

Bladder cancer: When it invades the muscle

Dr. Ronald Moore
Urologist

Professor Surgery and Oncology, University of Alberta, Division of Urology, Edmonton, AB, Canada

Sarah J. Moore
Medical Student
University of Melbourne, Melbourne, Australia

Most (80%) bladder cancers are superficial tumours. This means that the tumour is in the lining of the bladder and not in the muscle wall of the bladder. However, 20% of these cancers can progress to muscle invasive bladder cancer or high risk non-invasive bladder cancers that require more aggressive treatment. This happens when the cancer spreads from the lining to the muscle wall of the bladder. These muscle invasive tumours are highly lethal and can spread (metastasize) to anywhere in the body. Despite aggressive treatment, a little more than half of patients survive more than five years.

The best way to deal with this type of cancer is to completely remove the bladder (radical cystectomy) and surrounding structures (lymph nodes, prostate, anterior vaginal wall), and to create a new way to store urine (urinary diversion). The goal of treatment is either to cure or to relieve your symptoms.

Let's start by looking at the anatomy we're dealing with

Anatomy

The urinary system includes two kidneys, two ureters, the bladder and the urethra. The kidneys filter the blood to create urine which contains toxins and waste products. The urine is then transported from the kidneys to the bladder through tubes called ureters. The bladder's function is to store urine, until it's time to urinate, and then it pushes the urine out through the urethra.

The bladder and ureters are lined with urothelium (a special type of cell) that protects it from the harsh toxins found in the urine. These cells are surrounded by muscle that helps to get rid of the urine. It is this muscle that can be invaded by the cancer cells.

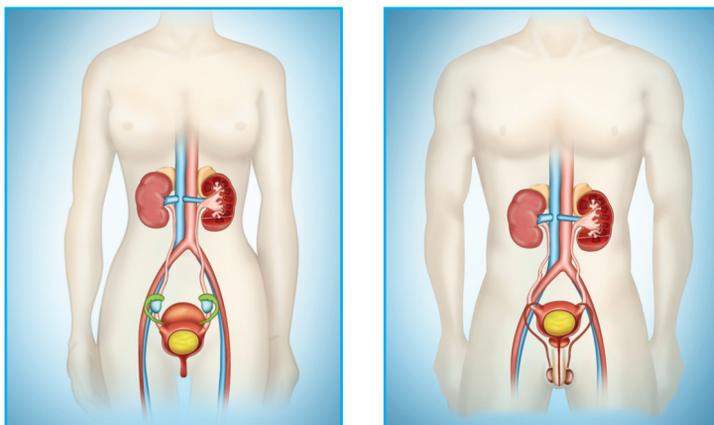


Figure 1. Normal anatomy of the male and female urogenital system **A.** Female anatomy with the reproductive organs surrounding the bladder. These include the vagina, uterus, fallopian tubes, and ovaries. **B.** Male anatomy with the reproductive organs associated with the bladder. These include the prostate, the seminal vesicles, and the ampulla of the ductus (vas) deferens.

The urinary system is intimately linked with our reproductive organs. In men, this includes the prostate, seminal vesicles and the vas deferens (tubes which transfers the sperm from the testes). In women, this includes the vagina, uterus, fallopian tubes and ovaries. Take a look at Figure 1 for a diagram of both anatomies).

Because the urine is stored in the bladder and is in contact with the urothelium (this is the tissue layer that lines most of the organs in the urinary system, including the bladder) for a long time, it's more likely for cancers to occur in the bladder. However, these same cancers can occur in the lining of the ureters and the kidneys and spread into the bladder (although this is rare).

All these organs are supplied with blood which travels to them through arteries and returns in veins. What leaks out between the arteries and veins during exchange of nutrients in the capillaries (the tiniest of vessels wrapped around the cells) is called lymph, which is blood lacking cells. This lymph fluid is collected by lymphatic vessels which are filtered by lymph nodes. The lymph nodes house the body's immune cells and help fight infection. Abnormal cancer cells can enter the lymphatics and get trapped in these filters (lymph nodes).

Risk factors

You are at risk for developing bladder cancer if:

- You are exposed to carcinogens: smokers, petro chemical workers, dye handlers. The most common risk factor is smoking. If you continue to smoke after being diagnosed with superficial bladder cancer, you have a chance of cancer recurrence and cancer progression to muscle invasive disease.
- You have been previously treated with pelvic radiotherapy or chemotherapy.
- If you have chronic bladder infections.
- If your bladder is not working properly.
- If you have high-risk superficial bladder cancer, your cancer may spread to the muscle wall of your bladder. It's important for you to follow your doctor's instructions and to go to your follow-up appointments. These visits may include bladder check cystoscopies (where the lining of your bladder is checked using a camera that goes into the bladder through the urethra) and intravesical therapies (when medications are put in the bladder). High-risk superficial bladder cancer means:
 - Your cancer is flat and hidden in the normal urothelial lining (carcinoma in situ, or CIS).
 - You have cancer cells in your urine.
 - Your intravesical therapy has failed.
 - There are signs that the tumour is spreading to a layer above the muscle (lamina propria).
 - If this is the case, your bladder would need to be removed (especially if it is not working properly).

Natural history of muscle invasive bladder cancer

- If your cancer is untreated, it can spread within the bladder and reduce your bladder capacity, ruining the function of your bladder and cause a blockage in the ureters and/or urethra which can result in kidney failure.
- Further growth can spread to your reproductive organs and intestines.
- It can also invade the blood stream or lymphatics and spread throughout your entire body.
- Most patients will die of this cancer within two to three years if it is left untreated.
- Even with the most aggressive treatment, the best case scenario is a 50% five-year survival at the time of diagnosis.
- So, it's very important to make the diagnosis at an early stage.

How do you know how bad my cancer is?

Staging simply means to determine the extent (burden) of the bladder cancer. The international staging system for bladder cancer is called the TNM system – see Figure 2 for a diagram of the different stages.

The TNM staging system:

T = tumour and describes the size of the tumour and whether it has spread to nearby tissue

N = lymph nodes and describes whether or not the tumour involves the lymph nodes

M = metastasis and describes if the tumour has spread to other sites throughout the body

For lymph nodes:

N₀ = no regional lymph node spread

N₁ = limited involvement; cancer spread to a single lymph node in the pelvis

N₂ = extensive involvement; cancer to 2 or more lymph nodes in the pelvis

N_x = unknown, lack of information

The same applies for the M status.

What sort of X-rays should I have to see how far my cancer has spread?

- A computer tomography (CT) scan.
- A physical exam.
- Recently, we developed another imaging device to see how sugar (glucose) is used by cancer cells. This device is called a positron emission tomography (PET) scanner. This device is like the CT scanner and can be used to look for metastatic disease.

If your doctor suspects that there is cancer in your ureters or kidney, you will need a retrograde pyelogram (where dye is injected back up the ureter at the time of cystoscopy) or a ureteroscopy (where a camera is passed up the ureter).

TREATMENT

Important points to remember:

- The best treatment is to completely remove your bladder (radical cystectomy) and surrounding structures (lymph nodes, prostate, anterior vaginal wall), and to create a new way to store urine (urinary diversion).
- Treatment depends on the stage of your cancer, your overall health (or performance status) and your age.
- Sometimes the doctor may not treat aggressively because the patient is likely to die of other causes. The overall health is often called the performance status of the patient.
- If you have a poor performance score or many other medical problems (comorbidities), you may not be a good candidate for aggressive surgery or chemotherapy.
- If your cancer is localized and you are otherwise healthy, your doctor will likely treat you with the goal of curing you.
- If the cancer is not curable, then chemotherapy, radiotherapy and TURBT (see other chapters for more on TURBT) can be used to relieve you of your symptoms, prolong your life and control bleeding from the bladder.

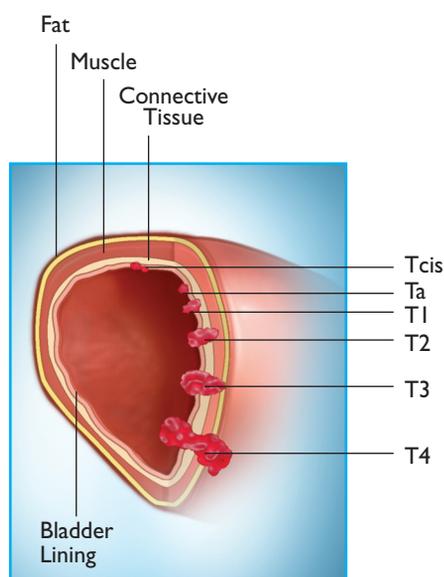


Figure 2. TNM staging of bladder cancer. N1: The cancer has spread to a single lymph node in the true pelvis.

Surgery

TURBT

A TURBT or a transurethral resection of the bladder tumour is a procedure to remove the tumour sections in your bladder. A TURBT should be as complete as possible. If you are not a candidate for radical surgery or chemotherapy, then a complete TURBT alone or with additional radiotherapy (adjuvant treatment) may be enough to control the cancer during the remaining life expectancy.

Surgically removing the diseased tissue and subsequent microscopic examination (pathology) is currently the best way to determine the stage of your bladder cancer.

Why is the stage of my cancer so important?

With this information, we can:

- Predict your long-term outcome or prognosis
- Figure out the best treatment
- Determine the best way to follow you up (surveillance)

Partial cystectomy

A partial cystectomy means that we remove part of the bladder. This surgery is considered if your tumour is small and located away from the trigone (the base of the bladder where the ureters enter and the urethra exits the bladder).

Radical cystectomy

A radical cystectomy involves complete removal of the bladder and surrounding organs.

In men, this means removing the prostate, seminal vesicles, ampulla of the vas deferens, distal ends of the ureters (part closest to bladder), surrounding fat and lymph nodes, and sometimes the urethra.

In women, this means removing the uterus, fallopian tubes, ovaries, anterior vaginal wall, surrounding fat and lymph nodes and the urethra if a neobladder (a new bladder usually made from bowel) is not planned.

Once these tissues are removed, then your doctor can create a new way to store urine. This is called a urinary diversion.

With this surgery in men, the nerves controlling erections are often injured or removed, which means a loss of erectile function. Your doctor may be able to spare the nerve loss in select patients. Also, if your prostate, seminal vesicles and ampulla of the vas deferens are removed, then you become infertile and cannot produce sperm. These organs are usually removed because advanced cancer can invade them (T4 disease) and you can develop prostate cancer. The loss of erections can be treated with drugs injected into the penis or erectile devices (penile prosthesis or vacuum pump and occlusive ring device). These treatments will allow you to engage in conventional penile vaginal intercourse. There is no loss of sensation (touch/feelings) and you can still experience an orgasm, but there is no ejaculation of semen. In very few patients, the prostate is sometimes saved when a new bladder section is created in the same place as the previous bladder (orthotopic location).

With this surgery in women, there is also nerve damage affecting the clitoris and vagina. This means that sexual pleasure is affected. Women will not be able to have children after this procedure, however most women are beyond childbearing years when they develop bladder cancer.

Lymphadenectomy

A lymphadenectomy is a procedure to remove your lymph nodes. This is an important part of the radical cystectomy for muscle invasive bladder cancer. It is known that the extent and number of lymph nodes removed affects your survival with all stages of bladder cancer.

Lymphadenectomy has been shown to produce cures (greater than five-year survival) in up to 30% of patients with lymph node metastasis. So, a lymphadenectomy is important for cure and staging to guide prognosis and adjuvant therapy. The risks of lymph node removal include injury to the blood vessels, some swelling of the legs which usually resolves and the development of a lymphocele (a balloon filled with lymph fluid).

Urinary diversion

Urinary diversion can be continent (holds urine inside the body) or non-continent (holds urine outside the body). Urinary diversion is usually performed with the bowel; however research is examining other materials, including growing bladders from cells seeded on scaffolding.

The type of urinary diversion is based on patient preference and the extent of disease, as well as how well the kidneys are functioning, how healthy the bowel is and other comorbidities.

When the bowel is placed in the urinary system, it can reabsorb waste products and salts from the urine. Different parts of the bowel reabsorb and secrete salts, water and waste products differently. For example, if your small bowel is used from close to the stomach (also called jejunal segment), then you lose more water and salt which could lead to metabolic acidosis (where your body becomes acidic). If your small bowel is used far away from the stomach (also called ileal segment), then your colon (large bowel) can reabsorb more sodium salt and ammonia waste and can lead to metabolic alkylolysis (where the body becomes more basic). Loss of large segments of bowel can result in malabsorption (poor uptake) of nutrients and vitamins as well as diarrhea. Likewise use of colon (also known as large bowel) can result in diarrhea.

Non-continent diversion

The most common non-continent urinary diversion is the ileoconduit (see Figure 3). This is usually performed using 12–20 cm of the most terminal portion of the small bowel (the most distant portion of the small intestine). However, any portion of the small or large bowel can be used avoiding the jejunum if possible. Non-continent diversion is less technically demanding and has fewer early and late complications and less metabolic problems.

After the segment of bowel is removed for the conduit, the bowel is rejoined together. The ureters are sewn to the bowel conduit over stents (drainage tubes that are later removed) and the conduit is brought out onto the skin to form a protruding nipple (stoma). Over this nipple a urostomy appliance (bag) is placed to collect the urine on the outside of the body and is normally concealed by clothing. The bag has a valve at the bottom to allow intermittent drainage as

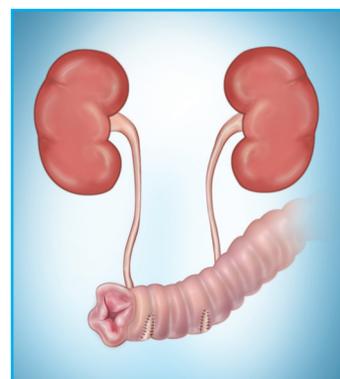


Figure 3. How the ileo conduit works. The ureters are sewn onto a short portion of small bowel (ileum) and brought out to the skin in the form of a nipple.

required. It is held on securely by glue and a belt; however it can be dislodged at times. The urostomy appliance is usually replaced every 3 days or as needed (Figure 4). An ostomy nurse is usually available to help you with long-term care. The most common early and late complications are bowel and ureteric obstruction.

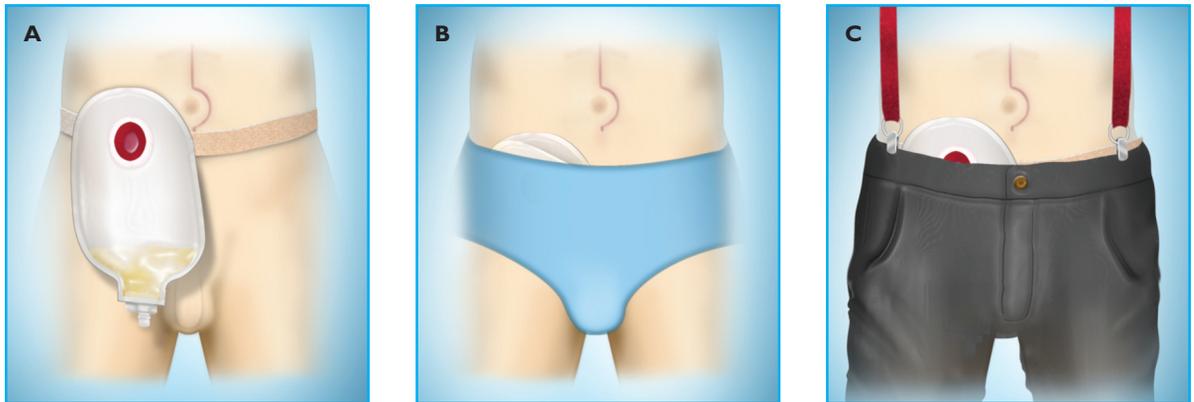


Figure 4. What the ileoconduit and urostomy appliance looks like. **A:** Ileoconduit nipple protruding through wafer into appliance bag with valve at bottom and appliance belt; **B:** Appliance hidden and supported by underwear; **C:** Appliance hidden by clothing.

Continent diversion

Continent diversion can be orthotopic (placed in the same location as the normal urinary bladder) or heterotopic (located elsewhere). The initial form of this type of diversion was to place the ureters into the side of the sigmoid colon (bottom section of the large bowel). The urine was stored with fecal waste and expelled at the time of bowel movement (defecation). This type of diversion where the urine is mixed with the fecal material has a higher risk of developing colon cancer and is now not usually performed.

Now, the most commonly used portion of bowel for continent diversion is the terminal ileum (last segment of small bowel), the proximal (beginning of) large bowel or a combination of both. The bowel has to be reshaped into a sphere to reduce pressure in the new bladder (neobladder). If the urethra and the urethral valve (sphincter) are preserved, then the neobladder can be placed orthotopically (normal spot). One of the most commonly performed neobladder is called a Studer (see Figure 5).

If the urethra and valve have to be removed for cancer control, then the neobladder is placed elsewhere with a one-way valve stoma (opening) that is catheterized to allow drainage. The one-way valve can be hidden in the umbilicus (belly-button) or located elsewhere (see Figure 6).

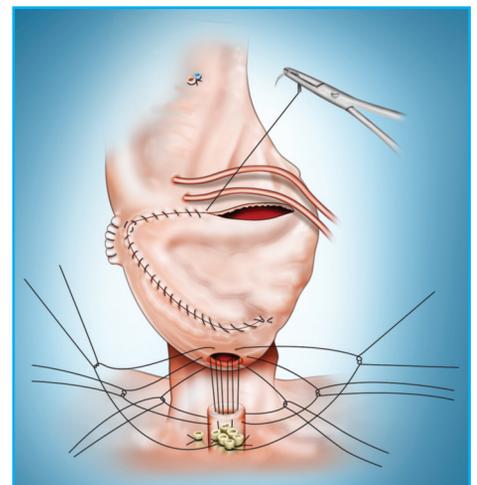


Figure 5. A Studer neobladder (orthotopic). A detubularized small bowel (ileum) being sutured closed attached to urethra. Bowel is folded to produce a sphere to store urine at the lowest possible pressure.

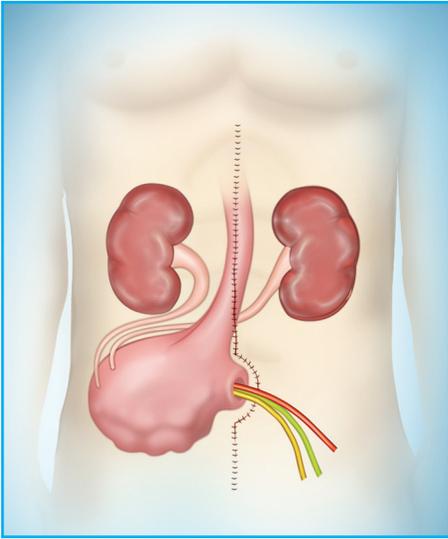


Figure 6. The catheterizable Indiana pouch (heterotopic). A detubularized large bowel (cecum) and small bowel (ileum) with catheterizable stoma and drains coming out to skin at umbilicus (belly button).

With orthotopic urinary diversion, you learn to void by straining (bearing down) to increase pressure on the low pressure bladder. Normally this tightens the valve which you need to relax. Most patients have good control during the day, but during the night, they may lose urine as the muscle of the bowel still contracts resulting in pressure of urine against the valve which may be compromised after bladder and prostate removal. Some doctors keep a portion of the prostate in the patient (as opposed to total removal) to improve urine control and to avoid loss of erectile function. This decision is balanced with the risk of leaving prostate and bladder cancer which can be difficult to manage.

With the heterotopic neobladder, you need insert a soft plastic/rubber tube yourself through the one-way stoma three to four times a day (sometimes more) to empty the bladder (this is called self-catheterization). You need good hand coordination. As long as the neobladder is completely emptied, there is little risk of infection. You may also have to rinse the neobladder to make sure it is clear of mucus. This is required more frequently at first.

If you have an orthotopic neobladder, you may also need to self-catheterize to rinse your bladder in case you can't completely empty it and to make sure it is clear of mucus. Continent urinary diversion requires a longer length of bowel (up to 90 cm). Neobladders result in greater reabsorption of waste products and salts requiring the kidneys to work harder. As such, good renal (kidney) function is required and it is important that it is assessed prior to planning surgery. Most centres require a creatinine clearance (a measure of renal function) of greater than 60 mL/minute before recommending continent diversion. Neobladders are at higher risk for requiring additional surgery for ureteric and stomal strictures (scar tissue that narrows or blocks these tubes). The incidence of this can be 20–30%.

You are not a candidate for continent diversion if:

- You are an elderly patient with other medical problems
- You have a spinal cord injury, such that you can't look after the neobladder
- You live in a remote area, far away from a specialized neobladder care
- You have renal disease that is likely to progress (proteinuria [protein in the urine] and low creatinine clearance)
- You have a bowel disease (Crohn's disease, ulcerative colitis, prior bowel resections)
- You have had high-dose radiotherapy to the abdomen and pelvis

Minimally invasive surgical techniques are being developed to reduce wound (incisional) complications. These include laparoscopic surgery done through large trocar type needle ports with a camera and working instruments placed inside an inflated belly through these ports. This type of surgery aims to have smaller openings into the abdomen and pelvis in hopes that it will speed recovery. However, the operation inside is just as extensive and carries similar risks. The operation usually takes longer and is now being done with the aid of robotic controls.

As of today, the minimally invasive operations seem to have the same outcomes as conventional open operations.

Complications of radical cystectomy

- Intestinal blockage (as high as 23%)
- Infection (second most common at 20%)
- Incisional hernia and bursting open of the wound (15%)
- Parastomal (around the stoma) hernias, in which the organs around the stoma are displaced (20-40%)
- Deep vein thrombosis (8%): a blood clot in a major vein that usually develops in the legs and/or pelvis
- Lymphoceles (balloon filled with lymph) (5%)
- Your risk of death depends on your health and other medical issues

Chemotherapy

Chemotherapy can be given before surgery or radiotherapy (neoadjuvant) or after surgery (adjuvant). Chemotherapy is most effective when there are a small number of cancer cells. It has a greater proven benefit when given in an neoadjuvant setting.

If you have chemotherapy before surgery or radiotherapy, then your survival increases by 5–7%. Up to 30% of patients treated with neoadjuvant therapy are tumour-free in the removed bladder. They have an increased five-year survival after their radical cystectomy.

Chemotherapy can also be given when the cancer has spread. When there is bulky spread of cancer in many places, chemotherapy usually doesn't cure the cancer, but slows the growth and delays death. This type of chemotherapy is referred to as palliative. The complete response rate can be as high as 36%, but over 66% of these patients relapse.

Things to know about chemotherapy in bladder cancer

- The most active single agent is cisplatin.
- Cisplatin is usually combined with methotrexate, vinblastine, adriamycin (MVAC) or gemcitabine.
- Gemcitabine + cisplatin is better tolerated than MVAC (methotrexate + vinblastine + adriamycin + cisplatin), but we are not clear on whether it is as effective.
- Cisplatin is harsh on the kidneys and the peripheral nervous system especially the hearing. These drugs are given directly into a vein in cycles with marked hydration (fluid loading) to produce a brisk diuresis (high urine production).
- If you have kidney or hearing problems, cisplatin is sometimes substituted with carboplatin.
- Carboplatin is not as effective as cisplatin and has more bone marrow toxicity. These cytotoxic agents selectively affect rapidly proliferating (dividing) cancer cells as well as normally rapidly proliferating cells in the body such as the bone marrow (the location of blood cell production) and the intestinal cells. As a result, one of the risks of chemotherapy is infection.
- If you have an infection, you cannot have chemotherapy until the infection is treated.
- With a 20% incidence of infection with radical cystectomy, adjuvant chemotherapy can be significantly delayed after cystectomy.
- Chemotherapy is also toxic to the heart and its use may be limited if you have cardiac disease.
- It can also cause blood clots (DVTs).
- Before going on chemotherapy, you have to have a good performance status (as discussed earlier).
- If you've had neoadjuvant chemotherapy and it hasn't worked, we have no other plan B after MVAC or gemcitabine and cisplatin.
- The best we can do at this point is to give you vinflunine and make sure your pain is relieved. The delay in cancer growth is short lived and overall survival is low and overall toxicity higher. You may be able to enter a clinical trial to test more drugs. Ask your doctor about this.

Things to know about radiotherapy in bladder cancer

- Radiotherapy has a significant role to play in MIUCB, but is limited by the amount (volume) of remaining cancer, the function of bladder, and by subsequent recurrences or progression of the cancer requiring close follow-up.
- Radiation generates a fibroproliferative healing process generating a large amount of scar tissue that can impair normal bladder function and make subsequent surgery, especially a thorough lymphadenectomy very difficult.
- Radiotherapy may limit the ability to perform a neobladder urinary diversion.
- It causes an abnormal blood vessel production and results in bladder and rectal bleeding. Radiotherapy combined with chemotherapy is the preferred treatment for small cell carcinoma of the bladder (a rare and special type of cancer).
- In patients that have bulky disease that cannot be resected, palliative radiotherapy can slow growth, reduce pain and prevent or reduce bleeding.

News about clinical trials for radiation therapy

- Further bladder preservation trials are ongoing with newer agents.
- Right now, these newer agents are saved for patients that are not suitable surgical candidates or are highly motivated to keep their bladder and are accepting of the risks and long-term side effects.
- This treatment with multiple therapies requires the close coordination of urologists, radiation and medical oncologists.

Follow-up

With any form of treatment for muscle invasive bladder cancer, close follow-up is important because of the high rate of recurrence and complications following treatment.

At the very least, you should be followed closely for five years. However, urothelial cancer carries a life-long risk of recurrence especially if the bladder is not removed. The chance of developing cancer in the upper tract (ureter and kidney) is low (5%), however there is risk of developing metabolic complications when the bowel is placed in the urinary tract and stricturing of the ureters where they join the bowel.

The follow-up regimen is usually driven by the stage (T,N,M), modality of treatment and associated carcinoma in-situ (CIS).

1. The first follow-up includes a physical exam, liver function tests, renal function tests, and ultrasonography at three months.
2. At six months, these investigations are sometimes repeated with a CT scan to look more closely for recurrent disease.
3. These investigations are repeated again at one year and then yearly depending on disease risk.
4. If you have a neobladder, the urethra needs to be monitored for recurrence of disease, especially if you've had a cystectomy for CIS.