**Reviewer’s Comments**

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**BLADDER CANCER: DIFFERENTIATION OF TYPES, AGE, SEX DISTRIBUTION AND ASSOCIATED VARIANTS WITH GRADATION, MUSCLE INVASION AND SCHISTOSOMIASIS IN A SINGLE YEMENI INSTITUTE**

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.



.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 qualitative (cancer histological type, sex, grades and quantity (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 mean age ± SD of the total was 57.1 ± 13.4 years.Of the 520 UBCs, 71.5% were urothelial neoplasms (UNs), 24.4% were squamous neoplasms (SNs), 2.3% were glnadular neoplasms (GNs), 0.6% were neuroendocrine glnadular neoplasms (NENs) and 0.96% were mesenchymalglnadular neoplasms (MNs).There was a cytologically high grade with a significance rate (64.2%) with UNs while no significant association with the remaining types of UBCs.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**)** andGNs (33.3%) as *OR=* 3.8 **(***p* = 0.02**).** Conclusion: The current study recorded 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: **Keywords:**,cytologically grade,Prevalence, schistosomiasis, Urinary bladder cancer, Yemen.

INTRODUCTION



Bladder cancer is a heterogeneous group of tumors and is the sixth most common cancer worldwide and the next most frequent malignancy of the genitourinary system subsequent to prostate cancer. The natural history of bladder cancers is their recurrence and progression to higher grades and stages8. Urothelial (transitional cell) carcinoma is the most common type of bladder cancer 9. Bladder tumors are more common in industrial areas and their incidence increases with exposure to cigarette smoking and arylamine10. *Schistosomahaematobium* is consideringto be 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 *Schistosomahaematobium*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 patients9Currently 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 2017, bladder cancer was responsible in 196,000 deaths, down 5.4% (by age) from 200713. 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 Lebanonhad 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. Histological studies are utilized as a criterion for the diagnosis of urinary bladder cancer and one of the most vital predictive factors in clinical practice17. 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, *schistosomiasishaematemesis*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 UBCs18.

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 201819,20 with 46% of the population under 15 years old and only 2.7% over 65 years old21,22 By the year 2050, it is estimated that the population will increase to about 60 million23 due to the high fertility rate in Yemen, which is 4.45 children per woman and this is among the top 30 in the world 24. Sana'a's population has grown rapidly, from about 55,000 in 197825 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 differentiation of types, age, sex distribution, and the associated different types with gradation, invasion muscles and schistosomiasis in the past ten years in one Yemeni institute.

**PATIENTS AND METHOD**

An observational descriptive study was conducted 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. Study variables were qualitative (cancer histological type, sex, grades and quantitative (age). Types, grading and histological diagnoses were formed in line with the World Health Organization and the International Society of Urology (WHO). / ISUP 1998) 26.According to the WHO classification, patients were divided into 5 groups: urothelial neoplasms (UNs), squamous neoplasms (SNs), glnadular neoplasms (GNs), neuroendocrine glnadular neoplasms (NENs) and mesenchymalglnadular neoplasms (MNs). Subgroups were then classified according to morphological diversity26.

**Inclusion criteria**:Inclusion criteria included the histopathological diagnosis of UBC of any age and gender, availability of clinical data, and histological slides to confirm the diagnosis.

**Exclusion criteria:**Exclusion criteria included no histopathological slides and insufficient clinical data.

STATISTICAL ANALYSIS

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

ETHICAL APPROVAL

The ethical approval was obtained from the Medical Research and Ethics Committee at the Faculty of Medicine and Health Sciences at Sana'a University with a reference number (421) dated 12-10-2021. Also, all data, including patient identification, have been kept confidential.

**RESULTS**

**For age and gender distribution**: Table 1shows the sex and age distribution of bladder cancer patients in Sana’a, Yemen. 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 ±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.

**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 glnadular neoplasms (GNs), and 3 (0.6%) ) were neuroendocrine glnadular neoplasms (NENs) and 5 (0.96%) were mesenchymalglnadular neoplasms (MNs). When the mean age ± SD for different types of UBC was considered, the largest mean age ± SD with urothelial tumors (UNs) was (59 ± 13.5 years), while with squamous neoplasms (SNs) it was lower (51.5 ± 11.5 years), and much lower with Glnadular neoplasms (GNs) (48.1 ± 11.4 years). Given the male: female ratio, UBC was predominant in males and the sum was 2.9:1, for urothelial tumors it was 3.5:1, for squamous tumors it was 1.7:1, for Glnadular neoplasms it was 5:1, for neuroendocrine tumors it was 3:0, and for mesenchymal neoplasms it was 2:3.

**The association between cytologically high grade with type of bladder neoplasms:** Consider the association between the high cytologicallygrade 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. *X2* = 157, *p*< 0.001 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, *X2* = 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**: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 (66.4%) with SNs as *OR=* 3.3, *CI* = 2.2-5.1, *X2* = 38.8, *p*< 0.001, followed by UNs (37.1%) with UNs as *OR=* 11.2, *CI* = 7.2- 17.6, *X2* = 135, *p*< 0.001, 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, *X2* = 44.2, *p*< 0.00, also there was a significant association between the low cytologically grade and MNs as *OR=* 10.6, *CI* = 1.2-95.7, *X2* = 6.8, *p*< 0.00, while there is no significant association between the low cytologically grade with the remaining types of UBCs (Table 6).

**The association between GI grade with type of bladder neoplasms**: Considering the association between histologically grade I andthe type of bladder tumors (UBC). There was a significance rate of GI grade (87.04%) with SNs as *X2* = 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: Considering the association between histologically grade II (GII) and the type of bladder tumors (UBCs). There was a significance rate ofGII grade (46.1%) with SNs as as*OR=* 64.1, *CI* = 124.8-165, *X2* = 175, *p*< 0.001, followed by GNs (33.3%) as *OR=* 3.8, *CI* = 1.1-13, *X2* = 5.2, *p* = 0.02 while there is no occurrence of GII with the remaining types of UBCs (Table 8).

DISCUSSION

Bladder cancer is the sixth most common type of cancer worldwide, the second most common malignancy of the genitourinary system after prostate cancer, and represents a heterogeneous group of tumors 8. Urinary bladder cancer is rarely researched in countries Middle East, and notably in Yemen. 71.5% of bladder cancers in this study were urothelialneoplasms (UNs), followed by squamous neoplasms which accounted for 24.4%. The observed number of urothelial tumors (71.5%) was remarkably similar to the number previously reported from Yemen by  [Al-Samawi](https://www.ncbi.nlm.nih.gov/pubmed/?term=Al-Samawi%20AS%5BAuthor%5D&cauthor=true&cauthor_uid=24044060) and [Aulaqi](https://www.ncbi.nlm.nih.gov/pubmed/?term=Aulaqi%20SM%5BAuthor%5D&cauthor=true&cauthor_uid=24044060)in 2013 27 and from neighboring Saudi Arabia (77%)28. However, lower numbers have been reported in Africa; Nigeria (42%) 29 and Tanzania (28%)30.In developed countries, over 90% of bladder cancer cases are urothelial neoplasms (UNs), and rare types of bladder cancer make up the remaining 10% 31. In the USA, a high frequency of urothelial neoplasms (98%) was reported by Schned*et al*.9. 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 England31 and 7% in the United States32, but up to 75% in Egypt33.Approximately 43.8% of SNs in this study were associated with chronic infection with *Schistosomahaematobium*. A previous study conducted in Egypt illustrated that about 80% of SNs were accompanied by persistent infection with *S. haematobium*34. Infection with *Schistosomahaematobium* may cause bladder cancer, in particular the squamous cell type35. Schistosoma eggs cause a chronic inflammatory condition in the bladder wall that leads to tissue fibrosis36.In recent times, transitional cell carcinoma has become the most common type in Egypt due to significant changes in the etiology of bladder cancer37. glnadular 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](https://www.ncbi.nlm.nih.gov/pubmed/?term=Al-Samawi%20AS%5BAuthor%5D&cauthor=true&cauthor_uid=24044060) and [Aulaqi](https://www.ncbi.nlm.nih.gov/pubmed/?term=Aulaqi%20SM%5BAuthor%5D&cauthor=true&cauthor_uid=24044060)in 2013 (3%)27; and Rosai in the USA where its prevalence was 3% 38. 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 in terms of the diagnostic approach and/or possibly due to the combined effects of environmental and genetic factors. 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 patients.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 27,39,40. On the other hand, a higher proportion was documented by Matalka*et al.* in Jordan; 1:941. One other reason is that androgen receptors, which are more active in men than in women, may compete a role in the occurrence of cancer42. 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 cancer43.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 endemic44. Nevertheless, females develop more aggressive disease and have worse outcomes than males. This dissimilarity in result is interrelated to many factors such as difference in exposure to carcinogens, genetics, social, and quality of care 45. 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 patients46.In the current study, patients' ages ranged from 20 to 99 years with a mean total age ± SD was 57.1 ± 13.4 years, for males 58.2 ± 13.6 years while for females it was less than 53.9 ± 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 investigations27,47,48.

According to WHO classification (1973) bladder cancers are histologically graded into:[49](https://en.wikipedia.org/wiki/Bladder_cancer#cite_note-80), 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, *CI* = 20.5-128.5. *X2* = 157, *p*< 0.001 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, *p*< 0.001, followed by UNs (37.1%) with UNs as *OR=* 11.2, *p*< 0.001, while there is no association of invasion of muscle fibers with the remaining types of UBCs (Table 5).In addition, there was a significance rate of GII grade (46.1%) with SNs as as*OR=* 64.1, *CI* = 124.8-165, *X2* = 175, *p*< 0.001, followed by GNs (33.3%) as *OR=* 3.8, *CI* = 1.1-13, *X2* = 5.2, *p* = 0.02 while there is no occurrence of GII with the remaining types of UBCs (Table 8).Both tumor grade and stage of UBCs are highly correlated with recurrence, progression, and patient survival rates [9].  The WHO/ISUP grading of UBC is of great prognostic significance. In Jordan, Matalka*et al*.41 reported 60% of low grade and 40% of high grade. While in Australia, Samaratunga*et al.*50 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. 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 CONTRIBUTION

This study was completed by Amin AbdulkaremOkbah, 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”.

REFERENCES

1- Al-Azri M, Al-Awisi H, Al-Rasbi S, El-Shafie K, Al-Hinai M, Al-Habsi H, et al. Psychosocial impact of breast cancer diagnosis among Omani women. Oman Med J. 2014;29:437–44. doi: 10.5001/omj.2014.115. [[PMC free article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4289498/)] [[PubMed](https://www.ncbi.nlm.nih.gov/pubmed/25584162)] [[CrossRef](https://dx.doi.org/10.5001/omj.2014.115)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Oman+Med+J&title=Psychosocial+impact+of+breast+cancer+diagnosis+among+Omani+women&author=M+Al-Azri&author=H+Al-Awisi&author=S+Al-Rasbi&author=K+El-Shafie&author=M+Al-Hinai&volume=29&publication_year=2014&pages=437-44&pmid=25584162&doi=10.5001/omj.2014.115&)]

2-Al-Lawati NA, Al-Bahrani BJ, Al-Raisi SS, Al-Lawati J. Twenty-year trends of cancer incidence in omanis, 1996–2015. Oman Med J. 2019;34:361–87. doi: 10.5001/omj.2019.74. [[PMC free article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6642706/)] [[PubMed](https://www.ncbi.nlm.nih.gov/pubmed/31360330)] [[CrossRef](https://dx.doi.org/10.5001/omj.2019.74)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Oman+Med+J&title=Twenty-year+trends+of+cancer+incidence+in+omanis,+1996%E2%80%932015&author=NA+Al-Lawati&author=BJ+Al-Bahrani&author=SS+Al-Raisi&author=J+Al-Lawati&volume=34&publication_year=2019&pages=361-87&pmid=31360330&doi=10.5001/omj.2019.74&)]

 3-Ahmed HG, Tom MA. The consequence of delayed fixation on subsequent preservation of urine cells. Oman Med J 2011. Jan;26(1):14-18 10.5001/omj.2011.04 [[PMC free article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3191613/)] [[PubMed](https://www.ncbi.nlm.nih.gov/pubmed/22043372)] [[CrossRef](https://dx.doi.org/10.5001/omj.2011.04)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Oman+Med+J&title=The+consequence+of+delayed+fixation+on+subsequent+preservation+of+urine+cells.&author=HG+Ahmed&author=MA+Tom&volume=26&issue=1&publication_year=2011&pages=14-18&pmid=22043372&doi=10.5001/omj.2011.04&)]

4-El-Zine MAY, Alhadi YA, Ishak AA, Al-Shamahy HA. Prevalence of Different Types of Leukemia and Associated Factors among Children with Leukemia in Children’s Cancer Units at Al-Kuwait Hospital, Sana’a City: A Cross- Sectional Study. Glob J of Ped&Neonatol Car. 3(4): 2021. GJPNC.MS.ID.000569. DOI: 10.33552/GJPNC.2021.03.000569.

5-Alhadi AM, El-Zine MAY, IshaK AA, Al-Shamahy HA*.* “Childhood Leukemia in Yemen: The Main Types of Childhood Leukemia, its Signs and Clinical Outcomes”. EC Paediatrics 2021;10.6 (2021): 75-82.

6-Al-Maktari L AS, Al-Nuzaili MAK, Al-Shamahy HA, Al-Hadi AA, Ishak AA, et al., Distribution of Hematological Parameters Counts for Children with Leukemia in Children’s Cancer Units at Al-Kuwait Hospital, Sana’a City: A Cross-Sectional Study. Adv Can Res & Clinical Imag. 3(2): 2021. ACRCI.MS.ID.000560. DOI: 10.33552/ACRCI.2021.02.000560.

7-El-Zine, M. A. Y., M. A. A. Ali, and H. A. Al-Shamahy. “Prevalence of CNS tumors and histological recognition in the operated patients: 10 years experience in Yemen”. Universal Journal of Pharmaceutical Research 2021; 6, (2): 20-27. doi:https://doi.org/10.22270/ujpr.v6i2.563.

8- Lopez-Beltran A. Bladder cancer: clinical and pathological profile. Scand J UrolNephrolSuppl 2008 Sep;218 (218):95-109.

9- Schned AR, Andrew AS, Marsit CJ, Kelsey KT, Zens MS, Karagas MR. Histological classification and stage of newly diagnosed bladder cancer in a population-based study from the Northeastern United States. Scand J UrolNephrol 2008;42(3):237-242.

10- Anton-Culver H, Lee-Feldstein A, Taylor TH. Occupation and bladder cancer risk. Am J Epidemiol 1992 Jul;136(1):89-94.

11- Fukushima S, Asamoto M, Imaida K, el-Bolkainy MN, Tawfik HN, Ito N. Comparative study of urinary bladder carcinomas in Japanese and Egyptians. ActaPatholJpn 1989 Mar;39(3):176-179.

12. Messing EM. Urothelial tumors of the urinary tract. in: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors.Campbell's Urology. 8th ed. Philadelphia (PA): WB Saunders; 2002; p2732-2784.

***13-***Roth, Gregory A.; Abate, Degu; Abate, KalkidanHassen; et al.  ["Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6227606). Lancet 2018. **392** (10159): 1736–1788. [doi](https://en.wikipedia.org/wiki/Doi_%28identifier%29):[10.1016/S0140-6736(18)32203-7](https://doi.org/10.1016/S0140-6736%2818%2932203-7). [PMC](https://en.wikipedia.org/wiki/PMC_%28identifier%29) [6227606](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6227606). [PMID](https://en.wikipedia.org/wiki/PMID_%28identifier%29) [30496103](https://pubmed.ncbi.nlm.nih.gov/30496103).

14- Lakkis NA, Adib SM, Hamadeh GN, El-Jarrah RT, Osman MH. ["Bladder Cancer in Lebanon: Incidence and Comparison to Regional and Western Countries"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6055109). Cancer Control 2018; **25** (1): 1073274818789359.  [doi](https://en.wikipedia.org/wiki/Doi_%28identifier%29):[10.1177/1073274818789359](https://doi.org/10.1177/1073274818789359). [PMC](https://en.wikipedia.org/wiki/PMC_%28identifier%29) [6055109](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6055109). [PMID](https://en.wikipedia.org/wiki/PMID_%28identifier%29) [30027755](https://pubmed.ncbi.nlm.nih.gov/30027755).

15-Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90. [[PUBMED](https://www.medknow.com/crt.asp?prn=3;aid=JCanResTher_2018_14_3_532_172134;rt=P;u=http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=21296855&dopt=Abstract)]

16-Roshandel G, Boreiri M, Sadjadi A, Malekzadeh R. A diversity of cancer incidence and mortality in west asian populations. Ann Glob Health 2014;80:346-57. [[PUBMED](https://www.medknow.com/crt.asp?prn=11;aid=JCanResTher_2018_14_3_532_172134;rt=P;u=http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=25512150&dopt=Abstract)]

17-Ye F, Wang L, Castillo-Martin M, McBride R, Galsky MD, Zhu J, *et al.* Biomarkers for bladder cancer management: Present and future. Am J ClinExpUrol 2014;2:1-14. [[PUBMED](https://www.medknow.com/crt.asp?prn=15;aid=JCanResTher_2018_14_3_532_172134;rt=P;u=http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=25374904&dopt=Abstract)]

18-Salim EI, Moore MA, Bener A, Habib OS, Seif-Eldin IA, Sobue T. Cancer epidemiology in South-West Asia – Past, present and future. Asian Pac J Cancer Prev 2010;11Suppl 2:33-48. [[PUBMED](https://www.medknow.com/crt.asp?prn=16;aid=JCanResTher_2018_14_3_532_172134;rt=P;u=http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=20553067&dopt=Abstract)

19- UN. [""World Population prospects – Population division""](https://population.un.org/wpp/). population.un.org. [United Nations Department of Economic and Social Affairs](https://en.wikipedia.org/wiki/United_Nations_Department_of_Economic_and_Social_Affairs), Population Division. Retrieved 9 November 2021.

20- UN**.** [""Overall total population" – World Population Prospects: The 2019 Revision"](https://population.un.org/wpp/Download/Files/1_Indicators%20%28Standard%29/EXCEL_FILES/1_Population/WPP2019_POP_F01_1_TOTAL_POPULATION_BOTH_SEXES.xlsx) (xslx).  population.un.org (custom data acquired via website). [United Nations Department of Economic and Social Affairs](https://en.wikipedia.org/wiki/United_Nations_Department_of_Economic_and_Social_Affairs), Population Division*.* Retrieved 9 November 2021.

21- ["The General Census of Population 2004"](http://www.sabanews.net/en/news85385.htm). Sabanews. 29 December 2004 [Updated 13 December 2013]*.* Retrieved 13 December2013.

22**-** ["The population explosion on Europe's doorstep"](http://entertainment.timesonline.co.uk/tol/arts_and_entertainment/books/article3952775.ece). Times (London). London. 18 May 2008. Retrieved 22 February 2013.

23**-**  [*"*Yemen: Government planning to curb population growth"](http://irinnews.org/Report.aspx?ReportId=79232). IRIN Middle East. 14 July 2008*. Retrieved 22 February 2013*.

24**-**  ["Country Comparison: Total fertility rate"](https://www.cia.gov/library/publications/the-world-factbook/rankorder/2127rank.html). Central Intelligence Agency. CIA World Factbook*.* Retrieved 23 February 2013.

**25-** Eric Hansen. ["Sana'a Rising"](https://web.archive.org/web/20131127165256/http%3A/www.saudiaramcoworld.com/issue/200601/sana.a.rising.htm). [Saudi Aramco World](https://en.wikipedia.org/wiki/Saudi_Aramco_World). Archived from [the original](http://www.saudiaramcoworld.com/issue/200601/sana.a.rising.htm) on 27 November 2013*.* Retrieved 13 December 2013.

26-Epstein JI,   [Amin](https://pubmed.ncbi.nlm.nih.gov/?term=Amin+MB&cauthor_id=9850170) MB,  [Reuter](https://pubmed.ncbi.nlm.nih.gov/?term=Reuter+VR&cauthor_id=9850170) VR, [Mostofi](https://pubmed.ncbi.nlm.nih.gov/?term=Mostofi+FK&cauthor_id=9850170) FK. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. Am J SurgPathol. 1998; 22(12):1435-48. PMID: 9850170. doi: 10.1097/00000478-199812000-00001.

27- Al-Samawi AS, Aulaqi SM. Urinary bladder cancer in Yemen. *Oman Med J*. 2013;28(5):337-340. doi:10.5001/omj.2013.97.

28-Kattan S, Yousef A, Onuora V, Patil M, Al-Jasser A, Al-Ariyan R. The clinicopathological features of bladder carcinoma among Saudis in Riyadh Central Hospital. Ann Saudi Med 1994 Mar;14(2):114-116.

29- Obafunwa JO. Histopathological study of vesical carcinoma in Plateau State, Nigeria. Eur J SurgOncol 1991 Oct;17(5):489-491.

30- Kitinya JN, Laurèn PA, Eshleman LJ, Paljärvi L, Tanaka K. The incidence of squamous and transitional cell carcinomas of the urinary bladder in northern Tanzania in areas of high and low levels of endemic Schistosomahaematobium infection. Trans R Soc Trop Med Hyg 1986;80(6):935-939.

31-Lynch CF, Cohen MB. Urinary system. Cancer 1995 Jan;75(1)(Suppl):316-329.

32-Costello AJ, Tiptaft RC, England HR, Blandy JP. Squamous cell carcinoma of bladder. Urology 1984 Mar;23(3):234-236.

33-El-Bolkainy MN, Mokhtar NM, Ghoneim MA, Hussein MH. The impact of schistosomiasis on the pathology of bladder carcinoma. Cancer 1981 Dec;48(12):2643-2648.

34- Felix AS, Soliman AS, Khaled H, Zaghloul MS, Banerjee M, El-Baradie M, *et al.* The changing patterns of bladder cancer in Egypt over the past 26 years. Cancer Causes Control 2008 May;19(4):421-429.

35- Mostafa MH, Sheweita SA, O'Connor PJ. ["Relationship between schistosomiasis and bladder cancer"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC88908). Clinical Microbiology Reviews 1999; **12** (1): 97–111.  [doi](https://en.wikipedia.org/wiki/Doi_%28identifier%29):[10.1128/CMR.12.1.97](https://doi.org/10.1128/CMR.12.1.97).  [PMC](https://en.wikipedia.org/wiki/PMC_%28identifier%29) [88908](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC88908). [PMID](https://en.wikipedia.org/wiki/PMID_%28identifier%29) [9880476](https://pubmed.ncbi.nlm.nih.gov/9880476).

36-Zaghloul MS. ["Bladder cancer and schistosomiasis"](https://doi.org/10.1016/j.jnci.2012.08.002). Journal of the Egyptian National Cancer Institute 2012; **24** (4): 151–9. [doi](https://en.wikipedia.org/wiki/Doi_%28identifier%29):[10.1016/j.jnci.2012.08.002](https://doi.org/10.1016/j.jnci.2012.08.002). [PMID](https://en.wikipedia.org/wiki/PMID_%28identifier%29) [23159285](https://pubmed.ncbi.nlm.nih.gov/23159285).

37- Gouda I, Mokhtar N, Bilal D, El-Bolkainy T, El-Bolkainy NM. Bilharziasis and bladder cancer: a time trend analysis of 9843 patients. J Egypt NatlCancInst 2007 Jun;19(2):158-162.

38-Rosai J. Bladder and male urethera. In: Akerman's surgical pathology 8th ed. New York (NY): Mosby; 1996. p.1185-1217.

39- Mungan NA, Kiemeney LA, van Dijck JA, van der Poel HG, Witjes JA. Gender differences in stage distribution of bladder cancer. Urology 2000 Mar;55(3):368- 371.

40- Cheng L, Neumann RM, Nehra A, Spotts BE, Weaver AL, Bostwick DG. Cancer heterogeneity and its biologic implications in the grading of urothelial carcinoma. Cancer 2000 Apr;88(7):1663-1670.

41- Matalka I, Bani-Hani K, Shotar A, Bani Hani O, Bani-Hani I. Transitional cell carcinoma of the urinary bladder: a clinicopathological study. Singapore Med J 2008 Oct;49(10):790-794.

42-URMC.  ["Scientists Find One Reason Why Bladder Cancer Hits More Men"](https://web.archive.org/web/20090111011106/http%3A/www.urmc.rochester.edu/pr/news/story.cfm?id=1436). University of Rochester Medical Center. 20 April 2007. Archived from [the original](http://www.urmc.rochester.edu/pr/news/story.cfm?id=1436) on 11 January 2009*.* Retrieved 20 April 2007.

43-Kim A, Kim MS, Ahn JH, et al. . "Clinical significance of 5-α reductase inhibitor and androgen deprivation therapy in bladder cancer incidence, recurrence, and survival: a meta-analysis and systemic review". The Aging Male 2019; **23** (5): 971–978. [doi](https://en.wikipedia.org/wiki/Doi_%28identifier%29):[10.1080/13685538.2019.1646238](https://doi.org/10.1080/13685538.2019.1646238). [PMID](https://en.wikipedia.org/wiki/PMID_%28identifier%29) [31724468](https://pubmed.ncbi.nlm.nih.gov/31724468). [S2CID](https://en.wikipedia.org/wiki/S2CID_%28identifier%29) [208017350](https://api.semanticscholar.org/CorpusID%3A208017350).

44- Hemelt M, Yamamoto H, Cheng KK, Zeegers MP. "The effect of smoking on the male excess of bladder cancer: a meta-analysis and geographical analyses". International Journal of Cancer 2009; 124 (2): 412–9. [doi](https://en.wikipedia.org/wiki/Doi_%28identifier%29):[10.1002/ijc.23856](https://doi.org/10.1002/ijc.23856). [PMID](https://en.wikipedia.org/wiki/PMID_%28identifier%29) [18792102](https://pubmed.ncbi.nlm.nih.gov/18792102). [S2CID](https://en.wikipedia.org/wiki/S2CID_%28identifier%29) [28518800](https://api.semanticscholar.org/CorpusID%3A28518800).

45-Marks P, Soave A, Shariat SF, Fajkovic H, Fisch M, Rink M. ["Female with bladder cancer: what and why is there a difference?"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5071204). Translational Andrology and Urology 2016; 5 (5): 668-682.  [doi](https://en.wikipedia.org/wiki/Doi_%28identifier%29):[10.21037/ tau.2016.03.22](https://doi.org/10.21037/tau.2016.03.22). [PMC](https://en.wikipedia.org/wiki/PMC_%28identifier%29) [5071204](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5071204). [PMID](https://en.wikipedia.org/wiki/PMID_%28identifier%29) [27785424](https://pubmed.ncbi.nlm.nih.gov/27785424).

46- Mumy A, Kohaar I, Porter-Gill P, *et al.* Prostate stem cell antigen (*PSCA*) and risk of bladder cancer: linking genotypes to functional mechanisms. Genome Biol. 2011;12(Suppl 1):P15. doi:10.1186/gb-2011-12-s1-p15

47-SEER.  ["Cancer of the Urinary Bladder - Cancer Stat Facts"](https://seer.cancer.gov/statfacts/html/urinb.html). SEER. Retrieved 30 October 2019.

48-Hodges, Stephanie C.; Holt, Harry R.; Degeorge, Katharine C. ["Bladder Cancer: Diagnosis and Treatment"](https://www.aafp.org/afp/2017/1015/p507.html). American Family Physician 2017; 96 (8): 507–514. [PMID](https://en.wikipedia.org/wiki/PMID_%28identifier%29) [29094888](https://pubmed.ncbi.nlm.nih.gov/29094888).

49- Seth P. Lerner. ["Overview of Diagnosis and Management of Non-Muscle Invasive Bladder Cancer"](https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM522817.pdf) (PDF). [Food and Drug Administration](https://en.wikipedia.org/wiki/Food_and_Drug_Administration). ODAC 14 September 2016

50-Samaratunga H, Makarov DV, Epstein JI. Comparison of WHO/ISUP and WHO classification of noninvasive papillary urothelial neoplasms for risk of progression. Urology 2002 Aug;60(2):315-319.

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

|  |  |  |  |
| --- | --- | --- | --- |
| Age groupsYears | Male  | Female  | Total |
| No(%) | % | No | % | No | % |
| 20-29 | 10 (2.6) | 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 in Sana’a city, Yemen.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Types of UBC** | **No** | **%** | **M:F ratio** | **Mean age ±SD years** | **Age Mode** | **Age Median** | **P 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 |
| Glnadular 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 | % | 2.9:1 | 57.1±13.4 | 60 | 60 | Reference  |

### Table 3: The association between cytologically high grade with type of bladder neoplasms **(UBC) for 520 patients in Sana’a city, Yemen**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Types of UBC** | **High Grade** | ***OR*** | ***CI 95%*** | ***X2*** | ***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 |
| Glnadular neoplasms (GNs) n=12 | 3 | 25 | 0.36 | 0.09-13 | 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%, *X2* = Chi square, *p*= p value

### Table 4: The association between schistosomiasis with type of bladder neoplasm **(UBC) for 520 patients in Sana’a city, Yemen**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Types of UBC** | **schistosomiasis** | ***OR*** | ***CI 95%*** | ***X2*** | ***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 |
| Glnadular 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%, *X2* = Chi square, *p*= p value

### Table 5: The association between invasion of muscle fibers with type of bladder neoplasms **(UBC) for 520 patients in Sana’a city, Yemen**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Types of UBC** | **Invasion of muscle fibers**  | **OR** | **CI 95%** | **X2** | **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 |
| Glnadular 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%, *X2* = Chi square, *p*= p value

Table 6: The association between low grade with type of bladder neoplasms **(UBC) for 520 patients in Sana’a city, Yemen**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Types of UBC** | **Low Grade** | **OR** | **CI 95%** | **X2** | **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 |
| Glnadular 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 in Sana’a city, Yemen**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Types of UBC** | **GI Grade** | **OR** | **CI 95%** | **X2** | **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 |
| Glnadular 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

Table 8: The association between GII grade with type of bladder neoplasms **(UBC) for 520 patients in Sana’a city, Yemen**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Types of UBC** | **GII Grade** | **OR** | **CI 95%** | **X2** | **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 |
| Glnadular 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