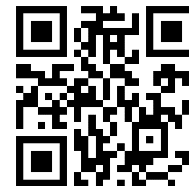


## Urinary Bladder Cancer-Epidemiological and Histopathological Study



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**ABSTRACT:** Urinary bladder cancer is the main reason for morbidity and mortality throughout the world. Urothelial carcinoma is a common primary tumor of urinary bladder (90%). To investigate the epidemiological and histopathological aspects in Libyan patients suffering from urinary bladder cancer, we performed a study on 39 bladder cancer biopsies from transurethral resection of bladder tumor (TURBT) and cystoscopic samples obtained from Oncology Department- Al Hawari Hospital, over the period of (2021- May 2022), Tiba Medical Laboratory (2021- July 2022), and Alnoon Medical laboratory (2019- January 2022) at Benghazi, Libya. Of the 39 cases, 34 (87.2%) were diagnosed in men, and 5 (12.8%) were found in women, the men/ women ratio being of 6.8/1. The highest incidence of bladder tumors was recorded in individuals aged between 61 and 80 years old. In this age group, there were admitted 24 patients with bladder cancer, representing 61.5%. The most common pathological types of urinary bladder carcinoma found was Invasive Urothelial Carcinoma TCC (48.72%) followed by noninvasive Urothelial Carcinoma TCC (46.15%), and Squamous Cell Carcinoma SCC in (5.13%). A case of SCC on top of Schistosomiasis was also seen. Grade III was found in 51.2% of our patients and 43.5% of them had stage II. This study has highlighted upon the importance of histopathological study in evaluating urinary bladder cancer. Cystoscopic studies and biopsies help in early detection of bladder neoplasms and they form the mainstay of the diagnosis and follow up. The objects of this work were to assess epidemiological features of the bladder cancer in Benghazi - Libya with regard to frequency, age and sex distribution. Furthermore, to describe the Histopathological features of the urinary bladder cancer, particularly Transitional Cell Carcinoma (TCC) in urinary bladder biopsies.

**KEYWORDS:** Bladder Cancer, Transitional Cell Carcinoma, Histopathology.

### LITERATURE REVIEW

Urinary bladder cancer is considered the ninth most common malignancy in the world, with a higher incidence in the developed countries (Parkin et al., 2002) with transitional cell carcinoma (TCC) as the most frequent microscopic type (Golka et al., 2004). Bladder cancer is a new tissue formation most often of urothelial origin with potential for local, locoregional and distant invasion. It is most often a tumor invading the bladder muscle (American Cancer Society, 2016). It is sometimes a tumor which does not directly infiltrate the bladder muscle but given that it is of high histological grade; this could presage an evolution towards the mode infiltrating the bladder muscle. This ambiguity in evolution will lead us to speak more often of a bladder tumor. Bladder cancer with 16,390 deaths in 2016 is one of the deadliest genitourinary tumors in the USA (American Cancer Society, 2016). In Europe, it is the second urological cancer after prostate cancer (Ferlay et al., 2015). Although it is more frequently diagnosed in males, female patients show worse prognosis (Scosyrev et al., 2010, Otto et al., 2012). Carcinogenesis of UCB often requires exposure to occupational carcinogens and environmental pollution (Letasiova et al., 2012). Smoking and occupational exposure are the main risk factors. In Africa, in bilharzia endemic areas, there is a histological type, squamous cell carcinoma, characterized by a high risk of local progression, recurrence and reduced sensitivity to chemotherapy and radiotherapy (Honoré et al, 2021). It has been estimated that around 50% of all Urinary

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Cancer Bladder (UCB) cases can be attributed to tobacco smoking, with considerable variation in groups of former and current smokers. Many of the ingredients in tobacco smoke such as aromatic amines are excreted by the kidneys, and therefore directly expose the urothelium to toxic metabolites. Due to its reservoir function the exposure time is the longest in the urinary bladder. Metabolites of tobacco smoke may cause inflammatory reactions and lead to perturbation of cellular processes which may alter gene expression. We have previously reported on changes of different gene expressions in UCB tissue depending on smoking status in microarray study (Worst et al., 2014). Most cases of urothelial carcinoma of the bladder present in patients over the age of 50 years, but they can also rarely occur in younger adults and children. The latter tend to be low-grade, indolent neoplasms, but occasional highly aggressive examples are reported in young adults. White individuals are more often affected than patients of African descent (Goldblum et al., 2018). In the present cross-sectional study, we proposed to evaluate the epidemiological, and Histopathological features of bladder cancer in the patients admitted to Oncology Department- Al Hawari Hospital over a period (2021- May 2022), Tiba Medical Laboratory (2021- July 2022), and Alnoon Medical laboratory (2019- January 2022).

### PATIENTS AND METHODS

This is a descriptive, retrospective study of histologically confirmed cases of urinary bladder cancer. Data of patients in this study was retrieved from the medical records in The Department of Oncology- Al Hawari Hospital within the period (2021- May 2022), Tiba Medical Laboratory (2021-July 2022), and Alnoon Medical laboratory (2019- January 2022) at Benghazi, Libya. The material for the study comprised of biopsies from TURBT and cystoscopic samples. In this study, all patients who were diagnosed with primary bladder cancer and registered in the mentioned records were included. Demographic (Epidemiological) data were examined regarding the frequency, age and sex. Data analyzed with the next considerations: pathological pattern, tumor grade and final diagnosis. Tumors were categorized according to histological grading using grading system. All cases of urothelial (transitional) carcinomas were further classified histologically according to WHO (2004) /ISUP classification.

**Statistical analysis:** The entire data were evaluated statistically by using the SPSS statistical package version 21 (Chi-square test). A P-value of less than 0.05 was considered as statistically significant. Microsoft Word and SPSS have been applied to make tables, graphs, pie diagrams, etc.

The histological and epidemiological data so received were evaluated. A comparison with other similar studies was done.

### RESULTS

A total of 39 patients were included in the study. For all patients, the median age was 63 years old with a range of (41-86 years). The mean age of the patients was  $64.5 \pm 10.4$  years. Mean age of the patients was calculated as  $63.7 \pm 10.6$  (41-86) in males and  $69.8 \pm 8.1$  (60-80) in females ( $p=0.22$ ). Males represented (87.18%) of the patients (34 cases) while; (21.8%) were female (5 cases) as shown in (Figure 1). There was a higher male predominance with a male to female ratio of 6.8:1. Figure 2 shows the age-wise distribution of the cases. Most of the cases were in the 6th and 7th decade of life in the age group 61-80 years that had a higher prevalence followed by 40-60 years, and 81-100 years. The least number of cases were seen in the extremes of age groups. The most common pathological types of urinary bladder carcinoma found was Invasive Urothelial Carcinoma TCC (48.72%) followed by noninvasive Urothelial Carcinoma TCC (46.15%), and Squamous Cell Carcinoma SCC in (5.13%) of the patients (Figure 3). Out of 19 invasive urothelial carcinomas, 18 had muscle invasion and 1 had invasion up to lamina propria. The non-squamous cell carcinoma to squamous cell carcinoma ratio was 18.5 (Table 1). One case of SCC on top of Schistosomiasis. As shown in Table 2, By analyzing the distribution of bladder tumor cases according to the age groups, we observed that the incidence of bladder cancer increased with the patient age, with commonest age group of tumor presentation was in 61-80 years. Fifty-one point two percent (51.2%) of tumors were of grade III, while grade II found in (43.5%) of them, grade I and IV were representing 2.5% of all cases as shown in (figure 4). So, high grade tumors in our study cases (51.4%) were more in occurrence compared with the low-grade tumors (48.6%) as seen in (Table 3). No significant difference was found between the sexes in terms of WHO tumor grade ( $P=0.77$ ).

Low grade papillary urothelial cancers, featured papillary architecture that composed of central fibrovascular core and multiple crowded layers of transitional epithelial cells having enlarged, irregular and hyperchromatic nuclei with prominent nucleoli. There is no evidence of urinary bladder smooth muscle bundles infiltration. High grade urothelial cancers, showed edematous and congested lamina propria that shows mixed inflammatory cells infiltration and malignant transitional epithelial cells infiltration that arranged in solid sheets and clusters and show degenerative changes along with papillary configurations. The malignant cells show enlarged, irregular and hyperchromatic nuclei with prominent nucleoli. The malignant transitional epithelial cells extend to infiltrate

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the urinary bladder smooth muscle bundles (Figure 5 & 6). Our study revealed a significant association between the age and tumor grade. This result was statistically significant ( $P=0.017$ ).

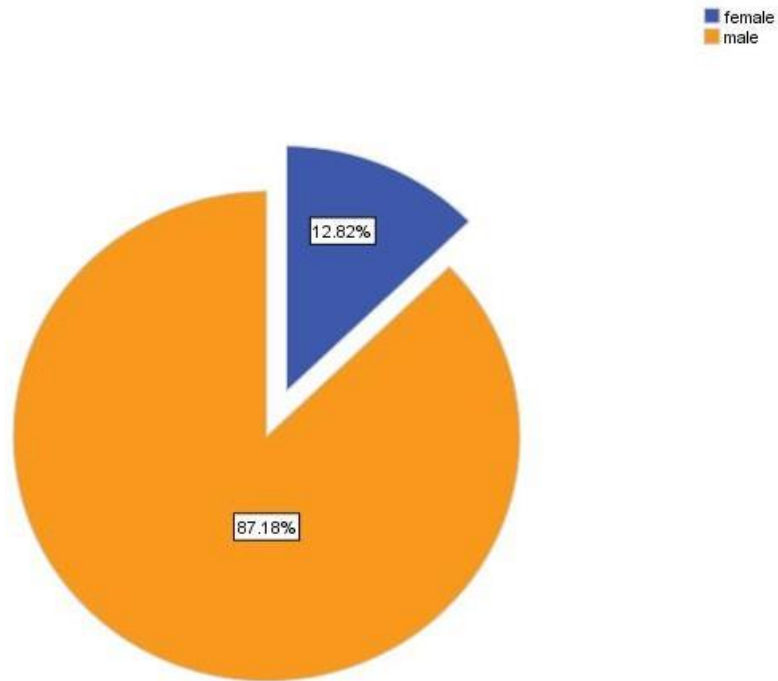


Figure 1. Sex Distribution Among All Patients

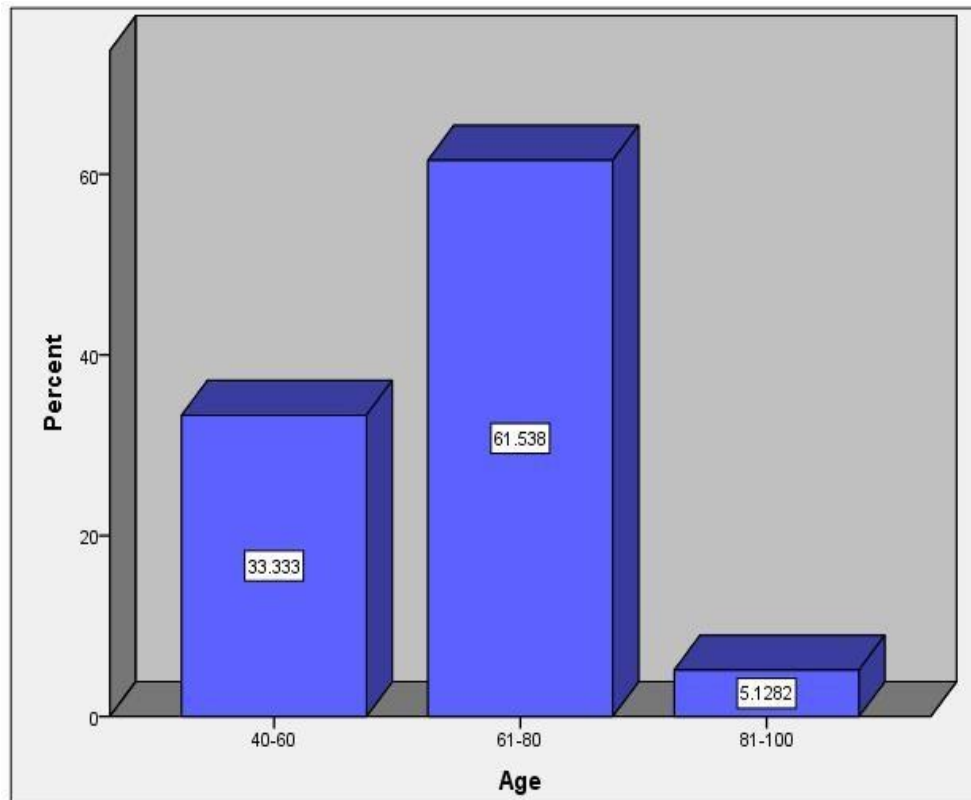


Figure 2. Age Distribution in 39 Patients with Primary Bladder Carcinoma

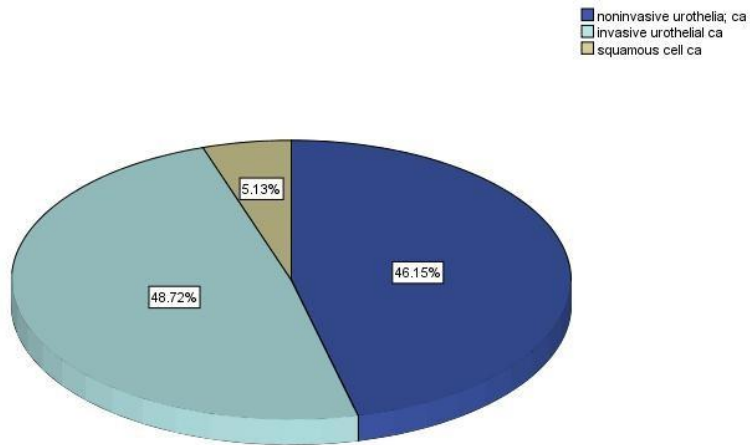


Figure 3. Frequency of Various Histological Cell Types in 39 Patients with Primary Bladder Carcinoma

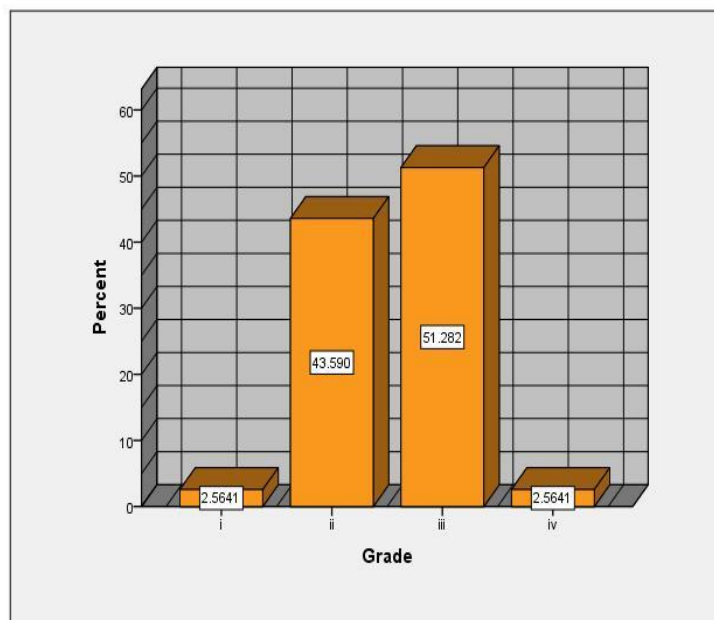


Figure 4. Histological Grading in 39 Patients with Primary Bladder Carcinoma

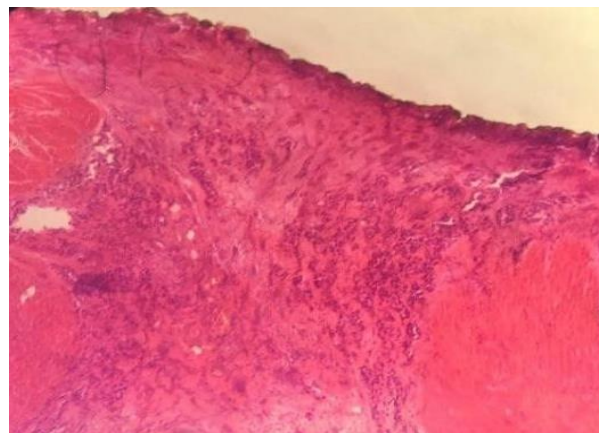


Figure 5. Photomicrograph showing High grade urothelial cancers, showing invasion into the muscular tissue (HE stain, X100)

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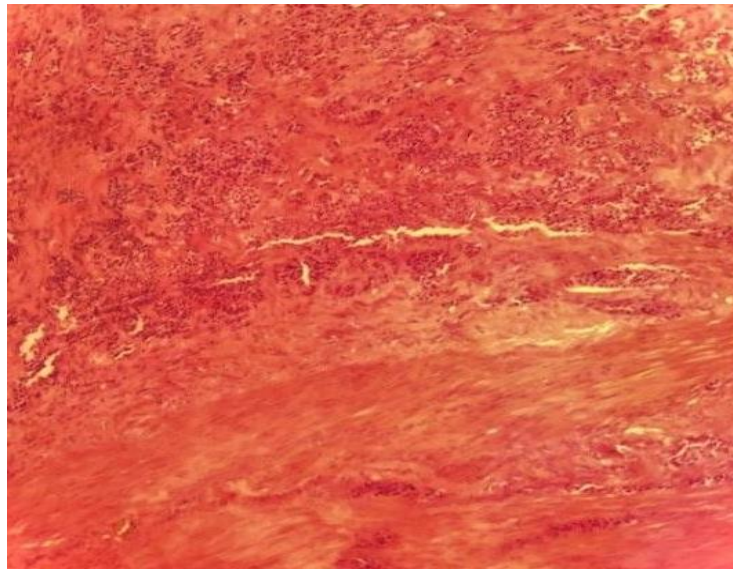


Figure 6. Photomicrograph showing High grade urothelial cancers, malignant transitional epithelial cells infiltration that arranged in solid sheets and clusters (HE stain, X100).

Table 1. Distribution of Urinary Bladder Cancers According To The Patients' Age

Age	Diagnosis			Total
	Noninvasiveurothelial Ca	Invasive urothelial Ca	Squamous cell Ca	
40-60	6	6	1	13
61-80	10	13	1	24
81-100	2	0	0	2
<b>Total</b>	18	19	2	39

$\chi^2 = 2.8$  P-value= 0.59

Table 2. Histopathological Diagnosis

Tumor	Frequency	Percent (%)
Nonsquamous Ca	37	94.9
Squamous cell Ca	2	5.1
<b>Total</b>	39	100.0

Table 3. WHO-Histological Grading of Transitional Cell Cancers

Tumor Grade	Frequency	Percent (%)
Low grade	18	48.6
High grade	19	51.4
<b>Total</b>	37	100.0

### DISCUSSION

At present, cancer is a major health problem worldwide, both due to its ever-growing incidence and to the very high medical and social costs. Urinary bladder cancer is the 7th most frequent cancer form in men and the 17th most frequent cancer form in women, all over the world (Ştefanescu et al, 2018). Several studies showed that males are more frequently diagnosed compared to females and the incidence rate of the disease increase with age. However, there are also a few other studies that tell the opposite. In this study, one of our primary objectives was to assess the patients with urinary bladder tumors in terms of age and sex aspect. UCB incidence show difference between the sexes. We saw a significantly increased diagnosis rate in male patients, most bladder cancers (87.1%) were

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recorded in males, this is in agreement with other study (Paudel *et al.*, 2021) with male to female ratio was 4.67. The possible causes for that difference are thought to be different exposure levels to environmental carcinogens, genetic differences, differences in hormonal balance, anatomical differences, social life differences (Türk *et al.*, 2017), where smoking always related to men in our society. This study found that the median age at diagnosis for urinary bladder cancer, was 63 which is in agreement with Egyptian study (Nagy *et al.*, 2018) with median age 60. Most cases were recorded in the age group between 61 and 80 years old (24 patients, representing about 61.5%); which were comparable with other studies (Paudel *et al.*, 2021). It is documented that the immune system plays an important part in the onset and development of cancer. After the age of 60 years old, the number and functions of T lymphocytes present a significant drop, being one of the characteristics of the aging immune system. Another mechanism that connects aging with cancer is the oxidative stress, a process by which the production of reactive oxygen species and free radicals may cause alterations of the DNA and of various proteins associated with aging and malignity (Ştefanescu *et al.*, 2018). After the age of 80 years old the incidence of bladder tumors decreased, but this decrease was due to the fact that the individuals over 80 years old represent a lower percent of the general population, as there is an increased mortality in this segment due to other conditions. As already known, a vast majority of tumors of the urinary bladder are of epithelial origin, which arises from urothelium, a transitional type epithelium that lines the bladder. Approximately 90% of malignant tumors are transitional cell carcinomas. The remaining 10% comprises all other types of carcinomas (Paudel *et al.*, 2021). In this study too, transitional cell carcinoma is the most common bladder tumor (94.8%), while squamous cell carcinoma constitutes (5.1%) of 39 bladder tumors seen over a multi-year period. These figures are similar to the published results by (Atallah *et al.*, 1997), and in contrast with (Honoré *et al.*, 2021) who documented SCC as the most frequent histological type (58.2%) followed by TCC in (26.0%) of cases. Unlike TCC, the main risk factors for SCC are not environmental exposures, but exposure to infectious agents. The main cause of SCC in developing countries is *Schistosoma haematobium* (Nagy *et al.*, 2018), however Schistosomiasis is not endemic in our country, consequently SCC does not appear frequent in the present study. Since almost the cases of squamous cell carcinoma are muscle-infiltrative at the time of diagnosis, the importance of early detection is obvious. Emphasis should be placed on the need for medical education programs aiming at early diagnosis of the disease by general practitioners and primary care medical personnel. If we are able to detect localized early stages, we might be able to improve the outcome of patients.

In our study, high-grade urothelial carcinoma was seen in 51.4% of cases and low-grade urothelial carcinoma was seen in 48.6%. This correlates with the study conducted by (Kumar & Yelikar, 2012). in which high-grade urothelial carcinoma comprised 53.5% compared to low-grade urothelial carcinoma which comprised 42.8%. In contrast, (Matalka *et al.*, 2008) found 60% of cases were low-grade urothelial carcinoma and only 40% were of high-grade urothelial carcinoma. Hence in our study, many of the cases were of high grade, may be because of the late presentation of the patient.

## CONCLUSION

Urinary bladder biopsy is one of the most common biopsies in urology practice. All neoplastic lesions in the present study were of epithelial origin (transitional cell carcinoma and squamous cell carcinoma). transitional cell carcinoma formed the bulk of the cases (94.9%), majority of which showed muscle invasion (48.72%), high grade lesions being the commonest with detrusor muscle invasion. Muscle invasion are the most important determinants of prognosis and treatment for bladder cancer. The age of presentation of TCC in Libya is similar to that in the west, but a higher male-to-female ratio was observed. Cystoscopic studies and biopsies help in early detection of bladder neoplasms and they form the mainstay of the diagnosis and follow up.

## REFERENCES

- 1) American Cancer Society. (2016). Cancer Facts & Figures 2016. *American Cancer Society*.
- 2) Atallah A. Shaaban, Saad A. Orkubi, Mohammad T. Said, Boshra Yousef, Mohammed S. Abomelha. (1997). SQUAMOUS CELL CARCINOMA OF THE URINARY BLADDER. *Annals of Saudi Medicine*, 17.
- 3) Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D. M., Forman, D. and Bray, F. (2015). Cancer Incidence and Mortality Worldwide: Sources, Methods and Major Patterns in GLOBOCAN 2012. *International Journal of Cancer*, 136.
- 4) Goldblum John R., Lamps Laura W. McKenney, Jesse K., Myers Jeffrey L. (2018). *Rosai and Ackerman's Surgical Pathology* (11 ed.). Philadelphia, PA: ELSEVIER.
- 5) Golka K, Wiese A, Assennato G, Bolt HM. (2004). Occupational exposure and urological cancer. *World J Urol*, 21, 391.

## Urinary Bladder Cancer-Epidemiological and Histopathological Study

- 6) Honoré Jean Gabriel Berthé, Dramane Cissé, Moussa Salifou Diallo, Amadou Kassogué, Alkadri Diarra, Mamadou Tidiani Coulibaly, Mamadou Lamine Diakitè, Modibo Coulibaly, Mory Koné. (2021). Bladder Cancer: Epidemiological, Clinical and Histopathological Aspects at the University Hospital Point G, Mali. *Open Journal of Urology*, 343-350, 343- 350.
- 7) Kumar U Mahesh & Yelikal B.R. (2012). Spectrum of Lesions in Cystoscopic Bladder Biopsies -A Histopathological Study. *Al Ameen J Med Sci*, 5 (2):132-136.
- 8) Letasiova S., Medvedova A. , Sovcikova A. et al. (2012). Bladder cancer, a review of the environmental risk factors. *Environmental Health*, 11.
- 9) Matalka I, Bani-Hani K, Shotar A, Bani Hani O, BaniHani I. (2008). Transitional cell carcinoma of the urinary bladder: a clinicopathological study. *Singapore Med J*. Oct;49(10):7.
- 10) Nagy AA, Darweish H, Hamdey HM, Elkalla R, Abdu-Allah H, et al. (2018) Factors Affecting Survival in Egyptian Patients Suffering from Urinary Bladder Cancer: A Multicenter Retrospective Study. *J Cancer Sci Ther* 10: 031- 035.
- 11) Otto W, May M, Fritsche HM, et al. (2012). Analysis of sex differences in cancer-specific survival and perioperative mortality following radical cystectomy: results of a large German multicenter study of nearly 2500 patients with urothelial carcinoma of the bladder. *Gen Med*, 9, 481-489.
- 12) Parkin DM, Bray F, Ferlay J, Pisani P. (2002). Global cancer statistics. *CA Cancer J Clin*, 55, 108.
- 13) Paudel Deliya , Regmi Himanshu , Bajracharya Uspal , Shrestha Guna K. (2021). Spectrum and Presentation of Urinary Bladder Growth: a Single-Center Retrospective Study. *Nepalese Medical Journal*, 4, 485-488.
- 14) Ștefanescu M.L., Tomescu P.I., Fortofoiu M.C., Stoica L.E., Badea Oana, Mogoanta L., Ionovic Nina. (2018). Urinary Bladder Tumors Clinical and Statistical Retrospective Study. *Current Health Sciences Journal*, 44:1.
- 15) Worst Thomas S. , Reiner Verena , Gabriel Ute , Weiß Christel , Erben Philipp . (2014). IL1RN and KRT13 Expression in Bladder Cancer: Association with Pathologic Characteristics and Smoking Status. *Advances in Urology*.



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