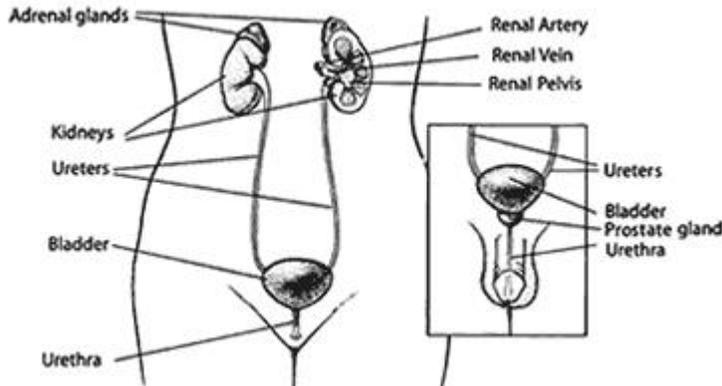


## What Is Bladder Cancer?

The bladder is a hollow organ that stores urine. Urine is made in the kidneys and flows into the bladder through thin tubes called ureters. Urine leaves the bladder through another tube called the urethra. In women the urethra is very short. In men it is longer since it passes through the prostate gland to the tip of the penis.



The wall of the bladder has several layers. Cancer begins in the lining layer and grows into the bladder wall. As the cancer grows through the layers into the wall of the bladder, it becomes harder to treat. The inside of the bladder is lined with a layer of cells called urothelial cells. The same type of cells also lines the kidneys, ureters, and urethra. Cancer can begin in the lining cells in any of these structures which are part of the urinary system.

## What Causes Bladder Cancer?

We do not yet know exactly what causes bladder cancer, but we do know that certain risk factors are linked to the disease. A risk factor is anything that affects a person's chance of getting a disease such as cancer. Different cancers have different risk factors. Some risk factors, such as smoking, can be controlled. Others, like a person's age or family history, can't be changed. But risk factors don't tell us everything. Having a risk factor, or even several, does not mean that you will get the disease.

### Risk factors for bladder cancer

**Smoking:** Smoking is the greatest risk factor for bladder cancer. Smokers get bladder cancer twice as often as people who don't smoke. Certain chemicals in tobacco smoke are absorbed from the lungs into the blood. From the blood, they are filtered by the kidneys and collect in the urine. These chemicals in the urine damage the cells that line the inside of the bladder and increase the risk of cancer.

**Work exposure:** Some chemicals used in the making of dye have been linked to bladder cancer. Industries that use certain chemicals may put workers at risk if good safety practices are not followed. The industries with highest risks include the makers of rubber, leather, textiles, and paint products, as well as printing companies. Workers with a higher risk of bladder cancer include painters, hairdressers, machinists, printers, and truck drivers. Smoking can increase the risk among these workers.

**Race:** Whites are twice as likely to get bladder cancer as are African Americans and Hispanics. Asians have the lowest rate of bladder cancer. We do not know the reason for this.

**Age:** The risk of bladder cancer goes up with age.

**Gender:** Men get bladder cancer 4 times as often as women.

**Chronic bladder inflammation:** While urinary infections, kidney stones, and bladder stones don't cause bladder cancer, they cause ongoing inflammation and have been linked to it.

**Personal or family history of bladder cancer:** People who have had bladder cancer have a higher chance of getting another tumor. People whose family members have had bladder cancer also have a higher risk. There are some diseases that run in families that are known to increase bladder cancer risk, too.

**Bladder birth defects:** Very rarely a connection between the belly button and the bladder doesn't go away as it should before birth and it can become cancerous. There is another, very rare, birth defect called exstrophy which can lead to bladder cancer.

**Earlier treatment:** Some drugs or radiation used to treat other cancers can increase the risk of bladder cancer.

**Arsenic:** Arsenic in drinking water has been linked to a higher risk of bladder cancer.

**Not drinking enough liquids:** People who drink lots of liquids each day have a lower rate of bladder cancer.

### **How Is Bladder Cancer Found?**

Bladder cancer can sometimes be found early. Finding it early improves the chances that it can be treated with success. *Screening tests* are used to look for a disease in people who have not had that disease before and do not have any symptoms. Screening tests for bladder cancer may be used if you are at very high risk. Risk factors that may lead to screening include having had bladder cancer in the past, certain defects of the bladder, and perhaps working with certain chemicals. If you are at high risk of bladder cancer, your doctor might suggest certain tests such as urine cytology or cystoscopy. These tests are explained below. If you don't have any known risk factors the best advice is to contact your doctor if you have any symptoms of bladder cancer.

### **Signs and symptoms of bladder cancer**

**Blood in the urine:** In most cases, blood in the urine (hematuria) is the first sign of bladder cancer. Sometimes, there is enough blood to change the color of the urine. Or the urine may be very pale yellow-red or, less often, darker red. In other cases, the color of the urine is normal but small amounts of blood can be found by urine tests done because of other symptoms or as part of a check-up. But blood in the urine does not mean you have bladder cancer. Much more often it is caused by other things, such as infection, benign tumors, stones in the kidney or bladder, or other causes.

**Changes in bladder habits:** Having to urinate more often, or feeling as if you need to go but not being able to do so can be a symptom of bladder cancer. But these problems are more often caused by something other than cancer.

### **Tests to find bladder cancer**

If there is a reason to suspect you might have bladder cancer, the doctor will use one or more of the methods below to find out if the disease is really there.

**Medical history and physical exam:** Your doctor will ask you about your medical history to check for risk factors and symptoms. The doctor might check the rectum and vagina (in women) to see how

big the tumor is and how far it may have spread.

**Cystoscopy:** A cystoscope is a thin tube with a lens and a light. The doctor places it into the bladder through the urethra. The area is first numbed or drugs may be used to put you into a deep sleep. With the cystoscope the doctor can see the inside of the bladder. If there is anything that doesn't look normal, a small piece of tissue is removed and looked at under a microscope.

**Urine cytology:** In this test, urine or cells "washed" from the bladder are sent to the lab to see if cancer cells (or pre-cancer cells) are present. This is often done at the same time as the cystoscopy. This test can help find some cancers, but it is not perfect. Not finding cancer on this test doesn't always mean you are cancer free.

**Urine culture:** A sample of your urine is sent to the lab to see if you might have an infection. An infection can sometimes cause symptoms that look like bladder cancer. It may take 2 or 3 days to get the results of this test.

**Biopsy:** When a piece of tissue is removed to see if it contains cancer cells, the test is called a biopsy. This test can tell if cancer is present, what type of bladder cancer it is, and how deep it has gone into the bladder wall. Bladder biopsy samples are most often taken during cystoscopy. Bladder cancers are graded on a scale from 1 to 4 based on how they look under the microscope. The lower the number, the more the cells look like normal tissue. A higher grade means the cancer is more likely to have spread outside the bladder and the outlook is not as good.

**Bladder tumor marker studies:** These tests look for certain substances released by cancer cells into the urine. Some doctors use these tests, but most think that cystoscopy is still the best way to find bladder cancer.

### **Imaging tests**

Imaging tests are done to allow your doctor to "see" your bladder and other organs. If you have bladder cancer, your doctor may order some of these tests to see if the cancer has spread to tissues near the bladder, nearby lymph nodes, or to distant organs.

**Intravenous pyelogram (IVP):** An IVP is an x-ray of the urinary system taken after putting a special dye into a vein. The dye passes into the ureters and bladder. This more clearly outlines these organs on x-rays and helps find tumors.

**Retrograde pyelography:** For this test, a thin, flexible tube called a catheter is placed into the bladder or into a ureter. Then, a dye is put through the catheter to make the lining of the bladder, ureters, and kidneys easier to see on x-rays. Like IVP, this test can be used to find tumors in the upper part of the urinary tract.

**Chest x-ray:** A chest x-ray may be done to look for a tumor or a spot on the lungs that might have spread from the bladder cancer.

**Computed tomography (CT):** The CT scan is a special kind of x-ray that gives detailed pictures of your insides. It can help find enlarged lymph nodes that might contain cancer and make a good picture of your kidneys and bladder. The CT scanner takes many pictures as it rotates around you. Before any pictures are taken, you may be asked to drink a liquid dye that helps to better outline your organs. You may also need an IV line through which you will get a different kind of contrast dye. CT

scans take longer than regular x-rays.

**Magnetic resonance imaging (MRI):** MRI pictures are useful in finding signs that the cancer has spread outside of the bladder into nearby tissues or lymph nodes. They are also helpful in finding cancer that has spread to the brain or spinal cord. This test is like a CT scan, but it uses powerful magnets and radio waves instead of x-rays to make pictures. For some scans, a contrast material may be put into your vein to help see some structures better. MRI scans take longer than CT scans -- often up to an hour.

**Ultrasound:** Ultrasound uses sound waves to make pictures of your insides. It can help show the size of a bladder cancer and whether it has spread beyond the bladder.

**Bone scan:** For this test, a small amount of a radioactive substance is put into a vein. This substance builds up in areas of bone that contain cancer. A scanner can spot these places and show them on a picture.

## General Information

**Transitional Cell Carcinoma (urothelial carcinoma):** Most bladder cancers arise in the lining of the bladder, which is composed of layers of a specific type of cell called a transitional cell. Transitional cells are found only in the urinary tract, and line the urinary tract from the kidneys down almost to the tip of the penis in men and almost to the vagina in women. In normal bladders, the layer of transitional cells lining the bladder is usually 6 to 10 cells thick, but in early cancer the abnormal cells produce a much thicker lining, sometimes dozens of cells thick. In many cases, the cells will project into the interior space of the bladder, producing papillary tumors that resemble miniature coral growths. In other tumors, the cells may project outwards and invade the muscle of the bladder, producing nodular thickening of the muscular wall of the bladder, and eventually penetrating through the wall into the fat tissue surrounding the bladder. These tumors are much more dangerous as they have a high likelihood of spreading to other organs within the body, a process known as metastasis.

**Grade and Stage:** Tumor grade refers to how closely the tumor cells resemble normal transitional cells. Low-grade or well-differentiated tumors are comprised of cells which - although cancerous - more closely resemble normal cells. High-grade or poorly differentiated tumors have cells which have little resemblance to normal cells. Poorly differentiated tumors generally behave more aggressively and progress to metastatic disease more frequently than well-differentiated tumors. Squamous carcinoma of the bladder is a tumor characterized by cells that appear to resemble cells of the skin surface. In some instances, squamous cancers are the most undifferentiated form of transitional cell cancer, and in other instances - such as in patients with a history of chronic bladder inflammation or who have acquired a specific type of bladder parasite - squamous cancer may arise from the outset.

Tumor stage refers to the extent of the tumor. When tumors remain limited to the cells of the lining of the bladder, they are described as superficial or low-stage tumors. When tumors invade the muscular wall of the bladder, extend outside of the bladder or involve adjacent structures, they are referred to as high-stage or invasive tumors. Tumors that spread to involve lymph nodes or distant organs are referred to as metastatic tumors.

Carcinoma-in-situ (CIS) refers to the finding of cancer cells in flat and often normal-appearing bladder lining, or there may be areas of the bladder lining that may appear red and irregular. This type of cancer requires careful follow-up, as many of these patients will progress to more advanced cancers.

**Other Tumors:** In the United States, most bladder tumors (90+ per cent) are transitional cell carcinomas, which arise from the bladder lining. A much smaller number are squamous carcinomas as noted above, and rarely tumors may exhibit unusual cell types or be due to spread to the bladder from another primary tumor site.

**Hematuria:** The first sign of bladder cancer may be the presence of blood in the urine. This is known technically as hematuria, and may be grossly visible, presenting as frankly bloody urine with clots, or may be microscopic, detectable only with the aid of a microscope or laboratory tests designed to detect minute amounts of blood in otherwise normal-appearing urine.

There are many conditions that can produce blood in the urine, most of which are benign, but hematuria should always be thoroughly evaluated to rule out cancer. Cancers arising in the lining cells of the kidney drainage system – the renal pelvis - and the ureters – the tubes which conduct urine from the kidneys to the bladder – may also produce blood in the urine. A different type of kidney cancer that arises in the cells of the kidney proper – renal cell cancer (hypernephroma or renal adenocarcinoma) – may also be a cause of hematuria. Benign causes of bloody urine may include infection, stones, inflammation, trauma, or medical diseases of the kidney. Patients on blood thinners such as coumadin or anticoagulants such as Plavix or aspirin may also have hematuria, but the bleeding cannot be automatically assigned to these medications without a thorough investigation having been performed to rule out other causes.

**Causes of Bladder Cancer:** Bladder cancers occur more commonly in patients with a history of smoking tobacco. In fact, in the United States, smoking is the most frequent cause of bladder cancer. Patients with exposure to certain chemicals – such as benzene or certain solvents are at risk for bladder cancer. In the past, exposure to some commercial dyes was associated with bladder – tumors, although regulation of dyes by the FDA has largely eliminated this. Although rare in North America, chronic Schistosoma bladder infection – a parasite found in the Nile River valley and in other parts of Africa – can cause squamous carcinoma of the bladder.

**Diagnosis of bladder cancer:** The definitive diagnosis of bladder cancer is made by directly inspecting the bladder lining, a procedure termed cystoscopy, that can be performed in the office. A flexible instrument can be inserted along the urethra in a very similar fashion as flexible scopes are used to negotiate and visualize the gastrointestinal tract for any abnormalities. The urologist can identify tumors within the bladder by direct inspection using cystoscopy. If abnormalities are noted it is necessary to obtain a biopsy to provide tissue for inspection by a pathologist. This requires cystoscopy under anesthesia which is a hospital procedure. The urologist will make every effort to completely remove all visible tumors and obtain tissue samples from the tumor base. This provides the pathologist with the material needed to evaluate the stage and grade of the cancer.

**Treatments:** As long as bladder cancers remain limited to the lining of the bladder, they can usually be managed with endoscopic resection using instruments passed through the urethra. Recent clinical research has also suggested that a single treatment of Mitomycin C – one of the chemotherapy agents sometimes used in intravesical therapy – given at the time of the surgical

resection of the tumor – will reduce recurrence of tumors. This has become routine with most urologists doing transurethral surgery of bladder tumors.

Occasionally, when tumors recur frequently, are of high grade, or appear to have other factors making them high risk, additional treatment with intravesical chemotherapy may be indicated. In this treatment, a solution of cancer chemotherapy medication and water is placed into the bladder via a catheter, and left in place for 60-90 minutes. The medication treats the lining cells of the bladder and is thought to kill the cancer cells. Usually intravesical therapy is begun several weeks after resection of a tumor, and usually consists of six weekly treatments. The bladder is re-examined with a cystoscope to look for recurrence 6 to 8 weeks following treatment. If no recurrence is seen, most urologists now also follow a schedule of maintenance intravesical treatments, giving a series of 3 weekly treatments at roughly 6 to 8 week intervals for some period following the initial 6-treatment course.

Once invasion of the muscular wall of the bladder is identified, the patient is at significant risk of spread of the cancer to other organs. Treatment for this stage of tumor usually requires surgical removal of the cancerous bladder, with creation of an alternative drainage system for the urine. This is a complex procedure and is discussed in detail elsewhere.

Once the cancer has spread outside the bladder to either the pelvic lymph nodes or to other organs, chemotherapy or combination treatment with chemotherapy and surgery provide the best outcomes. Recent developments in chemotherapy have been promising, with control of the disease in some patients. Often there are research projects using state-of-the-art combination chemotherapy, which may be made available to patients with metastatic disease.

## **SURGICAL TREATMENT OF BLADDER CANCER**

### **Surgery for Superficial or Low-Stage Bladder Cancers**

When bladder tumors remain limited to the lining of the bladder and do not invade the bladder (detrusor) muscle, they may often be managed with surgery performed using instruments passed through the urethra. Such tumors can often be successfully removed by excising the affected area using a cystoscope and a loop that employs an electric current to cut tissue. These procedures are done in the operating room under anesthesia, but often can be done on a “day surgery” basis – patients are treated and then sent home the same day. Often biopsies of other areas of the bladder lining may be taken and x-rays of the ureters and renal collecting systems may be made by injecting x-ray contrast dye up the ureters from below and taking x-rays of the abdomen. Such studies usually show the anatomy of the kidney drainage system in fine detail and may be helpful in detecting tumors of the lining of the ureters or renal pelvis.

These procedures may be done as an *excisional biopsy* to establish a diagnosis – determining the type and degree of invasion of a given tumor – or as a definitive treatment for a superficial low-stage tumor. In both cases, the goal is total removal of the superficial tumor.

### **Surgery for Invasive Bladder Cancers**

Invasion into the muscular wall of the bladder indicates that the bladder cancer is aggressive and that there is a great risk of metastatic spread of the cancer to sites outside of the bladder. When biopsy confirms muscle invasion, there is a narrow window of opportunity during which the bladder must be removed to provide a cure for the cancer. In the male, such surgery also involves removing the

prostate and seminal vesicles, and in some cases, the urethra. In the female, the uterus, fallopian tubes and ovaries, plus a portion of the vagina containing the urethra will typically be removed. In both instances, the pelvic lymph nodes are also removed to permit examination by the pathologist and to remove deposits of microscopic spread of cancer to the lymph nodes.

Removal of the bladder necessitates an alternative means for managing the urine produced by the kidneys. Conventionally, the surgeon “borrows” a small (6 to 8 inch) segment of small intestine and creates a tube or ileal conduit which he brings out through an opening in the patient’s abdomen, usually below and to the right of the umbilicus. The ureters are then connected to the base of this loop, and urine drains through it into a plastic collection bag affixed to the abdomen. The bag is emptied by the patient at intervals throughout the day. At night, a larger bag may be connected to allow the patient to sleep through the night.

In the last two decades, surgeons have perfected internal urine storage systems using extended segments of small or large intestine. These may be connected to the patient’s urethra, in which case they are termed neo-bladders (“new bladders”) or may be accessed by having the patient pass a small catheter into an opening in the abdomen to drain the urine, in which case they are termed continent reservoirs. In these cases there is no outside collection bag. Neo-bladders or reservoirs are not for everyone, and they are not without their own problems and challenges. Both the surgery to create them and the recovery take longer, and the potential for complications is increased. The patient must be able to care for himself at a higher level than for an ileal conduit. Nonetheless, the continent diversion may be preferable for younger, highly motivated and healthy patients who object to an outside collection bag. Your surgeon will discuss with you whether such a urinary diversion is feasible in your case.

Without question, major surgery for bladder cancer represents a life-changing event. Experience has shown, though, that motivated patients do recover well from such procedures and go on to live lives of quality, pursuing most – if not all - of the activities and interests they choose to. Our commitment is to assist our patients through these operations and help them to move on with their lives as effectively and safely as possible.

### **Intravesical Chemotherapy**

Most bladder tumors arise from the lining of the bladder, the innermost layer of cells in that organ. When these tumors are limited to the lining, they may be treated – in addition to surgical removal - using various medications introduced into the bladder via a catheter. The medication within the bladder is then in direct contact with the lining tissues from which the tumors arise. Because bladder cancer cells are more metabolically active than normal cells, they absorb the medication, which then acts on the cell mechanism to kill it. In some instances the inflammation produced by the medicine may augment its killing power against tumor cells.

There are several intravesical medications that are used to treat bladder tumors, but the two in most common use are BCG (Bacille Calmette-Guerin), referred to as intravesical immunotherapy, and Mitomycin C, referred to as intravesical chemotherapy. BCG was originally developed in the early 20<sup>th</sup> century as a vaccine for tuberculosis, but in the past three decades it has found application in treating various cancers. It has been shown to be very effective in reducing or delaying recurrence

in superficial bladder tumors and in bladder carcinoma-in-situ (CIS). At present, most urologists use BCG in cases where multiple superficial bladder cancers are found in the bladder, or for bladder tumors that recur frequently, especially if high grade, – 2 recurrences in a year, or 3 within 18 months. It has also been effective in controlling CIS. Administration of Mitomycin C has become almost standard following transurethral resection of tumors (TURBT) – a single dose of 40 mgm in 20 to 60 cc of water is placed in the bladder at the completion of the procedure and left in place for at least 60 minutes. Mitomycin C is also used as a second-line drug when BCG has not been effective or can't be used because of allergy or other contraindications.

BCG is usually administered weekly for 6 weeks beginning several weeks after TURBT. There is usually a rest period of 6-8 weeks, and then an interval cystoscopy is performed – usually in the office – to look for recurrent tumors. If none are found, several maintenance courses of three weekly treatments are given. Maintenance may continue for up to 2 years, or in some cases longer.

Mitomycin C is also usually administered weekly for 6 weeks, with cystoscopic follow-up performed as for BCG. Maintenance has been less well established than with BCG therapy, but most urologists will recommend some period of maintenance therapy.

The side effects of intravesical therapies include frequent urination, discomfort on urination, and occasionally bladder bleeding. BCG may cause fever and chills which require prompt attention and treatment. Mitomycin C. may result in a condition termed bladder contracture whereby the capacity of the bladder is reduced due to scarring of the muscle wall

From time to time there are research studies that employ new drugs using an intravesical approach. Requirements for participation in these studies are often fairly stringent, but if such studies are available, your urologist will discuss the details with you.