Bladder Cancer Diagnostic Tests

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Abstract

Bladder Cancer is a very frequent disease and represents the second most common genitourinary neoplasm. Bladder cancer refers to any of several types of malignant growths of the urinary bladder. It is a disease in which abnormal cells multiply without control in the bladder. The bladder is a hollow, muscular organ that stores urine; it is located in the pelvis The most prevalent form of the disease, superficial bladder cancer, can recur in more than 70% of cases, despite correct management. Any way to improve our disease diagnostic and treatment policy is therefore welcome.

1. Introduction

The bladder is a hollow organ in the lower abdomen (pelvis). It collects and stores urine produced by the kidneys. [1]

As it fills with urine, the muscular wall of the bladder stretches and the bladder gets larger.

When the bladder reaches its capacity of urine, the bladder wall contracts, although adults have voluntary control over the timing of this contraction. At the same time, a urinary control muscle (sphincter) in the urethra relaxes. The urine is then expelled from the bladder.

The urine flows through a narrow tube called the urethra and leaves the body. This process is called urination, or micturition. Cancer occurs when normal cells undergo a transformation whereby they grow and multiply without normal controls. [1]

As the cells multiply, they form an area of abnormal cells. Medical professionals call this a tumor. As more and more cells are produced, the tumor increases in size.

Tumors overwhelm surrounding tissues by invading their space and taking the oxygen and nutrients they need to survive and function.

Tumors are cancerous only if they are malignant. This means that, because of their uncontrolled growth, they encroach on and invade neighboring tissues.

Malignant tumors may also travel to remote organs via the bloodstream or the system. This process of invading and spreading to other organs is called metastasis. Bladder cancers are most likely to spread to neighboring organs and lymph nodes prior to spreading through the blood stream to the lungs, liver, bones, or other organs.

The wall of the bladder is lined with cells called transitional cells and squamous cells. More than 90 percent of bladder cancers begin in the transitional cells. This type of bladder cancer is called transitional cell carcinoma.

About 8 percent of bladder cancer patients have squamous cell carcinomas



2. Bladder Cancer

Bladder cancer refers to any of several types of malignant growths of the urinary bladder [2]. The Urinary bladder is a hollow organ located in the pelvis that collects and stores urine until it is ready to be excreted from the body. Urine is produced in the kidneys and is transported to the bladder through two tubes like structures called ureters. Pressure from the accumulation of urine in the urinary bladder forces the wall of the bladder to contract producing the urge to urinate. The urine is then excreted from the bladder via the urethra (a thin tube that carries urine from the bladder to the outside of the body).

2.1 Types of Bladder cancer [2] [3] [5]

There are four primary types of bladder tumours that can be distinguished on the basis of the appearance (morphology) of the cells under a microscope:[2],[3]

Transitional cell carcinoma- also known as urothelial carcinoma, this type of bladder cancer affects the transitional epithelium that lines the wall of the bladder.[3]

Squamous cell carcinoma [3] – it is associated with chronic irritation of the bladder that can be caused by long-term indwelling bladder catheters or by bladder calculi (stones).

Adenocarcinoma [2] – it is a rare form of bladder cancer that occurs in mostly younger patients.

Small cell carcinoma [2] – it is a very rare type of bladder cancer and represents about 1% of all bladder tumors.



Fig 1: Normal urothelial cells: Normal urothelial cells have a uniform appearance with abundant cytoplasm and small nuclei[10]



Fig. 2 High grade bladder cancer: Bladder cancer cells are enlarged with large and dark nuclei.[10]

2.2 Bladder Cancer Subtypes[2][4]

A basic understanding of the terminology used by doctors to describe the various subtypes of bladder tumours is as follows-

Superficial bladder tumors[4] are those that are localized to the transitional epithelium and is in direct contact with the urine but have not spread to the deeper layers of the bladder.

Invasive bladder cancer[4] refers to a bladder tumor that is either invading the muscular propri- the deeper layer of muscle cells that forms the wall of bladder- or the perivesical fat located beyond the bladder muscle.

Another important characteristic of bladder tumors that is useful in classification of the various subtypes is the morphology (appearance) of the cells under a microscope. In general, the shape of individual bladder cancer cells can be either papillary (cells that have thin, finger-like projections) or flat (no projections). Pappilary and flat bladder tumor cells can be further subdivided into noninvasive or invasive types depending upon their patterns of growth within the bladder.

2.3 Staging

As in most cancers, the chances of recovery are determined by the stage of the disease. Stage refers to the size of the cancer and the extent to which it has invaded the bladder wall and spread to other parts of the body. Staging is based on imaging studies (such as CT scans, <u>x-rays</u>, or ultrasound) and biopsy results. Each stage has its own treatment options and chance for cure. In addition, equally important is the grade of the bladder cancer. High-grade tumors are significantly more aggressive and life threatening than low-grade tumors.[5][11]

A simple staging system for bladder cancer is as follows:

Stage 0 : Cancer cells are only identified on the bladder's inner lining. This is considered to be superficial bladder cancer (sometimes called carcinoma in situ).

Stage I : Cancer cells are identified in the bladder's deeper tissues, but not in the bladder's layer of muscle.

Stage II : Cancer cells can be found in the bladder's muscles.

Stage III : Cancer cells have spread to the outermost layer of the bladder, and may have invaded the prostate (in men) or the cervix, uterus, or vagina (in women).

Stage IV : Cancer cells have spread to the tissue that lines the wall of the abdomen and/or pelvis. There may be

cancer cells identified within lymph nodes and/or in distant locations, such as the liver, lungs, or bone. [11]



Fig 3 Stages of bladder cancer[12]

3. Diagnostic Test for detecting Bladder Cancer

The following tests may be used to diagnose bladder cancer: [6], [9]

3.1 Physical Examination [6]

A doctor can sometimes detect lumps in the wall of the bladder by examining the rectum and the pelvis. Areas where the cancer has spread may also be found during a physical examination.

3.2 Urine Tests

It involves the following urine tests-[7]

Urine cytology: A sample of urine is examined under microscope to check for abnormal cells. The main disadvantage of this test is that it can miss low-grade cancers.

Urinalysis: This test checks the urine color and measures its components such as sugar, proteins, red and white blood cells.

Tumor marker tests: These are urine tests that measure the level of the substances released by the tumors (called tumor makers). There are two marker tests approved by the FDA, BTA and NMP22, but they are used only to detect recurrent bladder cancer.

3.3 Cystoscopy [7], [9]

This is the most common and reliable test used to detect bladder cancer. During this test, a thin tube with a camera attached at the one end (cystoscope) is inserted into the bladder through urethra to examine the inside walls of the bladder. The doctor can also remove a sample of tissue for laboratory examination. This test can be performed under local anesthesia (where an anesthetic jelly is inserted into the urethra) or general anesthesia (situation where the patient needs to stay in hospital). The most common side effect of cystoscopy is a soreness or mild pain when the patient urinates for the first time. The main disadvantage of this test is that it can miss flat lesions (Carcinoma in situ) or small papillary tumors. It is recommended that this test to be performed in combination with other tests (such as imaging and urine tests) for a correct diagnosis.



Fig. 4 Cystoscopy[10]

3.4 Haematuria Test [15]

In medicine, hematuria, or haematuria, is the presence of red blood cells (erythrocytes) in the urine. It may be idiopathic and/or benign, or it can be a sign that there is a kidney stone or a tumor in the urinary tract (kidneys, ureters, urinary bladder, prostate, and urethra), ranging from trivial to lethal. If white blood cells are found in addition to red blood cells, then it is a signal of urinary tract infection.



Fig 5 Haematuria test

3.5 BTA Stat Test [16]

The BTA *stat* test, manufactured by B.D.S., Inc., (ISO 9001) Redmond, WA, recently received FDA clearance. The test is now available by prescription for home use to detect recurrent bladder cancer as an aid in the



management of bladder cancer patients. This historic clearance for a tumor marker assay marks the second clearance for the BTA *stat* test, which was previously cleared for laboratory use.

The BTA *stat* test is a single step rapid immunoassay, which requires 5 drops of urine and provides results in 5 minutes. The appearance of a line in the patient window indicates a positive result.

The BTA *stat* test requires a single voided urine sample with no sample treatment or preparation.

The BTA *stat* device is supplied in an individual foil pouch, with a plastic dropper, and can be stored at room temperature (60 to 85^{0} F).



Fig 6: BTA Stat test

3.6 NMP22 Test [18]

The NMP22[®] BladderChek[®] Test is the only in-office test approved by the FDA as an aid in the diagnosis and management of bladder cancer.

The NMP22 BladderChek Test is a painless and noninvasive assay, performed on a single urine sample that detects elevated levels of NMP22 protein.

Healthy individuals generally have very small amounts of NMP22 protein in the urine. However, the level of NMP22 protein is often elevated in the urine of patients with bladder cancer, even at early stages of the disease.

The test can be performed in a physician's office with results delivered during the patient visit, allowing a rapid, accurate and cost-effective way to aid in the detection of bladder cancer in patients at risk.



Fig 7:NMP22 test

3.7 NMP22 and Cystoscopy [17]

The combination of the NMP22®BladderChek® urine test with cystoscopy provides an effective method for early detection of bladder cancer. The point-of-care NMP22 BladderChek assay from Inverness Medical measures the Nuclear Matrix Protein NMP22 in voided urine and has been shown to increase the detection of new and recurrent bladder tumours.[17]

Due to its rapid format and ease of use, when used in conjunction with standard diagnostic procedures, the NMP22 BladderChek test can be used to facilitate the screening of at risk groups such as smokers, fire fighters, petro-chemical workers, hairdressers, painters, textile workers, road construction workers (tar) and arson investigators(2).

As with many types of cancer, the outcome of bladder cancer depends on how advanced it is when it is diagnosed. Therefore, early detection whilst the tumour is still at a superficial stage is extremely important and can be aided with the introduction of urinary marker tests in conjunction with cystoscopy.

	NMP22 result is compared with cystoscopy result			
1	NMP22	cystoscopy	RESULT	
	negative	negative	99%negative predictive value Go for standard surveillance	
	negative	positive	Low grade cancer	
	positive	negative	Potential for undirected cancer Go for more investigation	
	positive	positive	99% cancer detected	
	<u></u>			

Fig 8:NMP22 and cystoscopy

3.8 Biopsy [9]

Biopsy is a medical procedure where a tissue sample is removed from the tumor or abnormal looking surface of an organ for a microscopic examination. In bladder cancer patients, the biopsy is removed during cystoscopy. In some cases, the entire tumor might be removed during biopsy. This procedure allows the pathologist to establish the nature of the cells and determine whether they are cancerous or not, and the cancer type.

A biopsy is a medical test involving the removal of cells or tissues for examination. It is the medical removal of tissue from a living subject to determine the presence or extent of a disease. The tissue is generally examined under a microscope by a pathologist, and can also be analyzed chemically.

When an entire lump or suspicious area is removed, the procedure is called an excisional biopsy. When only a sample of tissue is removed with preservation of the histological architecture of the tissue's cells, the procedure is called an incisional biopsy or core biopsy. When a sample of tissue or fluid is removed with a needle in such a way that cells are removed without preserving the histological architecture of the tissue cells, the procedure is called a needle aspiration biopsy.



Fig 8 Biopsy [10]

4. Conclusions

BladderCheck test could be a useful tool for improving detection of bladder cancer recurrences and reducing the cost of follow-up care, the researchers say[14]. A simple urine test may help doctors find more relapses in people who have had bladder cancer, according to a new study. The test was used along with cystoscopy and the two tests found 99% of occurrences[13], researchers reported in the Journal of the American Medical Association.

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