What you need to know about non-muscle invasive (superficial) bladder cancer

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The Canadian Cancer Society estimates that about half of Canadians will develop cancer at some point during their lives; 25% of these people will die of the disease.

Bladder cancer is the 9th most common cancer in the world and the 6th most common cancer in Canada. There were about 7800 new cases diagnosed in Canada in 2012 (5800 men and 2000 women). Men are three times more likely to develop bladder cancer than women.

The risk of developing bladder cancer increases with age. Caucasians are at the highest risk of developing this disease, followed by African-Americans and then Latinos. Although mostly older people develop bladder cancer, it is still seen in young adults and even children.

About 75% of Canadians with bladder cancer reach the five-year survival mark. Despite advances in diagnosis and treatment, this percentage has not changed in the last 10 years.

What are the risk factors?

There are various environmental, occupational, genetic and social risk factors associated with the development of bladder cancer. You can be exposed to carcinogens (cancer-causing agents) by inhalation, absorption through the skin and ingestion- see Table 1 for a quick list of risk factors.

Smokers have up to a six times higher chance of developing bladder cancer than non-smokers, and smoking is widely regarded as the most common cause of bladder cancer. Among others, miners and rubber workers have an increased occupational risk of developing bladder cancer. This is largely due to exposure to compounds called aromatic amines, such as arsenic and benzidine. Patients with chronic or recurrent urinary tract infections are also at an increased risk of bladder cancer development. Previous pelvic or abdominal exposure to radiation also leads to a significantly higher risk of developing bladder cancer. Cyclophosphamide, a chemotherapeutic agent used in the treatment of certain cancers, may increase the risk of getting bladder cancer later in life. Although still debatable, it is claimed that the long-term use of certain painkillers such as phenacetin, and artificial sweeteners such as saccharine or cyclamates, may lead to an increased risk of bladder cancer formation. Alcohol intake has not been shown to be related to bladder cancer formation. On the other hand, a diet rich in fruits and vegetables, such as the Mediterranean diet, has been shown to be associated with a decreased risk of developing bladder cancer. Hereditary forms of bladder cancer have proven difficult to elucidate for researchers.

There are different types of bladder cancer depending on the appearance of the tumour cells under the microscope.

- Urothelial carcinoma (UC), also called transitional cell carcinoma (TCC) is the most common subtype of bladder cancer (at least 90%).
- Squamous cell carcinoma (5%)
- Adenocarcinoma (2%)

Table 1: Risk factors for bladder cancer development

Smoking
Occupational exposure to aromatic amines
Chronic urinary tract infections
Chronic catheter use
Previous radiation exposure
Previous cyclophosphamide use
Analgesic abuse

What are the symptoms of bladder cancer?

- Hematuria or blood in the urine. This can either be gross hematuria, in which the urine is visibly red and is detected by the patient him/herself, or it can be microscopic hematuria, where red blood cells are discovered microscopically while performing a urinalysis. Either way, any sign of hematuria needs more investigation. The presence of hematuria doesn't automatically mean you have bladder cancer; the blood in your urine can be caused by stones, trauma, urinary tract or prostate infections, or an enlarged prostate. Even eating beets can make your urine red!
- Urgency (the sudden, immediate urge to go to the bathroom)
- Pain upon urination
- Frequency (going to the bathroom often throughout the day)
- Pain in the side of the abdomen (or flank pain)
- Difficulty voiding

What are the tests to confirm a diagnosis?

Cystoscopy

This is one of the most common urologic procedures performed on patients in Canada and worldwide. With this procedure, a narrow flexible or rigid scope, called a cystoscope, is inserted through the urethra so that your doctor can see inside your bladder and the urethra. A lubricating gel with or without a local anesthetic is used. The cystoscope is usually connected to a screen that you and your doctor see. This procedure doesn't take long; the preparation time is longer than the actual procedure!

After the procedure, you may have a burning sensation while urinating, which usually goes away with fluid intake and frequent voiding.

- On the cystoscopy, you will be able to see lesions that look like cauliflowers or are very flat and red. The lesions may vary in size from a few millimetres to occupying almost the entire bladder. You may have one or many tumours. Any abnormality on cystoscopy will prompt your urologist to go for further investigations. See Figure 1 for an example of a flexible cystoscope.

Urine cytology

This test is usually done to rule out bladder cancer. It's also used for follow-up in patients who have a history of bladder cancer. In this test, cells that are shed by the inner lining of the bladder are examined under a microscope to check if any of them are cancerous. This test is not highly sensitive and commonly used with a cystoscopy. Your urologist may ask you for a urine sample for cytology, while performing your cystoscopy, especially if an abnormality was found. You may also be asked to perform this test more than once to improve chances of detection.

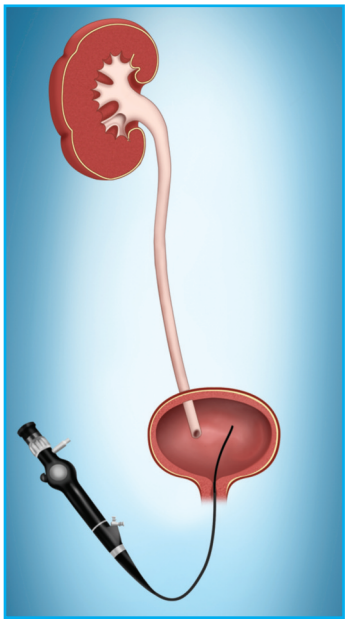

Figure 1. Flexible cystoscope.

Urine markers

Markers were developed to make bladder cancer diagnosis and follow-up less invasive. Urine markers are substances found in your urine that signal to your doctor that you may have bladder cancer. These include tests such as the BTA stat and BTA TRAK tests, ImmunoCyt test, NMP 22 and Urovysion FISH test. None of these tests have replaced conventional cystoscopy for the detection and follow-up of bladder cancer. Urologists may combine one of the above tests with a cystoscopy and urine cytology to improve your chances of detection.

Imaging studies

All patients with newly diagnosed bladder cancer undergo some form of imaging study, consisting of an ultrasound (US), intravenous pyelogram (IVP), computed tomography scan (CT scan) or magnetic resonance imaging (MRI). This is done for several reasons. To begin with, around 5 % of patients with urothelial carcinoma of the bladder (lower urinary tract) may also have urothelial carcinoma of the kidney or ureter (upper urinary tracts); so, these imaging studies are necessary to rule out such cancers. Imaging studies can also be used to assess bladder tumour size, location, and possible spread of the tumour outside of the bladder (extravesical extension).

Transurethral resection of bladder tumor (TURBT):

This is a surgical procedure in which a special cystoscope (resectoscope) is inserted through the urethra and into the bladder and is used to cut out (or resect) bladder tumours. Most bladder tumours can be resected in one procedure, although very large and extensive tumours may require staged procedures. TURBT serves both diagnostic and therapeutic goals. This is because diagnostically, the stage and grade of the disease are determined, and therapeutically, all visible tumours can be resected. You are anesthetised during this procedure because it is more painful than a regular cystoscopy and takes longer to perform. General or spinal anesthesia may be given. Ideally, the bladder tumour specimen removed must include a portion of the bladder muscle – the assessment of whether cancer is present in the muscle will influence your subsequent treatment.

Staging and grading

The pathologic staging and grading of your bladder cancer is crucial; knowing this will help you doctor choose the right treatment for you. Qualified pathologists do this after thoroughly examining the resected bladder cancer specimens under a microscope.

Pathologic stage

Your stage depends on the depth of tumour into the different layers of the bladder wall; it also takes into account any cancer spread to nearby organs. Staging follows the Tumour Node Metastasis (TNM) classification. Table 2 summarizes the T staging for bladder cancer. Figure 2 shows the different layers of the bladder wall as well as progressive bladder cancer stages.

This determination of tumor depth is important as the treatment for non-muscle invasive bladder cancer (NMIBC), or stages Ta, T1 and Tis, varies greatly from treatment for muscle-invasive bladder cancer (MIBC), stages T2 and higher. Around 70 to 75% of patients with bladder cancer present with NMIBC. Of those patients, 70 to 75% are stage Ta, whereas the remaining 25% are stage T1.

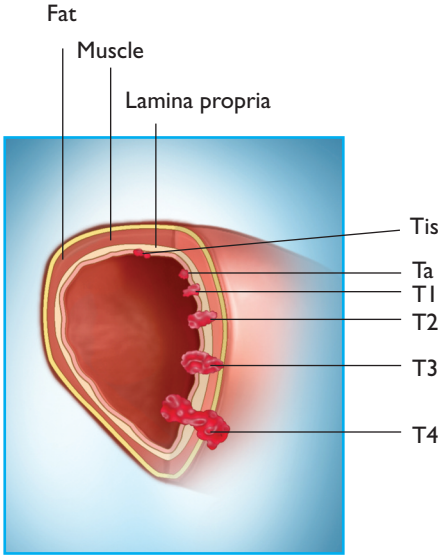

Figure 2. Bladder wall layers with tumors of different stages showing depth of invasion.

Pathologic grade

Determining your bladder tumour grade is also essential because it's an important indicator of tumour recurrence and progression. Pathologists who examine resected specimens also do determination of tumour grade. Whereas tumour stage is determined by the depth of penetration into the bladder wall, tumour grade is determined after microscopic examination of the cancer cells themselves. The greater the abnormality in certain features of the cancer cell, the higher the grade. In general, higher grade tumors are more worrying and are treated more aggressively.

Table 2. Tumour (T) staging of bladder cancer

Tx	Primary tumour cannot be assessed
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumour invades lamina propria (subepithelial connective tissue)
T2	Tumour invades muscularis propria
T2a	Invades superficial muscularis propria (inner half)
T2b	Invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue/fat
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades: prostate, seminal vesicles, uterus, vagina, pelvic or abdominal wall
T4a	Invades prostate, seminal vesicles, uterus or vagina
T4b	Invades pelvic or abdominal wall

Treatment

1. TURBT

As mentioned earlier, TURBT is done to diagnose and to treat bladder cancer. It is essential that all visible tumours be resected during surgery, and it's especially important that this resection includes a muscle layer. In some cases where no muscle is seen on initial pathology, your urologist may opt for a re-resection to accurately determine your stage and give you the best possible treatment. In some cases of Ta or T1 high-grade disease where benign muscle is found on final specimen, your urologist may still insist on a re-resection for more accurate staging and better treatment selection.

In addition to resecting all visible tumors, all suspicious areas that look "velvety" or abnormally red or boggy must also be resected or burned using the resectoscope. After the surgery, a urinary catheter is usually kept in place so that your urine drains into a bag. This catheter may be used to administer medications into your bladder after your surgery. These medications can help to destroy "floating" tumour parts and decrease the chance of the tumour coming back. The catheter is often kept overnight until the urine colour clears up, after which the catheter is removed. You may experience some discomfort and burning upon urination after the surgery. This may last a couple of weeks.

After a TURBT, you will have a raw surface that is eventually covered with normal cells. You may have blood clots and debris up to four weeks after surgery.

2. Intravesical therapy

With this, medication is inserted into your bladder. In most cases, some form of intravesical therapy is administered after TURBT. The two main forms of intravesical therapy are intravesical chemotherapy and intravesical immunotherapy (see Table 3). Chemotherapeutic agents usually cause a direct kill of cancer cells that may have remained after surgery whereas immunotherapeutic agents cause a local immune response in the bladder that helps in fighting cancer.

Table 3.

Intravesical Chemotherapy	Immunotherapy
Mitomycin-C (MMC)	Bacillus-Calmette Guerin (BCG)
Epirubicin	BCG + Interferon alpha
Doxorubicin, Valrubicin, Thiotepa, Gemcitabine	

Immediate postoperative chemotherapy instillation

It is now common to administer a single dose of an intravesical chemotherapeutic agent immediately after surgery. This is usually done within six hours (and up to 24 hours) from surgery through the urinary catheter that has already been placed. It serves to reduce recurrence rates, particularly if you have a single, low-grade non-muscle invasive tumour. The most commonly used chemotherapeutic agent in Canada is mitomycin-C (MMC). Once dissolved, the MMC solution has a dark blue to purple colour that is injected through the catheter and into the bladder. At this point, the catheter is usually clamped to allow the solution to remain in the bladder and exert its effect. The solution is kept for one to two hours in the bladder or until you can no longer tolerate it. After this, the catheter is unclamped and the solution, with all newly produced urine, is drained once again. While the catheter is clamped, you may have some discomfort as the bladder distends with increasing urine formation. The catheter is unclamped immediately if you are seriously bothered by it.

Induction therapy

In addition to an immediate postoperative instillation of a chemotherapeutic agent, you may also need induction therapy with either intravesical chemotherapy or immunotherapy. This would depend on your pathologic stage and grade and on the nature of your tumour (its appearance and number). The purpose of induction therapy is to try and decrease tumour recurrence and progression. Tumor recurrence is when the tumour simply comes back, regardless of stage and grade. Tumour progression is when the tumour that comes back is at a higher stage and/or grade. Induction therapy is usually started two to six weeks after TURBT according to a predetermined schedule that consists of weekly intravesical instillations lasting from six to eight weeks. The most commonly used agents are BCG (Bacillus Calmette-Guérin) and mitomycin C (MMC). Whereas intravesical chemotherapy (such as MMC) decreases tumour recurrence, BCG is the only agent to decrease both tumour recurrence and

progression. BCG was originally developed as a vaccine for tuberculosis and it is used for this purpose in many countries. In the 1980s, we found that inserting BCG in the bladder helps prevent tumour recurrence and progression. Unlike MMC, BCG cannot be used immediately after surgery; it has to be until two to four weeks after TURBT to allow healing of the bladder wall. This is to prevent potential side effects that may be caused by systemic absorption of the vaccine. It is usually an outpatient procedure; you come to the clinic and a catheter is inserted and your therapy is administered. After this, the catheter is removed. You void the solution through your urine.

Maintenance therapy

Maintenance therapy follows induction therapy and consists of weekly intravesical instillations at predetermined intervals that may go on for three years. Not all patients who receive induction therapy necessarily go on to receive maintenance therapy. Also, not all patients stick to their schedule of weekly visits. The most commonly used agent for maintenance therapy and the only one that has been shown to significantly reduce both tumour recurrence and progression is BCG. The most commonly followed maintenance protocol is the Lamm protocol, which consists of three weekly intravesical instillations of BCG at three and six months post-TURBT, followed by three weekly instillations every six months thereafter to complete a course of three years. BCG is usually used in patients with high-grade superficial disease; it can reduce recurrence rates to 30%.

Some forms of intravesical chemotherapy (MMC) are also used for maintenance therapy in some patients. Combinations of intravesical therapies, such as BCG and interferon, are also administered. This is sometimes done if your cancer comes back despite BCG therapy. If this is the case, you may need more radical treatment. You will usually be advised to have a radical cystectomy, which involves surgically removing the entire bladder.

Other therapies

Laser therapy

The use of laser energy to vaporize bladder tumours has gained popularity in recent years. However, it is not suitable for primary bladder tumours; the laser energy kills tumours and does not allow proper staging and grading. This is because no intact specimen containing the muscle layer can be obtained using this technique. Laser therapy is used in select patients with a known history of low-grade, low-stage tumours.

Optimized and device-assisted intravesical therapy

The objective of these devices is to enhance intravesical drug delivery into the bladder. One such therapy that has recently been approved for use in Canada is electromotive drug administration (EMDA). This is performed using a special catheter that is attached to a small electrode. In EMDA, an electric current is used to effectively deliver more of the intravesical therapy into the bladder wall. This allows you to get the best drug dosage into the bladder and also reap the benefits.

Conservative office management

Some patients may also be suitable for conservative follow-up of bladder cancer, which basically involves resection of recurrent tumors in an outpatient office setting rather than subjecting the patient to an operative procedure under anesthesia for every small recurrence. As with laser therapy, conservative management is reserved for patients with a well-known history of low-grade, low-stage disease presenting with tiny recurrences on cystoscopy.

Your follow-up visits

The bulk of your follow-up after TURBT for superficial bladder cancer includes cystoscopy. Cystoscopy at three months following TURBT is crucial. If you are tumour-free at this time, your cancer will likely not come back for a long time (reduced long-term recurrence).

Your follow-up schedule will depend on your tumour stage and grade. The most followed surveillance plan involves cystoscopy every three to four months for two years following TURBT, then every 6 months for the next 2 years, followed by a yearly cystoscopy thereafter. Follow-up regimens also commonly include urine cytology and tumour markers, as well as imaging studies.

Keep in mind:

Your follow-up schedule was put in place to try and detect potentially deadly recurrences early. You should try to adhere to your follow-up schedule.

Your challenges

Follow-up includes frequent visits to the urologist, particularly in the setting of intravesical therapy. This may be challenging if you are an elderly patient.

Long-term intravesical therapy is also sometimes a challenge. Only 20–30% of patients on maintenance BCG therapy go on to complete an entire three-year course. The complications of intravesical therapy can also be quite bothersome, and rarely fatal. However, it is important to note that the prognosis of patients with NMIBC is generally favorable.

You are not alone. Take advantage of the support groups!

Support and advocacy groups

Before 2009, there were no patient advocacy groups in Canada for patients with bladder cancer. Now we have a few:

- Bladder Cancer Canada is a charitable non-profit organization offering support and information for bladder cancer patients and caregivers. Go to **www.bladdercancercanada.org** or contact them at **info@bladdercancercanada.org** | 1-866-674-8889
- The Canadian Cancer Society is also a great resource. Go to **www.cancer.ca** for information on recent statistics and for more information.
- The Canadian Urological Society (CUA) is the voice of urology in Canada. The CUA has patient information on its website at **www.cua.org**.

Other online sites for patients with bladder cancer:

- **www.blcwebcafe.org**
- **www.bcan.org**
- **www.cancerview.ca**
- **www.wellspring.ca**