Bladder Cancer

Bladder cancer is the sixth most common cancer in the United States. About 53,200 Americans are diagnosed with bladder cancer each year and 12,200 die annually of the disease. In recent decades there has been a steady increase in the incidence of bladder cancer. However, doctors are making progress in treatment and survival rates are improving. But what are its symptoms? How should it be treated? The following information should help you talk to a urologist about this condition.

What happens under normal conditions?

The bladder is a hollow balloon-shaped mostly muscular organ that stores urine until ready for release. The urine is produced in the kidneys. It flows through tubes called the ureters into the bladder and is discharged through the urethra during urination. The bladder muscle aids urination by contracting (tightening) to help force out the urine.

A thin surface layer called the urothelium lines the inside of the bladder. Next is a layer of loose connective tissue called the lamina propria. Covering the lamina propria is the bladder muscle, covered on the outside by fat.

What causes bladder cancer?

The ways in which bladder cancers develop and progress are only partly understood. However, a number of substances that cause the cancers to develop have been identified. Chief among them are cancer-causing agents in cigarette smoke and various industrial chemicals. Cigarette smoking alone has been estimated to cause 50 percent of all bladder cancer cases in the United States. Long-term workplace exposure to chemical compounds such as paints and solvents has been estimated to cause another 20 to 25 percent of bladder cancer cases.

More than 90 percent of all bladder cancers originate in the urothelium. The majority of diagnosed bladder tumors are confined to the urothelium or the lamina propria and have not invaded the bladder muscle.

What are the symptoms of bladder cancer?

Painless blood in the urine (hematuria) is the most common symptom. It eventually occurs in nearly all cases of bladder cancer. In the majority of cases, the blood is visible during urination. In some cases, it is invisible except under a microscope, and is usually discovered when analyzing a urine sample as part of a routine examination.

Hematuria does not by itself confirm the presence of bladder cancer. Blood in the urine has many possible causes. For example, it may result from a urinary tract infection or kidney stones rather than from cancer. It is important to note that hematuria, particularly microscopic, might be entirely normal for some individuals. A diagnostic investigation is necessary to determine whether bladder cancer is present.

Other symptoms of bladder cancer may include frequent urination and pain upon urination (dysuria).

How is bladder cancer diagnosed?

The diagnostic investigation begins with a thorough medical history and a physical examination. The doctor will ask the patient about past exposure to known causes of bladder cancer, such as cigarette smoke or chemicals. Also, because hematuria can come from anywhere in the urinary tract, the doctor may order radiological imaging of the kidneys, ureter and bladder to check for problems in these organs.

Diagnostic tools to check for bladder cancer include various types of urinalysis. In one type, the urine is examined under a microscope to look for cancer cells that may have been shed into the urine from the bladder lining. Urine can also be tested for substances known to be closely associated with cancer cells.

The doctor's most important diagnostic tool is cystoscopy, which is a procedure that allows direct viewing of the inside of the bladder. This is most commonly performed as an office procedure under local anesthesia or light sedation. First, a topical anesthetic gel is applied, so the patient will feel little or no discomfort. The doctor then inserts a viewing instrument called a cystoscope through the urethra and into the bladder. Looking through the cystoscope, the doctor is able to examine the bladder's inner surfaces for signs of cancer.

If tumors are present, the doctor notes their appearance, number, location and size. As removal (resection) of the tumors cannot usually be done under local anesthesia, the patient is then scheduled to return for a surgical procedure to remove the tumor under general anesthesia or regional anesthesia. In a manner as before, the doctor inserts an instrument, called a resectoscope, into the bladder. This is a viewing instrument similar to the cystoscope, but contains a wire loop at the end for removing tissue. This procedure is done through the urethra and is called a transurethral resection of bladder tumors. The removed tissue is sent to a pathologist for examination. Pathologists are specialists who interpret changes in body tissues caused by disease.

In addition to removing visible tumors, the doctor may remove very small samples of tissue of any suspicious-looking areas of the bladder. A pathologist also examines this tissue.

If a biopsy is taken and bladder cancer is found, the pathologist who examines the tissue will grade the tumor according to how much cells differ in appearance from normal cells. The most widely used grading systems classify tumors into three main grades: low, intermediate and high. The cells of low-grade tumors have minimal abnormalities. In high-grade tumors, the cells have become disorganized and many abnormalities are apparent. The grade indicates the tumor's "aggression level" — how fast it is likely to grow and spread. High-grade tumors are the most aggressive and the most likely to progress into the muscle.

Staging of bladder cancers is based on how deeply a tumor has penetrated the bladder wall. Table 1 lists stages of penetration using the TNM classification system.

Table 1 -- Staging of primary bladder cancer tumors (T)	
Ta:	Noninvasive papillary tumor (confined to urothelium)
Tis:	CIS carcinoma (high grade “flat tumor” confined to urothelium)
T1:	Tumor invades lamina propria
T2:	Tumor invades bladder muscle
T2a:	Invades superficial bladder muscle
T2b:	Invades deep bladder muscle
T3:	Tumor invades perivesical fat
T3a:	Microscopic perivesical fat invasion
T3b:	Macroscopic perivesical fat invasion (and progressing beyond bladder)
T4:	Tumor invades prostate, uterus, vagina, pelvic wall or abdominal wall
T4a:	Invades adjacent organs (uterus, ovaries, prostate)
T4b:	Invades pelvic wall and/or abdominal wall

Stages Ta and Tis (in the urothelium) and stage T1 (in the lamina propria) are the non-muscle-invasive stages. Most Ta tumors are low grade, and most do not progress to invade the bladder muscle. Stage T1 tumors are much more likely to become muscle invasive. Stage Ta tumors often recur after treatment but they tend to recur with the same stage and grade.

The Tis stage classification is reserved for a type of high-grade cancer called carcinoma in situ (CIS). CIS usually appears through the cystoscope as a flat, reddish, velvety patch on the bladder lining. It is difficult to remove and is best treated with immunotherapy or chemotherapy. If untreated, CIS will likely progress to muscle-invasive disease.

How is bladder cancer treated?

Removing stage Ta and stage T1 tumors: Transurethral resection of the bladder (TURBT) is the usual treatment method for patients who, when examined with a cystoscope, are found to have abnormal growths on the urothelium (stage Ta) and/or in the lamina propria (stage T1).

Alternative methods, such as laser therapy, compare favorably with TURBT in terms of treatment results. However, TURBT has a major advantage — it can provide tissue suitable for a pathologist to use in determining a tumor's grade and stage. The tumor structure is left too distorted for this purpose after the alternative treatment methods, so biopsies of the tumor must be taken before treatment.

Intravesical chemotherapy and immunotherapy: Following removal, intravesical chemotherapy or intravesical immunotherapy may be used to try to prevent tumor recurrences. Intravesical means "within the bladder". These therapeutic agents are put directly into the bladder through a catheter in the urethra, are retained for one to two hours and are then urinated out.

The chief intravesical agents currently available are thiotepa, doxorubicin, mitomycin C and bacillus Calmette-Guérin (BCG). The first three are drugs. The fourth, BCG, is a live but weakened vaccine strain of bovine tuberculosis. It was first used to immunize humans against tuberculosis. It is now one of the most effective agents for treating bladder cancer and especially for treating CIS.

All four agents have some benefits and all four have risks. Among the benefits: Comparison studies have shown each of the four to be superior to TURBT alone for preventing tumor recurrences following TURBT. Studies have also shown both BCG and mitomycin C to be superior to doxorubicin or thiotepa for reducing recurrence of T1 tumors and high-grade Ta tumors. However, there is no absolute evidence that any intravesical therapy affects the rate of progression to muscle-invasive disease although some studies with BCG suggest this may be the case.

Among the risks: Each of the four agents produces irritative side effects such as painful urination and the need to urinate frequently. In addition, BCG therapy carries a 24 percent risk of flu-like symptoms and a small risk (4 percent) of systemic infections. Thiotepa has a 13 percent risk of suppressing bone marrow activity — causing a reduction in white blood cells and platelets. The main side effects for each intravesical agent are shown in Table 2, along with estimated probabilities of occurrence.

Table 2: Side effects of treatment and estimated probabilities of occurrence

	Intravesical Agent			
Side Effects	**BCG**	**Mitomycin C**	**Thiotepa**	**Doxorubicin**
Frequent urination	63%	42%	11%	27%
Painful urination	75%	35%	30%	20%
Flu-like symptoms	24%	20%	11%	7%
Fever or chills	27%	3%	4%	4%
Systemic infections	4%	Not available	0.3%	Not available
Skin rash	6%	13%	2%	2%
Suppression of bone marrow activity	1%	2%	13%	0.8%

Once the bladder has been assessed as free of disease at the first three to four month post-treatment cystoscopic inspection, many physicians consider it appropriate to apply additional treatments of these same drugs to forestall or prevent future recurrences. While recent studies demonstrate this concept of "maintenance therapy" is useful for some patients receiving BCG, it is of less certain benefit for those receiving the other three chemotherapeutic drugs. Whether additional treatments are given or not, periodic cystoscopies are required to make sure that tumors do not recur. During the first one to two years

surveillance is carried out on a quarterly basis but then can gradually be reduced to twice and eventually even once per year thereafter.

Cystectomy: Surgical removal of the bladder may be an option for patients with CIS or high-grade T1 cancers that have persisted or recurred after initial intravesical treatment. There is a substantial risk of progression to muscle-invasive cancer in such cases, and some patients may want to consider partial or full cystectomy as a first choice of treatment. If so, they should ask their doctor for information about both the risks of cystectomy and the methods of urinary reconstruction.

An alternative is to repeat intravesical therapy. There is some evidence that patients may respond to repeat therapy. However, the evidence is too weak to draw firm conclusions about whether any amount or type of intravesical therapy, in any combination, can affect progression of high-grade disease.

Frequently asked questions:

Do bladder tumors occur in children?

Fortunately, bladder tumors are rare in children.

What are some risk factors for bladder cancer?

Smokers develop bladder cancer at two to three times the rate of non-smokers. People who work with dyes, metal, paints, leather, textile and organic chemicals may be at a higher risk. People who have chronic bladder infections may also be at higher risk.

Is there a screening test for early detection of bladder cancer?

Not at this time.