American Urological Association Inc.

Doctor's guide for patients on

The Management of Bladder Cancer

Bladder Cancer Guidelines Panel

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Foreword

This guide focuses on non-muscle-invasive bladder cancer. Most of these types of tumors have not spread to the bladder muscle and can be treated without removing any of the bladder.

This guide provides you with information answering three basic questions: What is non-muscle-invasive bladder cancer? What are the choices for treating this type of bladder cancer? What are the likely benefits and risks of each treatment choice? We present this information to further your general understanding of bladder cancer and current treatments and to assist in discussing this information with your doctor.

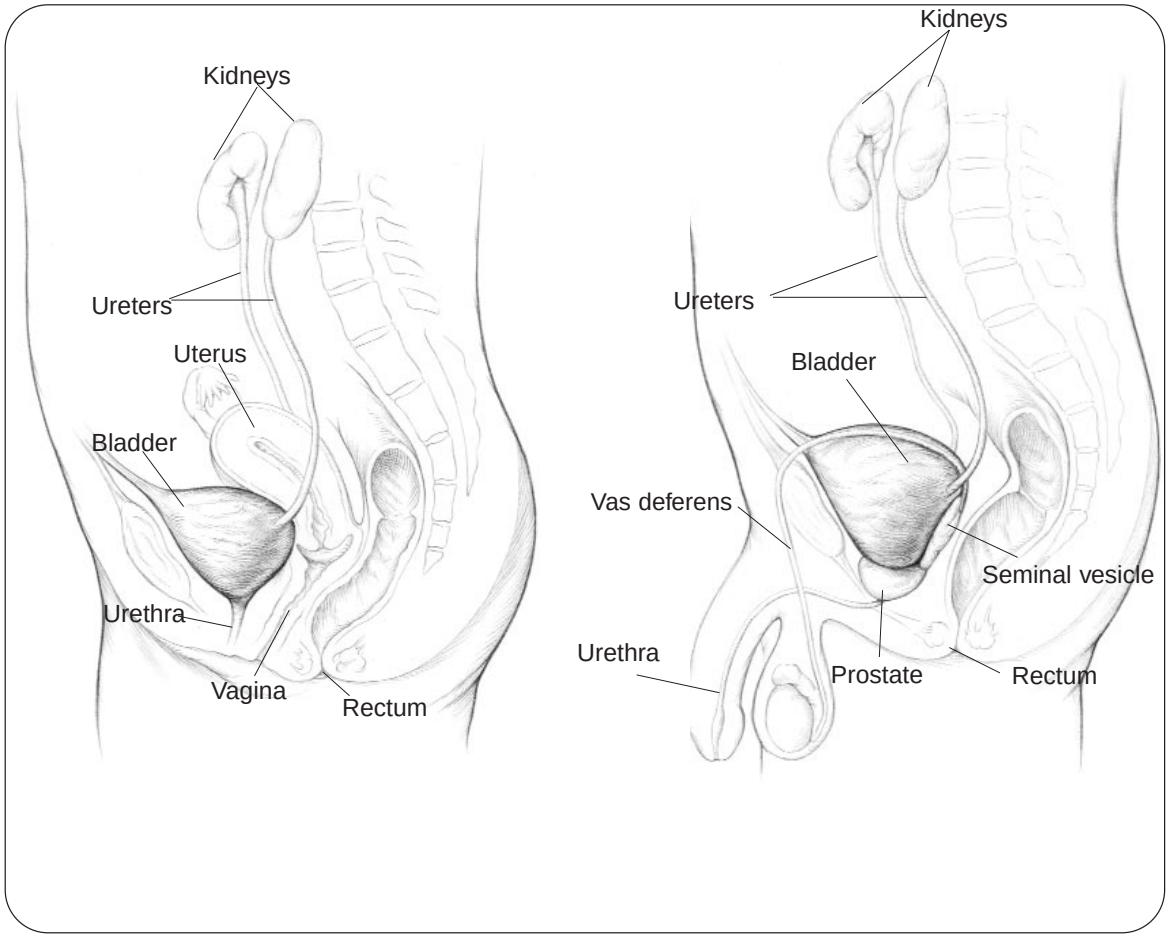
Illustrations prepared by Tim Phelps, C.M.I., Baltimore, MD

What is the bladder?

The urinary bladder is a hollow, 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. (See Figures 1 and 2 below for the bladder's location and relation to other body organs.)

The walls of the bladder are layered as shown in Figure 3 on page 2. A thin surface layer called the urothelium lines the inner sides. Next is a layer of loose connective tissue called the lamina propria. Bordering the lamina propria is the bladder muscle, covered on the outside by fat and a type of tissue called peritoneum. (For definitions of terms used in this guide, see the Glossary on page 7.)

Figures 1 & 2. Female & male bladder and adjacent body organs



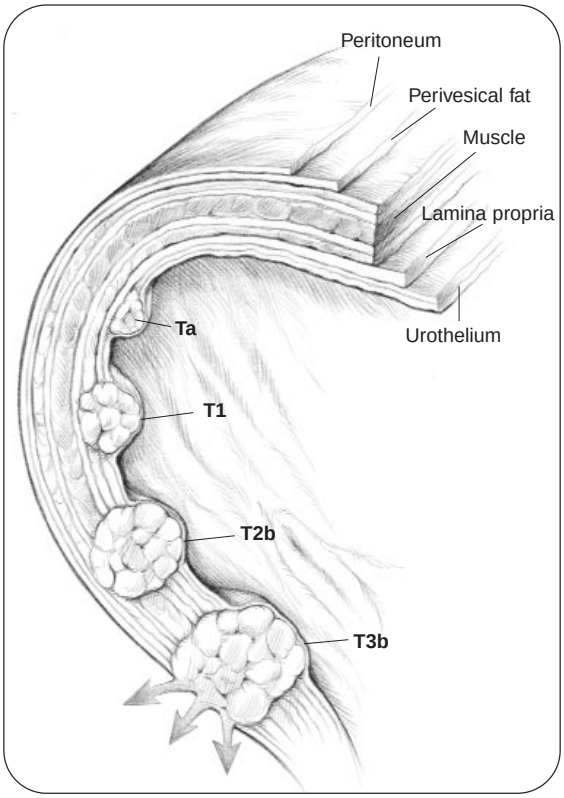
How does bladder cancer develop?

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 known cancer-causing agents in cigarette smoke and 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 20-25 percent of bladder cancer cases.

The changing of normal cells into cancerous cells usually begins in the urothelium (bladder lining). More than 90 percent of all bladder cancers originate there. The majority of newly diagnosed bladder cancer have not progressed beyond the urothelium or the lamina propria and have not invaded the bladder muscle (see Figure 3).

This patient's guide focuses on bladder cancers that have not spread beyond the urothelium and lamina propria. Most of these tumors that have not invaded the bladder muscle can be treated without removing any of the bladder. Cancers that have progressed to become muscle invasive tend to present more problems and fewer treatment choices. Often, there is no choice but to remove part or all of the bladder to prevent the cancer from spreading further.

Figure 3. Layers of the bladder wall and selected stages of cancer progression



What are the main symptoms of bladder cancer?

Painless hematuria (blood in the urine) 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 rather than from cancer. A diagnostic investigation is necessary to determine whether bladder cancer is present.

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, ureters and bladder to check for problems in these organs.

Diagnostic tools to check for bladder cancer include various types of urine analysis. In one type, the patient's 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. First, an anesthetic is administered, 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 surfaces for signs of cancer.

If tumors are present, the doctor notes their appearance, number, location and size before resecting (removing) them. The doctor removes the tumors using an instrument called a resectoscope. This is a viewing instrument similar to the cystoscope, but contains a wire loop at the end used for removing tissue. This procedure is done through the urethra and is called a transurethral resection of bladder tumors. The resected tissue is sent to a pathologist for examination. Pathologists are specialists who interpret changes in body tissues caused by disease.

In addition to resecting visible tumors, the doctor removes very small samples of tissue (biopsies) of any suspicious-looking areas of the bladder. This tissue is also examined by a pathologist.

How are bladder cancers graded?

If a biopsy is taken and bladder cancer is found, the pathologist who examines the tissue will grade the tumor according to how much their 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.

How are bladder cancers staged?

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. Selected stages from this list are illustrated in Figure 3, page 2.

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 resect and is best treated with immunotherapy or chemotherapy as described in the next section. If untreated, CIS will likely progress to muscle-invasive disease.

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

* Illustrated in Fig. 3, pg. 2

What are the choices for treating non-muscle-invasive bladder cancer?

Removing stage Ta and stage T1 tumors

Transurethral resection of bladder tumors (TURBT) is the usual treatment method for patients who, when examined with a cystoscope as described on page 3, 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 resected 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 resection, 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.

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 vaccine. BCG 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 evidence that any intravesical therapy affects the rate of progression to muscle-invasive disease.

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 (throughout the body). 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.

Cystectomy

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 conclusions about whether any amount or type of intravesical therapy, in any combination, can affect progression of high-grade disease.

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

Side effects	Intravesical Agent			
	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%

Questions to ask the doctor

- ❑ How deeply has my bladder cancer progressed? What is its stage?
- ❑ What is my cancer's grade ?
- ❑ Do I have carcinoma in situ (CIS)?
- ❑ If intravesical therapy is recommended, what type do you recommend and why? Is cost a factor?
- ❑ What are the possible complications of the recommended therapy? How likely are they to occur? If they occur, how will they be treated?
- ❑ How often will I need to be re-examined for tumor recurrence and/or progression after my present bladder cancer treatment is completed?
- ❑ If there is a chance that at some time I may need my bladder removed, what are the risks of this operation? How would I be able to urinate if my bladder is removed?

Additional questions to ask the doctor:

- ❑ _____
- ❑ _____
- ❑ _____
- ❑ _____
- ❑ _____

Glossary

Carcinoma in situ: The stage of high-grade cancer that appears as a flat, reddish, velvety patch on the bladder lining.

Kidney: One of two body organs, each about four inches long and two inches wide, that filter out waste products from the blood and discharge these waste products in urine (Figures 1 and 2).

Lamina propria (submucosa): In the bladder, a layer of loose connective tissue between the urothelium and bladder muscle (separated by a membrane from the urothelium) (Figure 3).

Papillary tumor: Tumor with nipple-like, stalk-like or finger-like appearance.

Peritoneum: Strong, smooth, colorless membrane that lines the walls of the abdomen and covers numerous body organs including the bladder (Figure 3).

Perivesical: Around the bladder.

Prostate: A walnut-sized gland located just below the bladder (Figure 2). The prostate's main purpose is to produce fluid for semen.

Ureter: One of two tubes that carry urine from the kidneys to the bladder (Figures 1 and 2).

Urethra (female): A short tube, not quite one and a half inches long and located above the vagina, through which urine flows from the bladder out of the body (Figure 1).

Urethra (male): A tube, extending from the bladder to the tip of the penis, through which urine flows from the bladder out of the body (Figure 2).

Urinary tract: General name for passageway and associated organs through which urine travels from kidney to urethra and out of the body.

Urine: Fluid excreted by the kidneys, about 96 percent of which is water and the rest waste products.

Urothelium (mucosa): Mucus lining in organs of the urinary tract, consisting in the bladder of three to seven cell layers (Figure 3).

Where to find more information

American Cancer Society
800.ACS.2345
www.cancer.org

American Foundation for Urologic Disease
1128 North Charles Street
Baltimore, MD 21201
410.468.1800
www.afud.org

Cancer Information Service
National Cancer Institute
National Institutes of Health
800.4.CANCER
800.422.6237
http://cis.nci.nih.gov

Doctor's Guide for Patients on the Management of Bladder Cancer

This publication is intended for patients and lay readers. It is derived from the Report on the Management of Non-Muscle-Invasive Bladder Cancer, developed by the American Urological Association, Inc., and its Bladder Cancer Clinical Guidelines Panel.

A Doctor's Guide for Patients is intended to stimulate and facilitate discussion between the patient and doctor regarding the types of treatment described in summary fashion in this booklet. The full Report of the guidelines panel provides the physician with a more detailed discussion of treatment standards, guidelines and options to be considered.

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