

**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. **Aims:** Describe different types, age, sex distribution and associated different types with gradation, invasion muscles and schistosomiasis in the last ten years in a single Yemeni 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 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  $\pm$  SD of the total was  $57.1 \pm 13.4$  years. Of the 520 UBCs, 71.5% were urothelial neoplasms (UNs), 24.4% were squamous neoplasms (SNs), 2.3% were glandular neoplasms (GNs), 0.6% were neuroendocrine glandular neoplasms (NENs) and 0.96% were mesenchymal glandular 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  $OR= 64.1$  ( $p < 0.001$ ) and GNs (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**

In Yemen as in the greater part of Arabic countries, there are only some specialized epidemiological studies devoted to malignancies<sup>1-7</sup>, 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 and impact on public health, with diagnosis early and appropriate treatment with the aim of enhancing survival and minimizing subsequent potential consequences. 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 stages<sup>8</sup>. Urothelial (transitional cell) carcinoma is the most common type of bladder cancer<sup>9</sup>. Bladder tumors are more common in industrial areas and their incidence increases with exposure to cigarette smoking and arylamine<sup>10</sup>. *Schistosoma haematobium* is considering to 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 *Schistosoma haematobium*<sup>11</sup>. 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 patients<sup>9</sup> Currently there is no standardized grading system for bladder cancer. The most commonly used regimens depend on the degree of metastasis<sup>12</sup>. 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 neoplasms<sup>12</sup>.

Internationally, in 2017, bladder cancer was responsible in 196,000 deaths, down 5.4% (by age) from 2007<sup>13</sup>. 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 world<sup>14</sup>. Occupational exposure and smoking are prospective risk factors for bladder cancer in Western Asia and Western countries<sup>15,16</sup>. Persistent infections, for instance schistosomiasis, account for 50% of urinary bladder cancer cases in a number of developing countries<sup>15</sup>. Histological studies are utilized as a criterion for the diagnosis of urinary bladder cancer and one of the most vital predictive factors in clinical practice<sup>17</sup>. 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)<sup>15</sup>. Principally, *schistosomiasis 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 UBCs<sup>18</sup>.

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<sup>19,20</sup> with 46% of the population under 15 years old and only 2.7% over 65 years old<sup>21,22</sup>. By the year 2050, it is estimated that the population will increase to about 60 million<sup>23</sup> 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<sup>24</sup>. Sana'a's population has grown rapidly, from about 55,000 in 1978<sup>25</sup> 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)<sup>26</sup>. According to the WHO classification, patients were divided into 5 groups: urothelial neoplasms (UNs), squamous neoplasms (SNs), glandular neoplasms (GNs), neuroendocrine glandular neoplasms (NENs) and mesenchymal glandular neoplasms (MNs). Subgroups were then classified according to morphological diversity<sup>26</sup>.

**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 1 shows 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  $\geq 70$  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  $57.1 \pm 13.4$  years, for male was  $58.2 \pm 13.6$  years while for female was lower  $53.9 \pm 12$  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 glandular neoplasms (GNs), and 3 (0.6%) were neuroendocrine glandular neoplasms (NENs) and 5 (0.96%) were mesenchymal glandular 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 ( $59 \pm 13.5$  years), while with squamous neoplasms (SNs) it was lower ( $51.5 \pm 11.5$  years), and much lower with Glandular neoplasms (GNs) ( $48.1 \pm 11.4$  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 Glandular 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 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,  $X^2 = 157$ ,  $p < 0.001$  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,  $X^2 = 130$ ,  $p < 0.001$  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:** 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,  $X^2 = 38.8$ ,  $p < 0.001$ , followed by UNs (37.1%) with UNs as *OR* = 11.2, *CI* = 7.2- 17.6,  $X^2 = 135$ ,  $p < 0.001$ , 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,  $X^2 = 44.2$ ,  $p < 0.00$ , also there was a significant association between the low cytologically grade and MNs as *OR* = 10.6, *CI* = 1.2-95.7,  $X^2 = 6.8$ ,  $p < 0.00$ , 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 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:** 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  $OR= 64.1$ ,  $CI = 124.8-165$ ,  $X^2 = 175$ ,  $p < 0.001$ , followed by GNs (33.3%) as  $OR= 3.8$ ,  $CI = 1.1-13$ ,  $X^2 = 5.2$ ,  $p = 0.02$  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<sup>8</sup>. Urinary bladder cancer is rarely researched in countries Middle East, 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 (71.5%) was remarkably similar to the number previously reported from Yemen by Al-Samawi and Aulaqi in 2013<sup>27</sup> and from neighboring Saudi Arabia (77%)<sup>28</sup>. However, lower numbers have been reported in Africa; Nigeria (42%)<sup>29</sup> and Tanzania (28%)<sup>30</sup>. In developed countries, over 90% of bladder cancer cases are urothelial neoplasms (UNs), and rare types of bladder cancer make up the remaining 10%<sup>31</sup>. In the USA, a high frequency of urothelial neoplasms (98%) was reported by Schned *et al.*<sup>9</sup>. 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 England<sup>31</sup> and 7% in the United States<sup>32</sup>, but up to 75% in Egypt<sup>33</sup>. Approximately 43.8% of SNs in this study were associated with chronic infection with *Schistosoma haematobium*. A previous study conducted in Egypt illustrated that about 80% of SNs were accompanied by persistent infection with *S. haematobium*<sup>34</sup>. Infection with *Schistosoma haematobium* may cause bladder cancer, in particular the squamous cell type<sup>35</sup>. *Schistosoma* eggs cause a chronic inflammatory condition in the bladder wall that leads to tissue fibrosis<sup>36</sup>. In recent times, transitional cell carcinoma has become the most common type in Egypt due to significant changes in the etiology of bladder cancer<sup>37</sup>. 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 Aulaqi in 2013 (3%)<sup>27</sup>; and Rosai in the USA where its prevalence was 3%<sup>38</sup>. 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<sup>27,39,40</sup>. On the other hand, a higher proportion was documented by Matalka *et al.* in Jordan; 1:9<sup>41</sup>. One other reason is that androgen receptors, which are more active in men than in women, may compete a role in the occurrence of cancer<sup>42</sup>. 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 cancer<sup>43</sup>. 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 endemic<sup>44</sup>. 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<sup>45</sup>. 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 patients<sup>46</sup>. 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<sup>27,47,48</sup>.

According to WHO classification (1973) bladder cancers are histologically graded into:<sup>49</sup>, 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  $OR = 51.3$ ,  $CI = 20.5-128.5$ ,  $X^2 = 157$ ,  $p < 0.001$  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  $OR = 64.1$ ,  $CI = 124.8-165$ ,  $X^2 = 175$ ,  $p < 0.001$ , followed by GNs (33.3%) as  $OR = 3.8$ ,  $CI = 1.1-13$ ,  $X^2 = 5.2$ ,  $p = 0.02$  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.*<sup>41</sup> reported 60% of low grade and 40% of high grade. While in Australia, Samaratunga *et al.*<sup>50</sup> 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

This is the second study of a sequence in Yemen looking at UBCs, which includes patients of all age groups over a period of 10 years. Even though this study is no more than a retrospective analysis of a single institution, it can be a strong indicator of the epidemiology of UBCs in Yemen. In addition, 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 6<sup>th</sup> 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 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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Table 1: Sex and age distribution of bladder cancer patients in Sana'a, Yemen

| Age groups<br>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 in Sana'a city, Yemen.

| Types of UBC                    | No  | %    | M:F ratio | Mean age $\pm$ SD years | Age Mode | Age Median | P value       |
|---------------------------------|-----|------|-----------|-------------------------|----------|------------|---------------|
| Urothelial neoplasms (UNs)      | 372 | 71.5 | 3.5:1     | 59 $\pm$ 13.5           | 60       | 60         | 0.03          |
| Squamous neoplasms (SNs)        | 128 | 24.6 | 1.7:1     | 51.5 $\pm$ 11.5         | 60       | 50         | <0.0001       |
| Glnadular neoplasms (GNs)       | 12  | 2.3  | 5:1       | 48.1 $\pm$ 11.4         | 38       | 44         | <0.0001       |
| Neuroendocrine neoplasms (NENs) | 3   | 0.6  | 3:0       | 70 $\pm$ 0              | 70       | 70         | Non available |
| Mesenchymal neoplasms ( MNs)    | 5   | 0.96 | 2:3       | 53 $\pm$ 12             | 40       | 50         | 0.49          |
| Total                           | 520 | %    | 2.9:1     | 57.1 $\pm$ 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%     | X <sup>2</sup> | 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%, X<sup>2</sup> = 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%    | X <sup>2</sup> | 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%, X<sup>2</sup> = 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)<br>n=372 | 138                       | 37.1 | 11.2 | 7.2-17.6 | 135  | <0.001 |
| Squamous neoplasms (SNs)<br>n=128   | 85                        | 66.4 | 3.3  | 2.2-5.1  | 33.8 | <0.001 |
| Glnadular neoplasms (GNs)<br>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 in Sana'a city, Yemen

| Types of UBC                        | Low Grade |      | OR    | CI 95%    | X2   | P      |
|-------------------------------------|-----------|------|-------|-----------|------|--------|
|                                     | No        | %    |       |           |      |        |
| Urothelial neoplasms (UNs)<br>n=372 | 133       | 35.8 | 6.7   | 3.6-12.6  | 44.2 | <0.001 |
| Squamous neoplasms (SNs)<br>n=128   | 2         | 1.6  | 0.028 | 0.007-0.1 | 56   | <0.001 |
| Glnadular neoplasms (GNs)<br>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%,  $X^2$  = 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)<br>n=372 | 0        | 0     | 0         | 0-0.01 | 196  | <0.001 |
| Squamous neoplasms (SNs)<br>n=128   | 68       | 87.04 | Undefined |        | 234  | <0.001 |
| Glnadular neoplasms (GNs)<br>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%,  $X^2$  = 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)<br>n=372 | 0         | 0    | 0    | 0-0.01   | 180   | <0.001 |
| Squamous neoplasms (SNs)<br>n=128   | 59        | 46.1 | 64.1 | 24.8-165 | 175.7 | <0.001 |
| Glnadular neoplasms (GNs)<br>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%,  $X^2$  = Chi square,  $p$ = p value