



Bladder Cancer: Review Article

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Abstract

Background: The carcinoma of urothelial, or "umbrella," cells which line the bladder's lumen is known as bladder cancer (BC). According to technical definitions, urothelial carcinoma comprises cancers of bladder, upper urinary tract (renal pelvis and ureters), and proximal urethra. Diagnosis typically involves urine testing, cystoscopy, and biopsy. Treatment varies depending on the stage yet often involves removing the bladder (cystectomy). Chemotherapy, either without or with radiation, might decrease the tumour prior to surgery, which might facilitate the procedure. Our goal in writing this study was to provide an overview of the state of knowledge on bladder cancer, with particular attention to its epidemiology, risk factors, stage and type, diagnosis, and current treatment options. Given the rise in cancer's rates of mortality and morbidity, it is imperative to offer the best preventative measures possible, keeping in mind that changing some risk factors may be essential to lowering the incidence of this disease and the good diagnostic, prognostic methods especially molecular biomarkers can increase treatment outcomes by allowing early detection and reducing relapse risks for BC.

Keywords: Bladder cancer; Risk factors & Types; Epidemiology; Diagnosis & Treatment

NOMENCLATURE

BC	Bladder cancer
CIS	Carcinoma in situ
cfDNA	Circulating cell-free DNA.
TURBT	Biopsy/Transurethral resection of bladder tumour
FGFR3	Fibroblast growth factor receptor 3

INTRODUCTION

Bladder Cancer

A disease that is referred to as cancer can occur in the cases where somebody's cells proliferate out of control then start invading other body parts. With billions of the cells that make up the human body, cancer could begin practically anywhere. Human cells normally divide and increase (Wei et al,2024). This process is known as cell division. Through a process known as metastasis, tumours could spread or invade surrounding tissues and even reach far-off body organs to develop new tumours. Another term for the tumours is malignant. Blood cancers, which include leukaemia, usually don't develop to solid tumours, even though many cancer types do, Benign types of tumours don't penetrate or spread to the adjacent tissues. Yet, benign tumours could occasionally grow to be rather enormous. Certain conditions, such as benign brain tumours, might have life-threatening symptoms or could even be fatal (Pang et al,2020, Tokarz et al,2022).

Bladder cancer is a prevalent cancer form, which starts in bladder cells. Urine is stored in bladder, which is a hollow muscular organ in lower abdomen. Cells which line the bladder lining, referred to as the urothelial cells, are where the bladder cancer often begins. The kidneys and tubes (i.e., ureters) joining one's kidneys to the bladder contain the urothelial cells as well. Even though it is more common in bladder, kidney ureteric cancer types could also develop the urothelial carcinoma (Tran et al,2021). The development of DNA changes (mutations) in bladder cells is the first step toward bladder cancer. Instructions informing a cell what to do are encoded within in its DNA. Alterations instruct the cell to divide quickly and to keep existing while other normal cells would have died. A tumour that is created by abnormal cells has the ability to penetrate and cause destruction to the normal body tissues. Abnormal cells have the potential to separate and travel throughout the body, or metastasis (Flores et al,2023).

Signs and symptoms

Bladder cancer includes many Signs and symptoms like Blood or blood clots in the urine, Burning or pain sensation throughout urination, Constant urination, frequent urges to urinate during the night, the urge to urinate yet having trouble passing the urination (Ling et al,2024).

Risk factors

Use of tobacco, particularly smoking cigarettes, Having a history of bladder cancer in the family. Workplace exposure to specific chemicals, Previous treatment with specific anti-cancer medications, like cyclophosphamide or radiotherapy to the pelvis, consuming well water with elevated arsenic content, A past record of bladder infections, encompassing infections brought on by schistosomiasis, Extended utilization of a urinary catheter (Juber et al,2024).

Bladder Cancer Types

Urothelial cancer represents the most prevalent kind of disease. Some are less common than others. These consist of small cell bladder cancer, sarcoma, adenocarcinoma, and squamous cell bladder cancer. The degree of bladder wall invasion is another factor that doctors use to characterize bladder cancer. They may have bladder cancer that is not muscle-invasive (Witjes et al,2024) or muscle-invasive (Benjamin et al,2022). There are various kinds:

1- Papillary bladder cancer

Non-muscle invasive bladder cancer typically manifests as small, mushroom-shaped growths. Those emerge from lining of the bladder. We refer to this as bladder papillary cancer. These growths could be removed by the surgeon, and they might never return (Gupta et al,2021).

2- Carcinoma in situ (CIS)

Areas of CIS appear flat, in contrast to other non-muscle invasive bladder cancers. The bladder wall does not support their growth. The cancer cells in CIS have an unusual appearance and are probably going to proliferate swiftly. We refer to this as high grade. Compared to other forms of the non-muscle invasive bladder cancers, it has a higher chance of recurrence (Subiela et al,2020).

Stage Types of Bladder cancer

1-High grade T1 tumours

Early-stage cancers known as T1 tumours have spread from the bladder lining into the layer beneath it. The lamina propria is the name of this layer. Although high grade T1 tumours are early-stage cancers, they have a rapid growth potential (Muñoz et al,2003).

2-Muscle invasive bladder

Compared to non-muscle invasive bladder cancer, cancer requires more extensive treatment. This is due to the possibility that it will spread to other bodily areas (Patel et al ,2020).

3-Metastatic bladder cancer

When bladder cancer spreads to another area of the body, it is known as metastatic bladder cancer. It has been referred to as advanced bladder cancer. When cancer is initially discovered, it may already be metastatic. Recurrent or relapsed cancer is the term for this. Secondary cancers are defined as cancers that have spread from another part of the body (Witjes et al,2021).

Epidemiology of bladder cancer

In adult males, bladder cancer represents the fourth most prevalent cancer type; in women, it is less common. Based on the American Cancer Society, there will be about 82,290 new instances of bladder cancer in US in 2023 (19,870 in women and 62,420 in men), while there will be about 16,710 bladder cancer-related deaths (4,550 in women and 12,160 in men). Recent years have seen a decline in both the incidence of new bladder cancers and the mortality rate from bladder cancer (Lobo et al,2022). Every instance of bladder cancer in Iraq was assessed for histological type and potential correlation with schistosomiasis. Only roughly 30% of schistosome ova were detected. Schistosomiasis was prevalent and accounted for around half of the cases, which were squamous cell carcinomas. The majority of the cases in the other half consisted of transitional cell carcinomas, which had a low incidence of Schistosoma. Urinary bladder cancer represents one of the most common cancer types in Iraq. It makes up almost 10% of all cancers, occurring in men 11–13% of the time and in women 5–7% of the time. These resemble those that are in Egypt. However, in comparison with Egypt (82–90%), the incidence of related schistosomiasis in Iraqi population is significantly lower (7–29%) (Botelho et al,2017).

Diagnosis of bladder cancer

The majority of people are identified with bladder cancer after they start exhibiting symptoms, as there is currently no test that is reliable enough to screen the general population for the disease. The tests listed below could be utilized to identify bladder cancer:

1-Urine tests: Urine cytology testing may be prescribed if the physician discovers any blood in the urine. For the purpose of determining whether the urine includes tumour cells, the cytology of the urine often takes random sample of the urine from an individual who urinates normally. There are numerous methods for testing the sample. Urinary cytology represents the most widely used method, which involves cell examination under microscope (Higgins et al,2003).

2-Cystoscopy: is the primary method of the diagnosis bladder cancer. With a flexible, thin, illuminated tube known as a cystoscope, it enables the physician to view into the body (Grossman et al,2006).

3-Biopsy/Transurethral resection of bladder tumour (TURBT): The physician performs a biopsy if, throughout a cystoscopy, suspicious tissues are discovered. The biopsy involves obtaining a little tissue sample for the purpose of examining it with the use of microscope. TURBT refers to this surgical operation. A bladder muscle sample near the tumour as well as the tumour are removed by the physician during a TURBT (Lopez et al,2024).

4-Genetic biomarkers: Methods, more and more attention is being paid to non-invasive biomarker tests that could complement current diagnostic procedures. These tests, based on the detection of circulating cell-free DNA (cfDNA) or specific genetic mutations in urine, show promising results as a complementary tool for early detection of BCa (Kong et al,2024).

Bladder Cancer Treatment by Stages

Stage of bladder cancer:

A non-invasive papillary carcinoma is bladder cancer. Yes, the cancer solely affects the bladder's inner lining layer. It hasn't penetrated the bladder wall further. Most frequently, transurethral resection (TURBT) with fulguration is used for treating this early stage of bladder cancer. Within 24 hours, intravesical chemotherapy is then administered. After that, every three to six months, a cystoscopy is performed to look for indications that the cancer has returned (Henning et al,2021).

Treatments could be repeated if the cancer returns. In order to attempt and prevent the cancer from returning, intravesical chemotherapy may be continued throughout the course of the following year. Rarely do Stage 0 bladder cancers require more invasive treatment. Radical cystectomy might be advised if the tumour is very large when it is initially discovered, if multiple tumours are present, or if the cancer is high grade. Radiation therapy, frequently in conjunction with chemotherapy, may be an alternative for individuals deemed too sick for a cystectomy, although the prognosis is not as favourable (Schmitz et al,2007).

1-Stage I bladder cancer (T1)

The muscle layer of bladder wall has not yet been penetrated by Stage I bladder cancers, which have developed to connective tissue layer. For those cancer types, transurethral resection (TURBT) combined with the fulguration is usually the initial course of treatment. However, instead of attempting to treat the cancer, it's done to help assess its extent (Sylvester et al,2006)

2-Stage II bladder cancer (T2)

The bladder wall's (T2) muscular layer has been penetrated by these tumours. Usually, the first treatment for such cancers is transurethral resection (TURBT), however the goal of this procedure is not to treat the disease directly, yet rather to help assess its extent (stage). The conventional treatment for cancer that has spread to the muscle is a radical cystectomy, which involves removing the bladder. Moreover, lymph nodes close to the bladder are frequently removed. An alternative procedure

could be a partial cystectomy if the cancer is limited to one area of the bladder. In patients who have had surgery but whose tumour characteristics indicate a high likelihood of recurrence, nivolumab, an immunotherapy medication, may be recommended. Nivolumab is administered for a maximum of one year following surgery (Kim & Lee,1989).

3-Stage III bladder cancer(T3)

These cancers have spread to bladder's outside and may have expanded to lymph nodes, surrounding organs or tissues. TURBT, or transurethral resection, is frequently performed first to assess the extent of the cancer's invasion of the bladder wall. The usual course of treatment then involves chemotherapy as well as radical cystectomy (bladder removal along with adjacent lymph nodes). Stage III tumours rarely respond well to partial cystectomies. Prior to surgery, chemotherapy (chemo) could reduce the tumour's size, either without or with radiation. This could make surgery less difficult. Chemotherapy could prolong life by eliminating cancer cells that may have already spread to other body parts (Konala et al,2022).

Markers of bladder cancer

Urinary cytology remains the only urine marker for bladder cancer recommended in guidelines as an adjunct to cystoscopy, although the sensitivity of this technique for detecting low-grade tumours is limited, and several other markers are available [Maas et al,2023, Ng et al,2021]. Regarding the Jumping Fan *et.al.* there are Eight biomarkers for diagnosis and Eight biomarkers for prognosis were identified. Between the diagnostic means, MSI, BLCA-4, and Apo-A4 have the greatest results. Still, there is a general lack of specific experimental data about prognostic biomarkers, and further investigation is needed. Exosomes have multifunctional properties as biomarkers, and it is benefitting as targeted treatment for bladder cancer (Junping et al ,2024). The use of genetic panels got from urine samples has consider a promising method for detection BCa, for example is the Cx Bladder test, which measures the expression of five mRNAs associated with BCa with sensitivity (82%) and a specificity (85%). Additionally, there are many other tests and analysing such as mutations in the fibroblast growth factor receptor 3 (FGFR3), TERT, HRAS genes (Papavasiliou et al,2023).

Conclusion

Our goal in writing this study was to provide an overview of the state of art regarding bladder cancer, emphasizing its forms, stages, epidemiology, diagnosis, risk factors, and potential treatment options. Given the rise in cancer's rates of mortality and morbidity, it is imperative to offer the best preventative measures possible, keeping in mind that changing some risk factors may be essential to lowering the incidence of these diseases. Future research on predictive biomarkers and targets for prospective biological treatments must be ongoing.

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