G2 (moderately differentiated), G3 (poorly differentiated). In the current study there was a cytologically high grade with significance rate (64.2%) with UNs as *OR* 51.3 and *CI*=20.5-128.5; while there is no significant association between the high cytologically grade with the remaining types of UBCs (Table 3). Also, there was a significance rate of invasion of muscle fibers (66.4%) with SNs as *OR*=3.3, followed by UNs (37.1%) with UNs as *OR*=11.2, while there is no association of invasion of muscle fibers with the remaining types of UBCs (Table 5). Both tumor grade and stage of UBCs are highly correlated with recurrence, progression, and patient survival rates⁹. The WHO/ISUP grading of UBC is of great prognostic significance. In Jordan, Matalka *et al.*,⁴⁵ reported 60% of low grade and 40% of high grade. While in Australia, Samaratunga *et al.*,⁵⁴ reported 2% papilloma, 22% low malignant potential, 13% low grade, and 22% high grade carcinoma. The variation found between these results could be explained in terms of diagnostic approach and/or techniques applied, number of patients studied, as well as geographical and immunological differences. Histological classification suffers from all the drawbacks of self-assessment, especially when performed on biopsy material. Additionally, differences in a specific tumor may vary from region to region, and thus endoscopic biopsy may show a low-grade malignancy compared to that found in the surgical specimen.

CONCLUSION

The current study recorded data matches with those in the global literature and neighboring country studies, with some differences. This study documents a high frequency of urothelial neoplasms (UNs), with a male preponderance and peak incidence in the 6th decade of age. The prediction for bladder cancer in the world showed a decrease of 16.1% from 2016 to 2020 and a decrease of 32.9% from 2016 to 2025. But the prediction in Yemen will be the opposite due to the increased potential factors for the occurrence of bladder cancer such as schistosomiasis, smoking and increased exposure to carcinogenic chemicals. Future studies are needed to determine in greater detail the

risk factors that increase inflammation of the bladder and examine genetic susceptibility of inflammation and markers of inflammation prior to cancer diagnosis. Understanding the role of inflammation may provide important insight on how to reduce bladder cancers worldwide.

AUTHOR'S CONTRIBUTION

This study was completed by Amin Abdulkarem Okbah, Professor of Histopathology at Sana'a University, and the National Center of Public Health Laboratories (NCPHL) Sana'a, Yemen; and Prof. Dr. Hassan Abdul-Wahab Al-Shamahy, Faculty of Medicine, Sana'a University. All authors analyzed the data, wrote the manuscript, and reviewed it.

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CONFLICT OF INTEREST

No conflict of interest associated with this work.

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