

REVIEW ARTICLE

BLADDER CANCER- REVIEW WITH EMPHASIS ON THE TREATMENT

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ABSTRACT:

Cancer occurs when normal cells undergo a degenerative, dangerous, or what is called a malignant change or transformation causing them to grow abnormally and multiply without normal controls. Bladder cancer is any of several types of cancer arising from the epithelial lining (i.e., the urothelium) of the urinary bladder. Rarely the bladder is involved by non-epithelial cancers, such as lymphoma or sarcoma, but these are not ordinarily included in the colloquial term "bladder cancer." It is a disease in which abnormal cells multiply without control in the bladder. The most common type of bladder cancer recapitulates the normal histology of the urothelium and is known as transitional cell carcinoma or more properly urothelial cell carcinoma. Five-year survival rates in the United States are around 77%. The optimum management of bladder cancer in the elderly remains unknown. The literature to date indicates that aging may have an adverse role in the response to treatment of superficial disease, and that outcomes for cystectomy may be adversely affected as well. Although authors of numerous retrospective studies have suggested that aggressive treatment is safe, few have been able to demonstrate a clear survival advantage for the elderly patient. Furthermore, only two studies have assessed geriatric function, which could be as important as, or more important than, survival for some patients. The mechanisms behind the high risk of developing bladder cancer are only beginning to be explored at the basic science level. A research agenda that incorporates age-related changes in the bladder, as well as treatment outcomes based on measurable criteria of frailty, will begin to help shed light on this costly and lethal disease that is most commonly seen in the geriatric population.

Keywords: Bladder cancer, Symptoms, Treatment

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INTRODUCTION

The bladder is a hollow organ that collects urine for storage and eventual removal from the body through the urethra. Urine is produced by the kidneys and travels to the bladder through tubes called ureters. The bladder stores the urine, which is made up of water and waste products that the body doesn't need.¹

When the bladder is full, it sends messages (nerve signals) to the brain so that you feel the need to empty your bladder. The bladder muscle contracts and squeezes the urine out of the body through the urethra. The urethra is a short tube that lies in front of the vagina in women. In men, it passes through the prostate gland to the tip of the penis.²

Cancer occurs when normal cells undergo a degenerative, dangerous, or what is called

a malignant change or transformation causing them to grow abnormally and multiply without normal controls. A mass of cancerous cells is called a malignant tumor or cancer. The cancerous cells are capable of spreading to other areas of the body through the process of metastasis.³

A cancer can become destructive locally to the tissues adjacent to where it arises. Cancer cells can also metastasize. Metastasis means that cells spread through the tissue fluid's circulation called the lymphatic system or through the blood stream where they can then stop off in other tissues or organs where they may grow as metastases or metastatic deposits and can become destructive in these new locations. The term cancer is further described by the tissue in which it has arisen. For example: bladder cancer is a different disease

than lung cancer. If a bladder cancer cell metastasizes – that is, spreads to the lungs through the bloodstream it is still called, and is treated as bladder cancer- not as lung cancer. Cells which transform in a less dangerous fashion may still multiply and form masses or tumors. These are called benign tumors. They do not metastasize.⁴

SYMPTOMS⁵

Blood in the urine is the most common symptom of bladder cancer. It is generally painless. Although blood may be visible, in most cases it is invisible except under a microscope. In these cases, blood is found when your urine is tested by your health care provider.

Blood alone does not mean that you have bladder cancer. There could be many reasons for blood in the urine, such as a urinary tract infection or kidney stones. Microscopic amounts of blood might even be normal in some people.

Frequent or painful urination is less common. If you have these symptoms, and do not have a urinary tract infection, you should talk to your health care provider to find out if bladder cancer is the cause.

Other possible symptoms include pain during urination, frequent urination, or feeling the need to urinate without being able to do so. These signs and symptoms are not specific to bladder cancer, and are also caused by non-cancerous conditions, including prostate infections, over-active bladder and cystitis. There are many other causes of hematuria, such as bladder or ureteric stones, infection, kidney disease, kidney cancers and vascular malformations. Patients with advanced disease refer pelvic or bony pain, lower-extremity edema, or flank pain. Rarely a palpable mass can be detected on physical examination.

CAUSES:

Tobacco smoking is the main known contributor to urinary bladder cancer; in most populations, smoking is associated with over half of bladder cancer cases in men and one-third of cases among women. There is a linear relationship between smoking and risk, and quitting smoking reduces the risk. Passive smoking has not been proven to be involved.⁶

Thirty percent of bladder tumors probably result from occupational exposure in the workplace to carcinogens such as benzidine, 2-Naphthylamine, which is found in cigarette smoke, has also been

shown to increase bladder cancer risk. Occupations at risk are bus drivers, rubber workers, motor mechanics, leather (including shoe) workers, blacksmiths, machine setters, and mechanics. Hairdressers are thought to be at risk as well because of their frequent exposure to permanent hair dyes.⁷

TYPES OF BLADDER CANCER⁸

Different types of cells in your bladder can become cancerous. The type of bladder cell where cancer begins determines the type of bladder cancer. Bladder cancer type determines which treatments may work best for you.

1) **Transitional cell carcinoma.** Transitional cell carcinoma occurs in the cells that line the inside of your bladder. Transitional cells expand when your bladder is full and contract when your bladder is empty. These same cells line the inside of your ureters and your urethra, and tumors can form in those places as well. Transitional cell carcinoma is the most common type of bladder cancer in the United States.

2) **Squamous cell carcinoma.** Squamous cells appear in your bladder in response to infection and irritation. Over time they can become cancerous. Squamous cell bladder cancer is rare in the United States. It's more common in parts of the world where a certain parasitic infection (schistosomiasis) is a prevalent cause of bladder infections.

3) **Adenocarcinoma.** Adenocarcinoma begins in cells that make up mucus-secreting glands in the bladder. Adenocarcinoma of the bladder is rare in the United States. Some bladder cancers include more than one type of cell.

STAGING⁹

The stage of a cancer describes its size and whether it has spread. Although test results provide a lot of information, the exact stage of the cancer won't be known until after surgery to remove it. Once your doctors know the stage of the bladder cancer, they can decide on the most appropriate treatment for you. The most commonly used staging system is the TNM system: 1) T is the size of the tumour (cancer). 2) N is whether it has spread to the nearby lymph nodes (sometimes called glands). 3) M is whether the cancer has spread to other parts of the body (metastases).

Non-invasive bladder cancer has not spread to the lymph nodes or to other parts of the body.

STAGES OF NON-INVASIVE BLADDER CANCER

Non-invasive bladder cancer will be staged as CIS, Ta or T1: 1) Carcinoma in situ (CIS): This is sometimes described as a flat tumour. Cancer cells are only in the very inner layer of the bladder lining. 2) Ta: The cancer is a mushroom-like growth (papillary cancer) growing only in the inner layer of the bladder lining. 3) T1: The cancer has started to grow into the layer of connective tissue beneath the bladder lining.

GRADING^{10, 11}

The grade of a cancer gives an idea of how quickly it might grow. Bladder cancer is graded according to how the cancer cells look when the biopsy sample is examined under a microscope. Knowing the grade of a cancer helps your urologist decide if you need treatment after surgery. 1) Grade 1 or low-grade - The cancer cells look very much like normal bladder cells, are usually slow-growing and less likely to spread. 2) Grade 2 or intermediate-grade - The cancer cells look more abnormal and grow slightly more quickly than grade 1 cancers. 3) Grade 3 or high-grade - The cancer cells look very abnormal and are more likely to grow more quickly. 4) Carcinoma in situ (CIS) is always classed as high-grade.

DIAGNOSIS.¹²

The following tests and procedures may be used:

Physical exam and history: An exam of the body to check general signs of health, including checking for signs of disease, such as lumps or anything else that seems unusual. A history of the patient's health habits and past illnesses and treatments will also be taken.

Internal exam: An exam of the vagina and/or rectum. The doctor inserts lubricated, gloved fingers into the vagina and/or rectum to feel for lumps.

Urinalysis: A test to check the color of urine and its contents, such as sugar, protein, red blood cells, and white blood cells.

Urine cytology: A laboratory test in which a sample of urine is checked under a microscope for abnormal cells.

Cystoscopy: A procedure to look inside the bladder and urethra to check for abnormal areas. A cystoscope is inserted through the urethra into the bladder. A cystoscope is a thin, tube-like instrument

with a light and a lens for viewing. It may also have a tool to remove tissue samples, which are checked under a microscope for signs of cancer.

Intravenous pyelogram (IVP): A series of x-rays of the kidneys, ureters, and bladder to find out if cancer is present in these organs. A contrast dye is injected into a vein. As the contrast dye moves through the kidneys, ureters, and bladder, x-rays are taken to see if there are any blockages.

BIOPSY: The removal of cells or tissues so they can be viewed under a microscope by a pathologist to check for signs of cancer. A biopsy for bladder cancer is usually done during cystoscopy. It may be possible to remove the entire tumor during biopsy.

TREATMENT.¹³

Treatment options for bladder cancer that has not entered the muscle (stages Ta, T1 and Tis) include:

- Surgery to remove the tumor
- Intravesical therapy
- Surgery to remove the bladder

Treatment options for bladder cancer that has entered the bladder muscle (stages T2, T3 and T4) include:

- Intravesical therapy
- Surgery to remove the bladder
- Chemotherapy
- Radiation therapy

A) SURGERY TO REMOVE THE TUMOR: This surgery, called TURBT (transurethral resection of bladder tumor), is the usual treatment for people who have tumors on the bladder lining (stage Ta and T1). The surgery is done during cystoscopy, so there is no cutting into the abdomen. You will be given general or spinal anesthesia.

If a tumor is clearly seen, the doctor can remove the entire tumor. A resectoscope is used to locate and remove tumor tissue. The doctor may also remove very small samples of other areas of the bladder that may be a concern. These samples will also be checked for grade and stage.

The doctor could use laser therapy, in which narrow beams of light cut and destroy the tumor. The results of laser therapy are like those of TURBT. However, an advantage of TURBT is that when the tissue is removed, it can be tested. With laser therapy the tumor tissue is damaged, so samples must be taken before the laser is used. Once the tumor(s) is removed, your doctor may suggest intravesical therapy to prevent another tumor from growing.

B) INTRAVESICLE THERAPY¹⁴: With intravesical (meaning "within the bladder") therapy, the drug is put directly into your bladder through a catheter (a thin tube that is placed through the urethra). The catheter only stays in for a few minutes. You hold the drug in your bladder for 1 to 2 hours and then urinate it out. In general, you receive 6 weekly treatments.

Intravesical therapy after TURBT is better than the surgery alone to prevent tumors from coming back. Your doctor may start intravesical chemotherapy right after surgery (in the recovery room). But immunotherapy is not used until after healing from surgery is complete.

INTRAVESICAL IMMUNOTHERAPY:

Immunotherapy is a treatment that boosts the ability of your immune system to fight the cancer. Bacillus Calmette-Guerin (BCG) is the immunotherapy drug used for bladder cancer. BCG has also been used as a tuberculosis vaccine. Generally, BCG is chosen for patients with stage T1 cancer or carcinoma in situ (CIS). These patients have a higher risk of cancer returning and spreading than those with stage Ta cancer. BCG is inserted into the bladder through a catheter. The therapy triggers the immune system to attack bladder cancer cells. It is one of the most effective treatments for bladder cancer, especially CIS. It is not recommended if you have a weak immune system or certain symptoms. Four out of 100 people given BCG end up with the bacteria infecting their whole body. More common side effects can include: needing to urinate often painful urination flu-like symptoms fever or chills joint pain.

INTRAVESICAL CHEMOTHERAPY:

Chemotherapy drugs kill cancer cells. With intravesical chemotherapy, these drugs are placed directly into the bladder, rather than in the bloodstream. As a result, many common side effects - like hair loss - can be avoided. Because the drugs only reach the bladder lining, this type of treatment is only recommended for noninvasive bladder cancers. Mitomycin C is the most common chemotherapy drug used for intravesical therapy of bladder cancer. Common side effects include: Needing to urinate often painful urination, flu-like symptoms, skin rash. Some patients may respond to repeat therapy if the cancer returns. However, if you have high-grade Ta or T1 cancer or CIS, or you tried BCG and it did not work, you may need something else to control the

cancer. In this case, you should talk to your doctor about surgery to remove the bladder.

Maintenance Therapy: After the bladder is free of disease, your doctor may suggest more treatment with the same drugs to keep the tumor from coming back. This may happen at the first 3-month appointment after treatment. Maintenance therapy seems to be more helpful for people who have had BCG than for those who have had chemotherapy drugs.

C) SURGERY TO REMOVE THE BLADDER¹⁵:

Surgery called cystectomy may be needed if you have cancer that could or has entered the bladder muscle. In this case, all or part of the bladder may be removed. If you have CIS, or high grade Ta or T1 cancer that has not improved or has returned after treatment, your doctor may recommend this surgery. If your cancer has a high risk of spreading into the muscle, you may want to consider cystectomy as a first choice. Partial Cystectomy (removal of part of the bladder): For some people with a single, small tumor in the bladder, the surgeon does not remove the entire bladder. The surgeon removes the tumor, the part of the bladder containing the tumor, and nearby lymph nodes. After part of the bladder is removed, you may not be able to hold as much urine in your bladder as before surgery. You may need to empty your bladder more often. This problem usually gets better with time. Radical Cystectomy (removal of the whole bladder): For bladder cancer that has invaded the muscle layer (Stage 2 or some Stage 3), the most common type of surgery is radical cystectomy. The surgeon removes the entire bladder, nearby lymph nodes, and part of the urethra. In addition, the surgeon usually removes the prostate from a man and may remove the uterus from a woman. Other nearby tissues may also be removed. When the entire bladder is removed, the surgeon makes another way for urine to be collected from the kidneys and stored. You may wear a flat bag outside the body under your clothes, or the surgeon may use part of your intestine to create a pouch inside the body. Ask your doctor about the risks of cystectomy and the methods of urinary reconstruction. Also called urinary diversion, this surgery creates a new way to store and remove urine after your bladder is removed. When the prostate or uterus is removed, a man can no longer father a child and a woman can no longer get pregnant. Also, a man may be unable to have sex after surgery. If

the surgeon removes part of a woman's vagina, sex may be difficult. Because bladder cancer surgery may affect your sex life, it may help you and your partner to talk about your feelings and help one another find ways to share intimacy during and after treatment. If you have a partner, you may be worried about maintaining sexual intimacy and your relationship. If you do not have a partner, you may want help talking through how to manage your dating life after bladder cancer surgery. Either way, you (and your partner) may benefit from the advice of a counselor who specializes in discussing sexual issues. Your urologist may be able to refer you to medical professionals and counselors who specialize in sexual issues after cancer treatment. You can also find a certified sex therapist near you on the website of the American Association of Sexuality Educators, Counselors and Therapists.

It takes time to heal after surgery, and the time needed to recover is different for each person. It's common to feel weak or tired for a while.

Also, you may have pain or discomfort for the first few days. Medicine can help control your pain. Before surgery, you should discuss the plan for pain relief with your doctor or nurse. After surgery, your doctor can adjust the plan if you need more pain control.

D) **Chemotherapy**¹⁶: Chemotherapy uses drugs to kill cancer cells. It may be used to treat bladder cancer before or after surgery. One may receive chemotherapy in different ways:

- **By mouth**: Some drugs are pills that you can swallow. They may be given before or after surgery.
- **Into a vein**: For cancer that has invaded the muscle of the bladder or spread to other tissues, drugs are usually given by vein (intravenous). The drugs enter the bloodstream and travel throughout your body. Intravenous chemotherapy may also be given before or after surgery.

Chemotherapy is usually given in cycles. Each cycle has a treatment period followed by a rest period. If the drugs are given by vein or taken by mouth, the side effects depend mainly on which drugs are given and how much. Chemotherapy kills fast-growing cancer cells, but the drugs can also harm normal cells that divide rapidly:

- **Blood cells**: When drugs lower the levels of healthy blood cells, you're more likely to get infections,

bruise or bleed easily, and feel very weak and tired. Your health care team will check for low levels of blood cells. If your levels are low, your health care team may stop the chemotherapy for a while or reduce the dose of the drug. There are also medicines that can help your body make new blood cells.

- **Cells in hair roots**: Chemotherapy may cause hair loss. If you lose your hair, it will grow back after treatment, but the color and texture may be changed.
- **Cells that line the digestive system**: Chemotherapy can cause a poor appetite, nausea and vomiting, diarrhea, or mouth and lip sores. Your health care team can give you medicines and suggest other ways to help with these problems. They usually go away when treatment ends.

E) **RADIATION THERAPY**¹⁷: Radiation therapy uses high-energy rays to kill cancer cells. It may be given after surgery. Usually it's given along with chemotherapy for cancer that has invaded the muscle layer of the bladder. However, it is sometimes given instead of surgery or chemotherapy. The radiation comes from a large machine. The machine aims beams of radiation at the bladder area in the abdomen. One'll go to a hospital or clinic 5 days a week for several weeks to receive radiation therapy. Each treatment session takes about 30 minutes. Although radiation therapy is painless, it may cause other side effects. The side effects include nausea, vomiting, or diarrhea. Also, you may feel very tired during radiation therapy. Your health care team can suggest ways to treat or control these side effects.

AFTER TREATMENT¹⁷: Once treatment is completed, your doctor will want to continue to watch you closely. With bladder cancer, it can be common for tumors to come back (recur). You may be asked to visit your doctor 3 to 4 times per year to check your health. These visits may include cystoscopy. If things look good, check-ups may drop to once or twice per year over time. If you have bladder cancer, taking good care of your health is important.

- Follow a healthy eating plan.
- Exercise regularly if you can.

COPING¹⁸: Living with the concern that your bladder cancer may recur can leave you feeling as if you have little control over your future. But while there's no way to ensure that your bladder cancer won't recur, you can take steps to manage the stress. Over time you'll find what works for you, but until then, you might: Have a schedule of follow-up tests and go to each appointment. When you finish bladder cancer treatment, ask your doctor to create a personalized schedule of follow-up tests. Before each follow-up cystoscopy exam, expect to have some anxiety. You may fear that cancer has come back or worry about the uncomfortable exam. But don't let this stop you from going to your appointment. Instead, plan ways to cope with your concerns. Write your thoughts in a journal, talk with a friend or use relaxation techniques, such as meditation. Take care of yourself so that you're ready to fight cancer if it comes back. Take care of yourself by adjusting your diet to include plenty of fruits, vegetables and whole grains. Exercise for at least 30 minutes most days of the week. Get enough sleep so that you wake feeling rested. Talk with other bladder cancer survivors. Connect with bladder cancer survivors who are experiencing the same fears you're feeling. Contact your local chapter of the American Cancer Society to ask about support groups in your area.

PREVENTION¹⁹: Although there's no guaranteed way to prevent bladder cancer, you can take steps to help reduce your risk. For instance: Don't smoke. Not smoking means that cancer-causing chemicals in smoke can't collect in your bladder. If you don't smoke, don't start. If you smoke, talk to your doctor about a plan to help you stop. Support groups, medications and other methods may help you quit. Take caution around chemicals. If you work with chemicals, follow all safety instructions to avoid exposure. Drink water throughout the day. In theory, drinking liquids, especially water, may dilute toxic substances that may be concentrated in your urine and flush them out of your bladder more quickly. Studies have been inconclusive as to whether drinking water will decrease your risk of bladder cancer. Choose a variety of fruits and vegetables. Choose a diet rich in a variety of colorful fruits and vegetables. The antioxidants in fruits and vegetables may help reduce your risk of cancer.

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