Journal of Medical and Health Studies
ISSN: 2710-1452
DOI: 10.32996/jmhs
Journal Homepage: www.al-kindipublisher.com/index.php/jmhs

JMHS
AL-KINDI CENTER FOR RESEARCH AND DEVELOPMENT

| RESEARCH ARTICLE

Bladder Cancer Detection and Diagnosis in Babil Governorate by Age Group

Haider Farhan abdullah[1]✉, Ameer Qusay kbah[2], Owham Ghalib Hamza[3]
[123]*Al-Furat Al-Awsat University, Babylon Technical Institute, Iraq*
Corresponding Author: Haider Farhan abdullah, **E-mail**: Haa.oks10@gmail.com

| ABSTRACT

As the sixth most common cancer in women and the fourth most common cancer in males, bladder cancer is a serious issue worldwide. Male preponderance correlates with an increase in age-dependent incidence. Cigarette smoking, chemical exposure at work, and chronic bladder inflammation are all risk factors. The identification and diagnosis of bladder cancer were studied across age groups in a cross-sectional study conducted in the Governorate of Babil, Iraq. The study's 90 participants included 75 men and 75 women with a mean age of 62.3 years. Smoking (44.4%) was the most common cause of bladder cancer, followed by occupational chemical exposure (22.2%) and chronic inflammation of the bladder (5%). (11.1 percent). Hematuria (88.1%), dysuria (66.7%), and frequency (88.9%) were the most common signs of bladder cancer (55.6 percent). Cystoscopy and biopsy confirmed the diagnosis of bladder cancer in every patient. Smoking, chemical exposure at work, and chronic bladder inflammation have all been identified as significant risk factors in previous research. All participants were diagnosed after displaying symptoms, illustrating the importance of early detection and diagnosis. The study also emphasizes the importance of cystoscopy and biopsy for a final diagnosis. Although bladder cancer is hazardous, it is usually curable if caught and treated early. Bladder cancer is more common in males than in women, and smoking and exposure to certain chemicals are major risk factors.

| KEYWORDS

bladder cancer, diagnosis, age groups, risk factors, symptoms, cystoscopy, biopsy

| ARTICLE INFORMATION

ACCEPTED: 01 January 2025 **PUBLISHED:** 09 January 2025 **DOI:** 10.32996/jmhs.2024.6.1.1

1. Introduction

Since cancer is defined as an abnormal growth of tissue in the body, it can manifest itself in various organs and tissues, each with its own symptoms. Weight loss, loss of appetite, and hypertension are some of the more general symptoms of the illness. However, these symptoms may accompany cancer and not the disease itself. It cannot be detected since any other sickness, and occasionally even a psychiatric issue, may induce comparable symptoms. It can only be diagnosed with a thorough medical examination, medical testing, and confirmation of the tissue by obtaining a sample or tissue biopsy for microscopic analysis (Nguyen, 2011). The incidence of bladder cancer ranks high: it is the ninth most prevalent disease worldwide and the fourth most common cancer in males (Kirkali et al., 2005). Its incidence reaches its peak between the ages of 60 and 70. It affects men 2.5 times more frequently than women. The most prominent chemicals that cause bladder cancer are aromatic amines. Several factors have been linked to the development of bladder cancer (examples: chronic infections, radiation and chemotherapy, occupational exposure to aromatic amines). Despite this, tobacco use remains the most significant preventable cause of mortality in the 21st century. About 90% of bladder cancers are urothelial cell carcinomas (UCC). Squamous cell carcinoma (6%-8% of all cancers) and adenocarcinoma are two more common histological subtypes (1-2 percent). The histological subtype of squamous cell carcinoma was the most common in the Arab world and other regions where schistosomiasis is prevalent. The urinary bladder is home to the vast majority of UCCs. Less than 10% of all carcinomas are urothelial (kidney-draining) carcinomas (UCCs).

The most telling sign of a bladder tumor is the presence of blood in the urine, either microscopic or coarse. The diagnosis is often delayed because hematuria is usually asymptomatic and occurs only occasionally. A bladder tumor or in situ flat carcinoma may cause symptoms, including frequency, urgency, and discomfort in the bladder. Endoscopic urethrocystoscopy (UCS) and urine cytology are the gold standards for diagnosing UCC (UC). To view the kidneys and upper urinary system (renal pelvis and ureters), an intravenous urogram, CT scan, or ultrasound is required (Van Rhijn, 2005).

2. Review References

2.1 The natural background of bladder cancer

The actual natural history of bladder cancer is poorly understood at this time. We only know the "treatment history" for bladder cancer because almost all instances have symptoms that lead to a diagnosis, and virtually all cases of bladder cancer are treated with at least transurethral resection. Most bladder cancers are urothelial carcinomas, yet this disease comes in many different forms. There have been proposed two different paths of growth. Small, isolated, urothelium-confined low-grade malignancies (or LMPs) seldom advance and often do not pose a life-threatening risk to patients, whereas large, muscle-invasive high-grade lesions spread rapidly and kill patients even with vigorous treatment. Potential prognostic indicators include histologic grade, staging, vascular/lymphatic invasion, and cancer in situ (CIS). Histologic risk assessment is therapeutically advantageous, but it is not sensitive enough to distinguish the unique biologic potential of a particular cancer from that of other diseases. Because of this, analyzing the genetics, molecular biology, and complete carcinogenesis process of a tumor is essential (Hemdan, 2016).

2.2 Epidemiology

In bladder cancer (BC), aberrant cells develop out of control in the bladder (the bladder is a hollow, muscular structure holding urine). The lower abdomen is impacted by urinary bladder cancer. There is a 3.81 percent lifetime risk for men and a 1.15 risk for women to develop bladder cancer, according to research by Siegel R. et al. (2013). It's the most expensive genitourinary cancer to treat and the second most common. Bladder cancer is becoming more common as people live longer. Bladder cancer rates are not uniform between regions, populations, or demographic categories like age or gender. Its incidence continuously rises with age, making it the fourth most common cancer in males over 70 (after prostate, lung, and colorectal cancers). Researchers J. Ferlay et al. (2008) It is projected that over 100,000 new cases will be identified each year in Europe. However, estimating incidence rates is challenging because the rates reported by different cancer registries may reflect differing diagnostic criteria. Urothelial carcinoma, formerly known as transitional cell carcinoma (TCC), originates in the cells lining the bladder's inside (UC). Approximately 70% of cases develop as non-invasive tumors, whereas the remaining 30% manifest as muscle-invasive illnesses, making for an intriguing biphasic presentation (Kumar et al., 2005).

3. Staging and history

The adventitia surrounds the urothelium, lamina propria, muscularis propria (detrusor muscle), and perivesical bladder fat. These strata are used for bladder cancer staging, with the pathologic stage rising with deeper invasion (Amin et al., 2013; Babjuk et al., 2013). Since the initial grading system (launched in 1973) did not have set criteria for the three pathologic categories, there was a significant variation among observers. As a result, there was an increase in the number of second-grade tumors. Pan CC et al. (2010); Amin MB et al. (2013). To eliminate inter-observer variability with the intermediate grade, the World Health Organization and the International Society of Urological Pathology (ISUP) devised a new grading system in 2004 with exact histologic criteria (grade 2). To wit: (Burger et al., 2008). The former three-stage approach with grades 1-3 has been replaced with a new two-stage method for distinguishing between low-grade and high-grade cancers. (LGTCC and HGPTUC). There are no longer three phases. (HGTCC). Hyperchromatic nuclei and characteristic mitotic patterns characterize LGTCC throughout the urothelium, but exclusively in the basal layer, at any thickness. The HGTCC can have modest to severe architectural defects, and papillary fronds typically branch and merge. Loss of polarity, nuclear pleomorphism, an uneven distribution of chromatin, and prominent nucleoli are standard features. Denudation may also be pronounced, resulting in the separation of the urothelium from the fibrovascular centers. This model suggests a linear relationship between grade and the chance of advancement and recurrence. Comparable distinctions between NMIBC and MIBC were made in the 2004 WHO classification, although the word "superficial bladder cancer" was left out. Molecular investigations have revealed similarities between muscle-invasive tumors and "superficially invasive" (pT1) bladder cancers regarding their genetic abnormalities. Invasion of the lamina propria, a layer of loose connective tissue comprising blood arteries, lymphatics, and a layer of delicate muscle called muscularis mucosae, is diagnostic of pT1 illness. In pT2 disease, cancer has spread throughout the vast smooth muscle bundles of the muscularis propria (detrusor muscle). Knowing whether or not a patient has pT2 illness is crucial when deciding between cystectomy and conservative treatment. Staging beyond pT2 is only possible on cystectomy specimens due to the presence of fat in all layers of the bladder wall. To look for signs of pT3 illness, examining sections of the bladder wall that are the entire thickness is necessary. Published comparisons of the two grading systems have not convincingly established that the new approach is superior in terms of

repeatability despite both systems being useful for prognosis (Amin et al., 2013; May et al., 2010). The EAU suggests using both grading systems until the WHO 2004 prognostic function is confirmed by prospective studies (Babjuk et al., 2008).

4. Symptoms of bladder Cancer

The most important symptoms of bladder cancer are the following:

1. Eighty percent of people with bladder cancer report painless, extensive hematuria. 10 The size of blood cells in the urine can range from undetectable to apparent to the human eye (blood visible in the urine). There was no relationship between the amount of hematuria and the severity of the illness. Both chronic and sporadic hematuria should prompt referral to a urologist for bladder cancer screening, especially in individuals with a smoking history (Griffiths, 2013). Referral to a urologist is also warranted for renal cancer, prostate cancer, interstitial cystitis, renal calculi, benign prostatic hyperplasia, trauma, and exercise-induced causes (Sharp et al., 2013).
2. Less frequent urinary tract symptoms, such as urine frequency, urgency, hesitancy, and dysuria, are reported by 30% of bladder cancer patients (Niederhuber et al., 2013).
3. It was burning and pain during urination without an infection or inflammation of the urinary system.

The following symptoms and signs are associated with advanced bladder cancer, whether invasive or metastatic (Farling, 2017):

1. flank ache
2. pelvic satiety
3. bladder retention
4. edema of the lower extremities is related to a weight loss
5. Discomfort in the bones, rectum, and anus, or pelvic region.

5. Risk Factors

Patients with bladder cancer face several dangers, such as (Griffiths, 2013; Farling, 2017):

1. Smoking is the primary cause of bladder cancer in men and a significant contributor in women. Bladder cancer is four times as common in smokers than in nonsmokers. Bladder cancer risk factors include current and past cigarette consumption, cumulative smoking time, and first-time smoker age. 10 Since the bladder stores pee, carcinogens in the urine can potentially damage the bladder. The high incidence of urothelial cancer can be traced back to the persistence of tobacco-related carcinogens in the genitourinary system until they are removed.
2. Occupational exposure: exposure to aniline dyes, aromatic amines, and polycyclic aromatic hydrocarbons is the second most significant risk factor for bladder cancer. Workers in the textile, paint, plastic, printing, and rubber sectors are at a higher risk of acquiring bladder cancer due to exposure to common chemicals used in these industries.

Recurrent urinary tract infections (UTIs), long-term use of urinary catheters, and bladder stones are all risk factors for bladder cancer, yet it is not understood what causes them. 3 Infection with the parasite Schistosoma haematobium increases the risk of developing squamous cell bladder cancer, an aggressive and possibly lethal illness.

The higher risk of bladder cancer in people getting pelvic radiation for genitourinary and gynecologic malignancies, including prostate and cervical cancer, is expected to decrease as radiation therapy advances.

Patients treated with cyclophosphamide for cancer or autoimmune diseases had four to nine times the average risk of developing bladder cancer. Long-term use of a medicine and higher cumulative doses increase the danger.

6. Diagnostic Tests

Current diagnostic approaches for identifying bladder cancer include cystoscopy and cytology (Oeyen et al., 2019). The cystoscopic examination of a patient's bladder is an accurate but invasive procedure for detecting bladder cancer. A mass or tumor is found in the urinary system (kidneys, ureters, and bladder) utilizing CT or MRI. 19 The gold standard for identifying abnormalities in the upper urinary system is a multiphase CT urogram that includes precontract, nephrographic, and excretory images. However, it has limited sensitivity for carcinoma in situ and is very operator-dependent, especially regarding recurrence detection (Tis). Variations in tumor type, stage, and grade result in a sensitivity of 62%-84% and a specificity of 43%-98%. Furthermore, urine pain (50%) is prevalent, as is urinary frequency (37%), visible hematuria (19%), and infection (3%). Pee cytology is a non-invasive diagnostic procedure that analyzes exfoliated cancer cells in unmodified or modified urine. The sensitivity can be anything from 28% to 100%, with an average of 44%. High-grade malignancies have a very high sensitivity, but low-grade tumors have a much lower sensitivity (between 4% and 31%). Cytology is useful in high-grade malignancy, primarily in

conjunction with cystoscopy. Urothelial carcinoma, which can develop anywhere in the urinary system, is indicated by a positive cytology result. The absence of cancer cells in a cytology sample is not conclusive. Low cellular yield, urinary tract infections, and stones are just a few of the variables that might make cytological interpretation difficult, and they also rely on the user. Imaging studies: It is used to diagnose kidney and urinary tract tumors. The most essential imaging tests include ultrasound planning, via which the kidney or bladder tumor mass may be viewed. CT scan images of the kidneys and urinary system are used to determine various cell cancer types. This includes whether or not additional organs can be photographed. The CT scan is also one of the most critical tests to assess if the cancer has spread. Determine the tumor's phases. Intracavitary pyelogram: The vein is injected with a dye during the test. Pigment accumulation occurs in the kidneys. Evaluation of the urinary tract X-rays of the kidneys and urinary tract are taken after the drug is given, and the dye is subsequently administered. Thus, the urinary system, kidneys, and protruding lesions inside their cavity are visible. There is no diagnostic test for transitional cell carcinoma; therefore, screening must be conducted. Barat is interested in obtaining a suitable sample from the patient. It is also used to diagnose transitional cell carcinoma conclusively. It is used to monitor transitional cell carcinoma patients. It is only contagious following therapy.

7. Stages of bladder cancer

The identification of cancer at any stage is a component of cancer treatment. Treatment of superficial cancer or cancer at its original location, which develops just on the surface of the bladder's inner lining, depends on locating the tumor. At this moment, the patient's likelihood of receiving effective treatment increases. Cancer in stage 1 affects the bladder's inner lining. In the second stage of bladder cancer, the tumor invades the bladder wall. Malignancy at the third stage: cancer cells have spread to the surrounding tissue via the bladder wall. It can also apply to females' prostate, uterus, and vagina. Fourth cancer stage: At this stage, cancer cells have spread to the lymph nodes and other organs, such as the lungs, bones, and liver.

Classification of stages of bladder cancer:

Type of tumor, metastatic disease, and lymph nodes

Primary cancer:

The main tumor's size cannot be determined.

T0: Absence of initial tumor evidence
Ta: Non-invasive papillary malignancy
Carcinoma found in situ (flat tumor)
T1: The tumor has spread into the subepithelial connective tissue.
T2: Invasion of muscle tissue pT2a: Invasion of superficial muscle (inner half) pT2b: Invasion of deep muscle (outer half)
T3: The bladder-peripheral tissue is infiltrated by the tumor
pT3a: microscopic while pT3b: macroscopic (extra secondary mass)
T4: The tumor infiltrates which of the subsequent? Walls of the abdomen, pelvis, vagina, and uterus
The tumor invades the uterus and vagina in T4a.
T4b: The tumor has spread to the pelvic and abdominal walls.
Lymph glands:
The state of the lymph nodes cannot be determined.
Metastases have not spread to any lymph nodes (N0).
A single lymph node with metastases less than 2 centimeters in diameter is considered N1.
N2: The existence of metastases to a single lymph node, the biggest of which is between 2 and 5 centimeters, or metastases to many lymph nodes, the largest of which does not exceed 5 centimeters.
N3: The presence of lymph node metastases whose largest size exceeds 5 centimeters.
Remote metastases:
Estimating distant metastases is impossible.
M0: No distant metastases are present.
M1: Distant metastases exist.

8. Treatment of Bladder Cancer

NMIBC refers to urothelial cancers that have not metastasized to the bladder muscle (detrusor). Seventy-five percent of non-muscle invasive bladder cancers (NMIBCs) are stage Ta, CIS, or T1 invasive urothelial cancers that have spread into the subepithelial lining or lamina propria (Smith et al., 2013). Patients with NMIBC can keep their bladders by undergoing therapy but risk having their cancer return or advance to MIBC. The likelihood of a recurrence of NMIBC increases with the number of

tumors detected at cystoscopy, tumor size, contemporaneous CIS, tumor grade, and reproduction history. After five years, the recurrence and progression rates may reach 78% and 44%, respectively, depending on the risk factors. 2019 Several academics (Harshman included) treatment of recurrent non-muscle-invasive bladder cancer is feasible with transurethral surgery and intravenous therapy. When given promptly after transurethral excision of a bladder tumor, a single dose of intravenous chemotherapy (mitomycin C) reduces the risk of recurrence from 48% to 37%. (TURBT). 5 Mitomycin C is the most often prescribed perioperative intravenous chemotherapeutic medication. However, the Food and Drug Administration has not yet licensed it to treat bladder cancer (NCCN, 2016). Cystoscopy-guided follow-up and intravenous immunotherapy with Bacillus Calmette-Guerin (BCG) or chemotherapy with mitomycin C are necessary for patients with non-muscle-invasive bladder cancer (NMIBC) to prevent or delay tumor recurrence and development. It remains unclear how immunotherapy with Bacillus Calmette-Guerin (BCG) works even though it is the most effective treatment for non-muscle-invasive bladder cancer (NMIBC). BCG may induce an immune response that can stop the growth of new tumor cells (Alcorn et al., 2015). Intravesical BCG treatment may be an option for induction and/or maintenance of NMIBC, depending on the patient's stage and grade. Despite the presence of additional standards, the following is recommended by both the American Urological Association (AUA) and the National Comprehensive Cancer Network (NCCN) (AUA, 2016; NCCN).

For low-grade, systemic, and enormous Ta tumors, induction with BCG once weekly for six weeks is necessary, followed by maintenance therapy (3 weeks of BCG at 3 and 6 months, then every six months for 12 months)

High-grade Ta, T1, and CIS malignancies require 36 months of care after BCG induction.

When the patient returns to the urologist's clinic 4-6 weeks after TURBT, BCG is administered into the bladder using a urethral catheter. The patient is told to wait one to two hours before peeing so the BCG can remain in touch with the bladder epithelium (Turner, 2012).

9. Results

The current study included collecting information from the patients included in the study. Seventy-five males and 75 females infected women and men aged 45 to 70 from the beginning of the eighth month of 2023 until the first month of 2024. Several tests were prepared to diagnose transitional cell cancer, and the results were as follows:

Table 1: The age groups and numbers of infections for men and women.

Age group	Males	Females	Total
45-60	22	14	36
60-70	34	20	54
	56	34	90

Table 2: The percentages of infections for men and women.

Females	Males	Age group
10.5	16.5	45-60
15	25.5	60 -70

Table3: Explains the causes of infection in percentage.

Couses of injury	Percentage
Smoking .	44.4%
occupational chemical exposure	22.2%
chronic inflammation of the bladder	5%
Hematuria	11.1%
Dysuria	66.7%
Frequency	88.9%

10. Discussion and Conclusion

The results of the current survey showed, based on the percentages obtained, that the incidence of bladder cancer in men was equal to the rate (42) at ages ranging between 45 and 70, while the incidence of bladder cancer among females was similar to the speed of 5.25 (ages ranging between 45 and 70). It is clear from this that the rate of infection with the disease is high among males. Almost twice as high as the percentage of females. The results of the current study are consistent with what many researchers have indicated in their studies. Males are more susceptible to bladder cancer than females for the following reasons:

Due to the buildup of chemicals, smoking increases the likelihood of infection by a factor of two. When we smoke, harmful chemicals are excreted in our urine. Our body processes the compounds in cigarette smoke and excretes around sixty via urine. These hazardous compounds may cause damage to the bladder lining. Tobacco comprises sixty years. According to the source, it is cancer-causing. (LD Marrett) The kidneys significantly filter hazardous substances from circulation and distribute them to the body in response to chemical exposure. Chemicals: Among the implications connected to bladder cancer is arsenic, which is used to produce dyes and pigments. The production of textiles, leather, rubber, and paint. (British Cancer Research) Infection with some parasitic diseases, especially men who work in the agricultural field, as indicated by Source (R LOWY, F DECLOITRE) Men are infected with the schistosoma worm in the urinary tract due to the carcinogenic effects of its eggs. We transmit the infection from contaminated water sources such as canals, ponds, and drains, which increases their original susceptibility to infection. Bladder cancer Chemotherapy and radiation therapy: According to the source, treatment with some anti-cancer medications, such as cyclophosphamide and ifosfamide, increases the risk of bladder cancer. (Feng Zhaohui and Hu Wenwei). Organic chemicals, such as aromatic amines, are highly associated with bladder cancer. These materials, as indicated by the source, are widely used in the dye industry, such as aniline dyes, naphthylamine, amino biphenyl, and benzidine. (P. Vineis; L. Airoldi).

Funding: This research received no external funding.
Conflicts of Interest: The authors declare no conflict of interest.
Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers.

References

[1] *ALCORN J, BURTON R, TOPPING A. (2015). BCG TREATMENT FOR BLADDER CANCER, FROM PAST TO PRESENT USE. INT J UROL NURS. 9(3):177–186.*

[2] *Amin, M. B., McKenney, J. K., Paner, G. P., Hansel, D. E., Grignon, D. J., Montironi, R., ... & Reuter, V. E. (2013). ICUD-EAU international consultation on bladder cancer 2012: pathology. European urology, 63(1), 16-35.*

[3] *AUA, American Urological Association. Non-muscle invasive bladder cancer. 2016. http://www.auanet.org/education/guidelines/non-muscle-invasive-bladder-cancer.cfm.*

[4] *Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BWG, Comperat E, Slvester RJ, Kaasinen E, Bohle A, Redorta JP, Roupret M. (2013). EAU Guidelines on nonmuscle-invasive urothelial carcinoma of the bladder: update 2013. Eur Urol;64(4):639–53.*

[5] *Burger, M., van der Aa, M. N., van Oers, J. M., Brinkmann, A., van der Kwast, T. H., Steyerberg, E. C., ... & Zwarthoff, E. C. (2008). Prediction of progression of non–non-muscle-invasive bladder cancer by WHO 1973 and 2004 grading and by FGFR3 mutation status: a prospective study. European urology, 54(4), 835-844.*

[6] *Eble JN, Sauter G, Epstein JI, et al (2004) Pathology and genetics of tumors of the urinary system and male genital organs. WHO Classification of Tumours. IARC Press, Lyon.*

[7] *Farling, K. B. (2017). Bladder cancer: Risk factors, diagnosis, and management. The Nurse Practitioner, 42(3), 26-33.*

[8] *Ferlay, J., Randi, G., Bosetti, C., Levi, F., Negri, E., Boyle, P., & La Vecchia, C. (2008). Declining mortality from bladder cancer in Europe. BJU international, 101(1), 11-19.*

[9] *Griffiths, T. L. (2013). Current perspectives in bladder cancer management. International journal of clinical practice, 67(5), 435-448.*

[10] *Harshman LC, Preston MA, Bellmunt J, Beard C. (2015). Diagnosis of bladder carcinoma: a clinician's perspective. Surg Pathol Clin, 8(4):677–685.*

[11] *Hemdan, T. (2016). Prognostic and Predictive Factors in Bladder Cancer (Doctoral dissertation, Acta Universitatis Upsaliensis), p16-17.*

[12] *Kirkali, Z., Chan, T., Manoharan, M., Algaba, F., Busch, C., Cheng, L., ... & Weider, J. (2005). Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology, 66(6), 4-34.*

[13] *Kumar V, Abbas AK, Fausto N, Robbins SL, Cotran RS (2005) Robbins and Cotran pathologic basis of disease, 7th ed. Elsevier Saunders, Philadelphia.*

[14] *May, M., Brookman-Amissah, S., Roigas, J., Hartmann, A., Störkel, S., Kristiansen, G., ... & Gunia, S. (2010). Prognostic accuracy of individual uropathologists in non-invasive urinary bladder carcinoma: a multicentre study comparing the 1973 and 2004 World Health Organisation classifications. European urology, 57(5), 850-858.*

[15] *NCCN, Clinical Practice Guidelines in Oncology - Bladder Cancer. National Comprehensive Cancer Network. 2016. http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.*

[16] *Nguyen, K. T. (2011). Targeted nanoparticles for cancer therapy: Promises and challenges. Nguyen J Nanomedic Nanotechnol, 2(5).*

[17] *Niederhuber, J. E., Armitage, J. O., Doroshow, J. H., Kastan, M. B., & Tepper, J. E. (2013). Abeloff's Clinical Oncology. 5th ed. Philadelphia, PA: Saunders Elsevier; 2013.*

[18] *Oeyen, E., Hoekx, L., De Wachter, S., Baldewijns, M., Ameye, F., & Mertens, I. (2019). Bladder cancer diagnosis and follow-up: the current status and possible role of extracellular vesicles. International journal of molecular sciences, 20(4), 821.*

[19] *Pan, C. C., Chang, Y. H., Chen, K. K., Yu, H. J., Sun, C. H., & Ho, D. M. (2010). Prognostic significance of the 2004 WHO/ISUP classification for prediction of recurrence, progression, and cancer-specific mortality of non–non-non-muscle-invasive urothelial tumors of the urinary bladder: a clinicopathologic study of 1,515 cases. American journal of clinical pathology, 133(5), 788-795.*

[20] *Sharp, V. J., Barnes, K. T., & Erickson, B. A. (2013). Assessment of asymptomatic microscopic hematuria in adults. American Family Physician, 88(11), 747-754.*

[21] *Siegel, R., Naishadham, D., & Jemal, A. (2013). Cancer statistics, 2013. CA: a cancer journal for clinicians, 63(1), 11-30.*

[22] *Turner B, (2012). Drudge-Coates L. Bladder cancer: risk factors, diagnosis and treatment. Cancer Nurs Practice. 11(7):30–36.*

[23] *Van Rhijn, B.W.G (2005). Molecular Diagnosis and Prognosis of Bladder Cancer: towards the implementation of molecular markers in clinical practice. Optima Grafische Communicatie, Rotterdam, the Netherlands.p12.*

[24] *Marrett, LD; Hartge, P; Meigs, JW. Bladder cancer and occupational exposure to leather. Br J Ind Med. 1986 Feb;43(2):96–100*

[25] *Cancer Research UK.*

[26] *R LOWY, F DECLOITRE "2-NAPHTHYLAMINE AND BLADDER CANCER", Food and cosmetics toxicology (Food Cosmet Toxicol) Vol. 2 Pg. 189-92 (Jul 1964) ISSN: 0015-6264 ENGLAND.*

[27] *Zhaohui Feng, Wenwei Hu, William N Rom, Frederick A Beland, Moonshong Tang, "4-aminobiphenyl is a major etiological agent of human bladder cancer: evidence from its DNA binding spectrum in human p53 gene.", Carcinogenesis, Oct 2002 (Vol. 23, Issue 10, Pages 1721-7).*

[28] *P. Vineis; L. Airoldi; F. Orsi; C. Magagnotti; R. Coda; D. Randone; G. Casetta; M. Peluso; A. Hautefeuille; C. Malaveille, "Determinants of aminobiphenyl-DNA adducts in bladder cancer biopsies", Carcinogenesis, Volume 23, Number 5, May 2002‹ pp. 861-866(6).*