

Treating Bladder Cancer

If you've been diagnosed with bladder cancer, you'll likely need more <u>tests</u> so your doctors can learn more about your cancer. Your treatment team will then discuss your options with you. It's important to weigh the benefits of each treatment option against the possible risks and side effects.

How is bladder cancer treated?

Depending on the stage of the cancer and other factors, treatment options for people with bladder cancer can include:

- Bladder Cancer Surgery
- Intravesical Therapy for Bladder Cancer
- Chemotherapy for Bladder Cancer
- Radiation Therapy for Bladder Cancer
- Immunotherapy for Bladder Cancer
- Targeted Therapy Drugs for Bladder Cancer

Common treatment approaches

Surgery, alone or with other treatments, is used to treat most bladder cancers.

Early-stage bladder tumors can often be removed. But a major concern in people with early-stage bladder cancer is that new cancers often form in other parts of the bladder over time. Removing the entire bladder (with a radical cystectomy) is one way to lower the risk of the cancer coming back, but it causes major side effects. If the entire bladder is not removed, other treatments may be used to try to lower the risk of new cancers. Whether or not other treatments are given, close follow-up is needed to watch for signs of new cancers in the bladder. Surgery is also often part of the treatment for more advanced bladder cancers, although other treatments are typically used as well, sometimes even before surgery.

• Treatment of Bladder Cancer, Based on the Stage and Other Factors

Who treats bladder cancer?

Based on your treatment options, you might have different types of doctors on your treatment team. This might include:

- **Urologist:** A doctor who specializes in treating diseases and conditions of the urinary system and male reproductive system
- Radiation oncologist: A doctor who treats cancer with radiation therapy
- **Medical oncologist:** A doctor who treat cancer with medicines such as chemotherapy, immunotherapy, and targeted therapy

You might have many other specialists on your treatment team as well, including physician assistants (PAs), nurse practitioners (NPs), nurses, nutrition specialists, pharmacists, social workers, and other health professionals.

Health Professionals Who Are Part of a Cancer Care Team

Making treatment decisions

It's important to discuss all of your treatment options, including goals and possible side effects, with your doctors to help make the decision that best fits your needs. Some important things to consider include:

- Your age and overall health
- The stage and grade of your cancer
- The likelihood that treatment will cure your cancer or help in some other way
- Your feelings about the possible side effects from treatment

You may feel that you need to decide quickly, but it's important to give yourself time to absorb the information you have just learned. It's also very important to ask questions if there is anything you're not sure about.

It is often a good idea to seek a second opinion. A second opinion can give you more information and help you feel more confident about the treatment plan you choose.

- Questions to Ask About Bladder Cancer
- <u>Seeking a Second Opinion</u>

Thinking about taking part in a clinical trial

Clinical trials are carefully controlled research studies that are done to get a closer look at promising new treatments or procedures. Clinical trials are one way to get state-ofthe art cancer treatment. In some cases they may be the only way to get access to newer treatments. They are also the best way for doctors to learn better methods to treat cancer.

If you would like to learn more about clinical trials that might be right for you, start by asking your doctor if your clinic or hospital conducts clinical trials.

<u>Clinical Trials</u>

Considering complementary and alternative methods

You may hear about alternative or complementary methods to relieve symptoms or treat your cancer that your doctors haven't mentioned. These methods can include vitamins, herbs, and special diets, or other methods such as acupuncture or massage, to name a few.

Complementary methods are treatments that are used **along with** your regular medical care. **Alternative** treatments are used **instead of** standard medical treatment. Although some of these methods might be helpful in relieving symptoms or helping you feel better, many have not been proven to work. Some might even be harmful.

Be sure to talk to your cancer care team about any method you are thinking about using. They can help you learn what is known (or not known) about the method, which can help you make an informed decision.

<u>Complementary and Integrative Medicine</u>

Help getting through cancer treatment

People with cancer need support and information, no matter what stage of illness they may be in. Knowing all of your options and finding the resources you need will help you make informed decisions about your care.

Whether you are thinking about treatment, getting treatment, or not being treated at all, you can still get supportive care to help with pain or other symptoms. Communicating with your cancer care team is important so you understand your diagnosis, what treatment is recommended, and ways to maintain or improve your quality of life.

Different types of programs and support services may be helpful, and they can be an important part of your care. These might include nursing or social work services, financial aid, nutritional advice, rehab, or spiritual help.

The American Cancer Society also has programs and services - including rides to treatment, lodging, and more - to help you get through treatment. Call our Cancer Knowledge Hub at 1-800-227-2345 and speak with one of our caring, trained cancer helpline specialists. Or, if you prefer, you can use our chat feature on cancer.org to connect with one of our specialists.

- Palliative Care
- Programs & Services

Choosing to stop treatment or choosing no treatment at all

For some people, when treatments have been tried and are no longer controlling the cancer, it could be time to weigh the benefits and risks of continuing to try new treatments. Whether or not you continue treatment, there are still things you can do to help maintain or improve your quality of life.

Some people, especially if the cancer is advanced, might not want to be treated at all. There are many reasons you might decide not to get cancer treatment, but it's important to talk to your doctors as you make that decision. Remember that even if you choose not to treat the cancer, you can still get supportive care to help with pain or other symptoms.

If Cancer Treatments Stop Working

The treatment information given here is not official policy of the American Cancer Society and is not intended as medical advice to replace the expertise and judgment of your cancer care team. It is intended to help you and your family make informed decisions, together with your doctor. Your doctor may have reasons for suggesting a treatment plan different from these general treatment options. Don't hesitate to ask your cancer care team any questions you may have about your treatment options.

Bladder Cancer Surgery

Surgery is part of the treatment for most bladder cancers. Different types of surgery might be done, depending on the <u>stage</u>¹ (extent) of the cancer, as well as a person's overall health and preferences.

- Transurethral resection of bladder tumor (TURBT)
- Cystectomy
- More information about Surgery

Transurethral resection of bladder tumor (TURBT)

During a transurethral resection of bladder tumor (TURBT), or transurethral resection (TUR), the doctor removes any tumors from the inner lining of the bladder, as well as some of the muscle layer of the bladder wall around the tumors.

TURBT is often used to find out if someone has bladder cancer and, if so, whether the cancer has grown into (invaded) the muscle layer.

TURBT is also the most common treatment for superficial bladder cancer, also known as **non-muscle invasive bladder cancer (NMIBC)**. Most people with bladder cancer have NMIBC when they're first diagnosed, so this is usually their first treatment. Sometimes, a second, more extensive TURBT is done, usually a few weeks later, to help ensure that all the cancer has been removed. The goal is to take out the cancer cells and nearby tissues down to the muscle layer of the bladder wall.

How a TURBT is done

This procedure is done using a long, thin instrument put in through your urethra, so there's no cutting into the skin. You'll get either general anesthesia, which puts you into a deep sleep so you don't feel pain, or regional anesthesia, which numbs the lower part of your body.

A type of thin, rigid cystoscope called a **resectoscope** is put into your bladder through your urethra. The resectoscope has a small telescope the doctor can see through and a wire loop at the end that's used to remove any abnormal tissues or tumors. The

removed tissue is <u>sent to a lab for testing</u>².

After the tumor is removed, more steps may be taken to try to ensure that there is no more cancer in the bladder wall. For instance, the tissue in the area where the tumor was may be burned (using an electrical current) while being viewed through the resectoscope. This is called **fulguration**. Cancer cells can also be destroyed using a high-energy laser through the resectoscope. Most often, medicine is given into the bladder at some point after the TURBT to try to kill any remaining cancer cells. This is known as intravesical therapy.

Possible side effects

The side effects of TURBT are generally mild and don't usually last long. Right after TURBT you might have some bleeding and pain when you urinate. You can usually go home the same day or the next day and can return to your usual activities within a week or two.

Even if the TURBT removes the tumor completely, bladder cancer often comes back (recurs) in other parts of the bladder. This might be treated with another TURBT. But if TURBT needs to be repeated many times, the bladder can become scarred and might not be able to hold much urine. This can lead to side effects like frequent urination, or even incontinence (loss of control of urine).

In people with a long history of recurrent, non-invasive low-grade tumors (slow-growing tumors that keep coming back), the surgeon may just use fulguration to burn small tumors that are seen during cystoscopy rather than removing them. This can often be done using local anesthesia (numbing medicine) in the doctor's office. It's safe but can be mildly uncomfortable.

Cystectomy

If bladder cancer has invaded the muscle layer of the bladder wall (muscle-invasive bladder cancer, or MIBC), or if there's a high risk it might invade the muscle, all or part of the bladder may need to be removed. This operation is called a **cystectomy**.

Partial cystectomy

If the cancer has invaded the muscle layer of the bladder wall but it's not very large and is only in one place, it can sometimes be removed along with part of the bladder wall, without taking out the whole bladder. The hole in the bladder wall is then closed with stitches. Nearby lymph nodes are also removed and tested for cancer spread. Only a small portion of people with MIBC can have this surgery. The main advantage of this surgery is that the person keeps their bladder and doesn't need reconstructive surgery (see below). But the remaining bladder may not hold as much urine, which means they'll have to urinate more often. The main concern with this type of surgery is that cancer might still occur in another part of the bladder wall. Because of this risk, this approach isn't used very often.

Radical cystectomy

If the cancer is larger or is in more than one part of the bladder, a radical cystectomy is often the best option. This operation removes the entire bladder and nearby lymph nodes. In men, the prostate and seminal vesicles are also removed. In women, the ovaries, fallopian tubes (tubes that connect the ovaries and uterus), the uterus (womb), cervix, and a small part of the vagina are removed, too.

How a cystectomy is done

General anesthesia, which puts you into a deep sleep, is used for either type of cystectomy.

A cystectomy might be done through a long cut (incision) in the belly (known as an "open" approach). In some cases, the surgeon may operate through several smaller incisions using special long, thin instruments, one of which has a tiny video camera on the end to see inside your body. This is called **laparoscopic surgery**. It might also be referred to as "minimally invasive" or "keyhole" surgery.

Most often, laparoscopic surgery is done with the surgeon sitting at a control panel in the operating room and using robotic arms to do the surgery. Known as a **robot**-**assisted cystectomy**, or just **robotic cystectomy**, this type of surgery tends to result in less pain and quicker recovery because of the smaller cuts. But it hasn't been around as long as the standard type of surgery, so there isn't long-term data yet to show if it works as well.

Regardless of which approach is used, it's important that a cystectomy is done by a skilled surgeon with experience in treating bladder cancer. If the surgery is not done well, the cancer is more likely to come back.

You'll probably need to stay in the hospital for about a week after the surgery. Hospital stays tend to be a few days shorter after robotic cystectomy than after an open cystectomy. You can usually go back to your normal activities after several weeks.

Reconstructive surgery after radical cystectomy

If your whole bladder is removed, you'll need another way to store urine and pass it out of your body. Several types of reconstructive surgery can be done.

For more details on these different approaches, see <u>Types of Urostomies and Pouching</u> <u>Systems</u>³.

Incontinent diversion (standard or conventional urostomy)

One option may be to detach and clean a short piece of your small intestine (from the section known as the **ileum**) and then connect it to the ureters (the tubes that carry urine out of the kidneys). One end of the section is then connected to an opening (**stoma**) in the skin on the front of your belly. This creates a passageway, known as an **ileal conduit**, for urine to pass from the kidneys to the outside of the body.

After this procedure, a small bag can be attached to the skin around the stoma to collect the urine. Urine slowly drains out non-stop, so the bag must be worn all the time and emptied when it's full. This is called an **incontinent diversion**, because you can't control the flow of urine out of your body.

Continent diversion (continent urostomy)

In a continent diversion, a pouch is made from a piece of intestine that's attached to the ureters. One end of the pouch is connected to an opening (stoma) in your skin on the front of your belly. A one-way valve is created at this opening. This allows urine to be stored in the pouch. You then empty it several times a day by putting a thin drainage tube (catheter) into the stoma through the valve. Some people prefer this method because there's no bag on the outside.

Neobladder

This method routes the urine back into the urethra, so you pass urine the same way you did before the operation. To do this, the surgeon creates a new bladder (neobladder) from a piece of intestine. As with the incontinent and continent diversions, the ureters are connected to the neobladder. The difference is that the neobladder is also attached to the urethra. This lets you urinate normally on a schedule. You won't have the urge to urinate, so a schedule is needed. Over time, most people regain the ability to urinate normally during the day, but incontinence at night may be a problem.

Urinary diversion without a cystectomy

In some situations, such as if the cancer has spread or if it can't be removed with a cystectomy, some type of diversion may be made without taking out the bladder. In this case, the purpose of the surgery is to prevent or relieve blockage of urine flow, rather than as part of treatment to try to cure the cancer.

Risks and side effects of cystectomy

The risks with any type of cystectomy are much like those with any major surgery. Serious problems during or shortly after surgery aren't common, but they can include:

- Reactions to anesthesia
- Bleeding
- Blood clots in the legs or lungs
- Damage to nearby organs
- Infection

Most people will have at least some pain after the operation, which can usually be controlled with pain medicines.

Effects of cystectomy on urination

Bladder surgery can affect how you pass urine.

If you have had a **partial cystectomy**, this might be limited to having to go more often because your bladder can't hold as much urine.

If you have a **radical cystectomy**, you'll need reconstructive surgery (described above) to create a new way for urine to leave your body. Depending on the type of reconstruction, you might need to learn how to empty your urostomy bag or put a catheter into your stoma.

Aside from these changes, urinary diversion and urostomy can also lead to:

- Infections
- Urine leaks
- Incontinence
- Pouch stones
- Blockage of urine flow
- Absorption problems, depending on the amount of intestine that was used

The physical changes that come from removing the bladder and having a urostomy can affect your quality of life, too. Discuss your feelings and concerns with your health care team.

To learn a lot more about urostomies, see <u>Urostomy Guide</u>⁴.

Sexual effects of radical cystectomy in men

Radical cystectomy removes the prostate gland and seminal vesicles. Since these glands make most of the seminal fluid, removing them means that a man will no longer make semen. He can still have an orgasm, but it will be "dry."

After surgery, many men have nerve damage that affects their ability to have erections. In some men, this may improve over time. For the most part, the younger a man is, the more likely he is to regain the ability to have full erections. If this issue is important to you, discuss it with your doctor before surgery. Newer surgical techniques may help lower the chance of erection problems.

For more on sexual issues and ways to cope with them, see <u>Sex and the Adult Male</u> <u>With Cancer.</u>⁵

Sexual effects of radical cystectomy in women

This surgery often removes the front part of the vagina. This can make sex less comfortable for some women, though most of the time it's still possible. One option is to have the vagina rebuilt (called **vaginal reconstruction**). There's more than one way to do this, so talk with your surgeon about the pros and cons of each. Whether or not you have reconstruction, there are many ways to make sex more comfortable.

Radical cystectomy can also affect a woman's ability to have an orgasm if the nerve bundles that run along each side of the vagina are damaged. Talk with your doctor about whether these nerves can be left in place during surgery.

If the surgeon takes out the end of the urethra where it opens outside the body, the clitoris can lose some of its blood supply, which might affect sexual arousal. Talk with your surgeon about whether the end of the urethra can be spared.

For more on ways to cope with these and other sexual issues, see <u>Sex and the Adult</u> <u>Female With Cancer⁶</u>.

Sexual effects of urostomy

It's normal people to be concerned about having a sex life with a urostomy. Having your ostomy pouch fit correctly and emptying it before sex reduces the chances of a major leak. A pouch cover or small ostomy pouch can be worn with a sash to keep the pouch out of the way. Wearing a snug fitting shirt may be more comfortable. You might also choose sexual positions that keep your partner's weight from rubbing against the pouch. For more tips, see Living With an Ostomy⁷.

More information about Surgery

For more general information about surgery as a treatment for cancer, see <u>Cancer</u> Surgery⁸.

To learn about some of the side effects listed here and how to manage them, see <u>Managing Cancer-related Side Effects</u>⁹.

Hyperlinks

- 1. <u>www.cancer.org/cancer/types/bladder-cancer/detection-diagnosis-</u> <u>staging/staging.html</u>
- 2. <u>www.cancer.org/cancer/types/bladder-cancer/detection-diagnosis-staging/how-diagnosed.html</u>
- 3. <u>www.cancer.org/cancer/managing-cancer/treatment-</u> <u>types/surgery/ostomies/urostomy/types.html</u>
- 4. <u>www.cancer.org/cancer/managing-cancer/treatment-</u> types/surgery/ostomies/urostomy.html
- 5. <u>www.cancer.org/cancer/managing-cancer/side-effects/fertility-and-sexual-side-effects/sexuality-for-men-with-cancer.html</u>
- 6. <u>www.cancer.org/cancer/managing-cancer/side-effects/fertility-and-sexual-side-effects/sexuality-for-women-with-cancer.html</u>
- 7. <u>www.cancer.org/cancer/managing-cancer/treatment-</u> types/surgery/ostomies/stomas-or-ostomies.html
- 8. www.cancer.org/cancer/managing-cancer/treatment-types/surgery.html
- 9. www.cancer.org/cancer/managing-cancer/side-effects.html

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Intravesical Therapy for Bladder Cancer

With intravesical therapy, the doctor puts a liquid drug right into your bladder rather than giving it by mouth or putting it into your blood. The drug is given through a tube (urinary catheter) that's been put into your bladder through your urethra.

- When is intravesical therapy used?
- Types of medicines for intravesical therapy

When is intravesical therapy used?

Intravesical therapy is used mainly for some early-stage bladder cancers that are still only in or very close to the inner lining of the bladder, where almost all bladder cancers start.

Drugs given directly into the bladder affect the cells lining the inside of the bladder but have very little effect on cells elsewhere. This means that intravesical therapy isn't likely to be helpful in treating cancer cells that have grown deeply into the bladder wall, or cancer cells in other parts of the body.

After a transurethral resection of bladder tumor (TURBT)

A <u>TURBT</u>¹ is often done both to confirm the diagnosis of bladder cancer and to see how deeply it has invaded into the bladder wall. Often, a single dose of intravesical chemotherapy (see below) is given within a day of the TURBT. This can help lower the risk of bladder tumors coming back later.

To treat non-muscle invasive bladder cancer (NMIBC)

These early-stage cancers have not grown deep enough to reach the muscle layer of the bladder wall, nor have they spread to other parts of the body. This includes cancers that:

- Are only in the inner lining of the bladder (stage 0 bladder cancers, including carcinoma in situ [CIS])
- Have grown only into the layer below the lining (stage I bladder cancers)

Most often, intravesical therapy is used after a TURBT.

As noted above, a single dose of intravesical chemotherapy is usually given within 24 hours of the procedure.

If further intravesical treatments (immunotherapy or chemotherapy) are needed, they're usually started a few weeks later. Treatment schedules vary, depending on the <u>risk of</u> <u>the bladder cancer coming back</u>² after treatment, which treatment is used, how well the cancer responds to the treatment, and other factors:

- For some **low-risk cancers**, no further treatment might be needed.
- For **intermediate- and high-risk cancers**, intravesical therapy is often given weekly for about 6 weeks, and then less often (for about a year for intermediate-risk cancer or up to 3 years for high-risk cancer).

Your doctor will talk with you about a treatment schedule based on your bladder cancer and how it responds to treatment.

To treat muscle invasive bladder cancer (MIBC)

These cancers have reached the muscle layer of the bladder wall.

If a TURBT is done as the initial surgery (which isn't often for MIBC), a dose of intravesical chemotherapy is often given within 24 hours. But intravesical therapy isn't likely to be helpful for most stage II or higher bladder cancers because they have

already spread beyond the inner lining of the bladder wall.

More advanced bladder cancers are rarely treated with intravesical therapy.

Types of medicines for intravesical therapy

There are 2 main types of medicines used in intravesical therapy:

- Immunotherapy
- Chemotherapy

Intravesical immunotherapy

Immunotherapy helps the body's own immune system attack the cancer cells.

Bacillus Calmette-Guerin (BCG)

BCG is the most common intravesical immunotherapy for treating early-stage bladder cancer.

BCG is a vaccine made from a germ that's related to the one that causes tuberculosis (TB), but it doesn't cause serious disease. When BCG is put into the bladder as a liquid through a catheter, it helps "turn on" the immune system cells there, which then attack the bladder cancer cells.

Side effects of BCG: Treatment with BCG can cause a wide range of symptoms. It's common to have flu-like symptoms, such as fever, aches, chills, and fatigue, which can last for 2 to 3 days after treatment. It can also cause a burning feeling in the bladder, the need to urinate often, and even blood in the urine.

While getting BCG doesn't usually make people very sick, serious BCG infections can occur in people who have a weakened immune system. Though these infections are rare, this treatment typically isn't recommended for people with weakened immune systems.

If a serious infection does happen, one sign of this can be a high fever that doesn't go away. If this happens, call your doctor right away.

You might want to ask about other serious side effects you should watch for and call your doctor about.

Nadofaragene firadenovec (Adstiladrin)

This treatment is made up of a virus that contains the gene to make interferon alfa-2b, an important immune system protein. When the virus is put into the bladder as part of a liquid, it delivers the gene into the cells lining the bladder wall. The cells then start making extra interferon alfa-2b, which helps the body's immune system attack the cancer cells. Because this treatment involves adding a gene to some cells in the body, it can be thought of as a type of **gene therapy**.

Adstiladrin can be used to treat NMIBC that is at high risk of returning and that isn't being helped by treatment with BCG. It is typically given once every 3 months.

Side effects of Adstiladrin: Some people getting this treatment might have side effects such as feeling tired, having bladder spasms, feeling the need to urinate often, or having blood in the urine.

The virus used in this treatment doesn't usually cause disease in people with healthy immune systems. It's just a way to get the gene inside the cells. Still, this is a live virus that might cause more serious infections in people who have weakened immune systems. Because of this, this treatment typically isn't recommended for people with a weakened immune system.

Nogapendekin alfa inbakicept (Anktiva)

This medicine is an interleukin-15 (IL-15) receptor agonist. When put into the bladder as a liquid, it activates some of the body's immune cells, including natural killer (NK) cells and T cells, which then attack the cancer cells.

Anktiva is used along with BCG to treat NMIBC that hasn't been helped by treatment with BCG alone. Both drugs are typically given once a week for 6 weeks, then less often for up to about 3 years, for as long as they are still helpful.

Side effects of Anktiva: Side effects from this medicine can include bladder symptoms such as pain or burning when urinating, blood in the urine, or having to go more often. Because this medicine is given along with BCG, side effects from BCG (see above) are also possible.

Intravesical chemotherapy

For this treatment, a chemotherapy (chemo) drug is put right into the bladder through a catheter. These drugs kill actively growing cancer cells. Many of these same drugs can

also be given systemically (usually into a vein) to treat more advanced stages of bladder cancer. Intravesical chemotherapy is most often used when intravesical immunotherapy with BCG doesn't work or if it isn't available.

Gemcitabine and **mitomycin** are the drugs used most often for intravesical chemotherapy.

Other chemo drugs such as **valrubicin**, **epirubicin**, and **docetaxel** might also be options in some situations.

Researchers are also studying newer ways of delivering these drugs that might help them work better (see <u>What's New in Bladder Cancer Research?</u>³).

Side effects of intravesical chemo: The main side effects of intravesical chemo are irritation and a burning feeling in the bladder, and blood in the urine.

A major advantage of giving chemo right into the bladder instead of injecting it into the bloodstream is that the drugs usually do not reach and affect other parts of the body. This helps people avoid many of the side effects linked to chemo.

Hyperlinks

- 1. <u>www.cancer.org/cancer/types/bladder-cancer/detection-diagnosis-staging/how-diagnosed.html</u>
- 2. www.cancer.org/cancer/types/bladder-cancer/detection-diagnosisstaging/staging.html
- 3. www.cancer.org/cancer/types/bladder-cancer/about/new-research.html

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Chemotherapy for Bladder Cancer

Chemotherapy (chemo) is the use of drugs to treat cancer.

- How is chemotherapy given?
- When is chemotherapy used?
- Which chemo drugs are used to treat bladder cancer?
- Side effects of chemotherapy
- More information about chemotherapy

How is chemotherapy given?

Chemo for bladder cancer can be given in 2 different ways:

- Intravesical chemotherapy: For this treatment, the chemo drug is put right into the bladder. This type of chemo is used most often for bladder cancer that hasn't invaded deeply into the lining of the bladder. It's described in Intravesical Therapy for Bladder Cancer.
- Systemic chemotherapy: When chemo drugs are given in pill form or injected into a vein (IV) or muscle (IM), the drugs go into the bloodstream and travel throughout the body. Systemic chemo can affect cancer cells anywhere in the body.

When is chemotherapy used?

Systemic chemo can be used:

- Before surgery to try to shrink a tumor so that it's easier to remove and to help lower the chance the cancer will come back. Giving chemo before surgery is called **neoadjuvant therapy**.
- After surgery or sometimes after radiation therapy. This is called **adjuvant therapy**. The goal of adjuvant therapy is to kill any cancer cells that may remain after other treatments. This can lower the chance that the cancer will come back later.
- In people getting radiation therapy, to help the radiation work better.
- As a treatment for more advanced bladder cancers.

Doctors give systemic chemo in cycles, with each period of treatment followed by a rest period to allow the body time to recover. Each cycle typically lasts for a few weeks.

Which chemo drugs are used to treat bladder cancer?

Some of the most common chemo drugs used to treat bladder cancer include:

- Gemcitabine
- Cisplatin
- Carboplatin
- Paclitaxel
- Docetaxel
- Ifosfamide
- Doxorubicin
- Methotrexate
- Vinblastine
- Mitomycin
- 5-fluorouracil (5-FU)

Chemo drugs may be used alone or in combination, depending on what they're being used for, a person's overall health, and other factors. Some of the more common combinations of drugs include:

- Gemcitabine and cisplatin (or carboplatin)
- Dose-dense methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin

(DDMVAC)

Gemcitabine and paclitaxel

Some newer combinations include other types of drugs as well, such as immunotherapy drugs.

For some people, the side effects of getting more than one chemo drug might be too much to handle. For these people, treatment with a single drug, such as gemcitabine or cisplatin, may be an option.

Antibody-drug conjugates (ADCs)

These medicines are made up of a chemo drug linked to a monoclonal antibody, which is a lab-made version of an immune system protein that's designed to attach to a specific target on cancer cells. Once inside the body, the antibody part of the ADC acts like a homing device, bringing the chemo directly to the cancer cells.

ADCs that can be used to treat bladder cancer include:

- Enfortumab vedotin (Padcev)
- Sacituzumab govitecan (Trodelvy)

For more on these drugs, see Immunotherapy for Bladder Cancer.

Most bladder cancers are transitional cell (urothelial) cancers, but there are <u>other</u> <u>types</u>¹ as well, including squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. These rare types of bladder cancer may be treated with chemo drugs different from those listed above.

Side effects of chemotherapy

Chemo drugs attack cells that are dividing quickly, which is why they work against cancer cells. But they can also affect other cells in the body, which can lead to side effects.

The side effects of chemo depend on the type and dose of drugs given and how long they are taken. When chemo and radiation are given at the same time, side effects tend to be worse.

Side effects of chemo can include:

- Nausea and vomiting
- Loss of appetite
- Hair loss
- Mouth sores
- Diarrhea
- Constipation
- Increased risk of infections due to a shortage of white blood cells
- Easy bleeding or bruising, even after minor cuts or injuries, due to a shortage of blood platelets
- Fatigue due to a shortage of red blood cells

These side effects usually go away over time after treatment ends. There are often ways to lessen these side effects, and some can even be prevented. For instance, drugs can be used to help prevent or reduce nausea and vomiting. Ask your health care team about which side effects your chemo drugs may cause and what can be done to prevent and/or treat them.

Some chemo drugs can cause other, less common side effects. For example:

Drugs like cisplatin, docetaxel, and paclitaxel can damage nerves. This can sometimes lead to symptoms, mainly in the hands and feet, such as pain, burning or tingling, sensitivity to cold or heat, or weakness. This is called <u>peripheral neuropathy</u>².

Be sure to report any side effects to your medical team so that they can be treated right away. In some cases, the doses of the chemo drugs may need to be reduced or treatment may need to be delayed or stopped to keep side effects from getting worse.

More information about chemotherapy

For more general information about how chemotherapy is used to treat cancer, see <u>Chemotherapy</u>³.

To learn about some of the side effects listed here and how to manage them, see <u>Managing Cancer-related Side Effects</u>⁴.

Hyperlinks

- 1. <u>www.cancer.org/cancer/types/bladder-cancer/about/what-is-bladder-cancer.html</u>
- 2. <u>www.cancer.org/cancer/managing-cancer/side-effects/pain/peripheral-</u> <u>neuropathy.html</u>
- 3. www.cancer.org/cancer/managing-cancer/treatment-types/chemotherapy.html
- 4. <u>www.cancer.org/cancer/managing-cancer/side-effects.html</u>

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Radiation Therapy for Bladder Cancer

Radiation therapy uses high-energy radiation to kill cancer cells.

- When is radiation therapy used for bladder cancer?
- How is radiation therapy given?
- Possible side effects of radiation therapy
- More information about radiation therapy

When is radiation therapy used for bladder cancer?

Radiation therapy can be used:

- As part of the treatment for some early-stage bladder cancers, after surgery that doesn't remove the whole bladder (such as TURBT)
- As part of the treatment for people who can't have (or don't want) a cystectomy (surgery to take out the bladder)
- As part of treatment for advanced bladder cancer (cancer that has spread beyond the bladder)
- To help prevent or treat symptoms caused by advanced bladder cancer

Radiation therapy is often given along with <u>chemotherapy</u> (using drugs such as cisplatin, gemcitabine, capecitabine, or 5-FU plus mitomycin) to help the radiation work better. This is called **chemoradiation**.

How is radiation therapy given?

The type of radiation most often used to treat bladder cancer is called **external beam radiation therapy**. It focuses radiation from a source outside of the body on the cancer.

Before your treatments start, your radiation team will take careful measurements to find the exact angles for aiming the radiation beams and the proper dose of radiation. This planning session, called **simulation**, usually includes getting imaging tests such as CT or MRI scans. This helps the doctor map where the tumor is in your body. You'll be asked to empty your bladder before simulation and before each treatment.

Most often, radiation treatments are given 5 days a week for many weeks. The treatment is a lot like getting an x-ray, but the radiation is stronger. Radiation doesn't hurt. Each treatment lasts only a few minutes, but the setup time, which includes getting you into place for treatment, usually takes longer.

Possible side effects of radiation therapy

Side effects of radiation depend on the dose given and the area being treated. They tend to be worse when chemo is given along with radiation. They can include:

 Skin changes in areas getting radiation, ranging from redness to blistering and peeling

- Nausea and vomiting
- Bladder symptoms, like burning or pain when you urinate, feeling the need to go often, or blood in your urine
- Diarrhea
- Blood in stool and/or urine
- Tiredness (fatigue)
- Low blood counts, which can lead to fatigue, easy bruising or bleeding, or increased risk of infection

These effects usually go away over time after treatment, but some people can have longer-term problems. For instance:

- In some people, radiation treatments can lead to **incontinence** (problems holding urine) later on.
- Radiation can damage the lining of the bladder (**radiation cystitis**). This might cause long-term problems such as blood in the urine or painful urination.
- Nearby nerves and blood vessels might be damaged, leading to erection problems in men.

Ask your health care team what symptoms you should watch out for. If you have side effects from radiation therapy, be sure to let your health care team know. They can suggest ways to ease many of them.

More information about radiation therapy

To learn more about how radiation is used to treat cancer, see <u>Radiation Therapy</u>¹.

To learn about some of the side effects listed here and how to manage them, see <u>Managing Cancer-related Side Effects</u>².

Hyperlinks

- 1. www.cancer.org/cancer/managing-cancer/treatment-types/radiation.html
- 2. www.cancer.org/cancer/managing-cancer/side-effects.html

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Immunotherapy for Bladder Cancer

Immunotherapy is the use of medicines to help a person's own immune system recognize and destroy cancer cells. This type of treatment is sometimes used to treat bladder cancer.

- Intravesical immunotherapy
- Immune checkpoint inhibitors
- Antibody-drug conjugates
- More information about immunotherapy

Intravesical immunotherapy

These treatments are put directly into the bladder. They are used mainly for early-stage bladder cancers that haven't grown deeply into the wall of the bladder.

Bacillus Calmette-Guerin (BCG) is made from a type of bacteria related to the one that causes tuberculosis. While it doesn't usually make a person sick, it can help trigger an immune response. BCG can be put right into the bladder as a liquid. This activates immune system cells in the bladder, which then attack the bladder cancer cells.

Nadofaragene firadenovec (Adstiladrin) is made up of a virus that contains the gene to make interferon alfa-2b, an important immune system protein. When the virus is put into the bladder as part of a liquid, it delivers the gene into the cells lining the bladder wall. The cells then start making extra interferon alfa-2b, which helps the body's immune system attack the cancer cells.

Nogapendekin alfa inbakicept (Anktiva) is an interleukin-15 (IL-15) receptor agonist. When put into the bladder as a liquid, it activates some of the body's immune cells, including natural killer (NK) cells and T cells, which then attack the cancer cells.

For more details on these treatments, see Intravesical Therapy for Bladder Cancer.

Immune checkpoint inhibitors

An important part of the immune system is its ability to keep itself from attacking normal cells in the body. To do this, it uses "checkpoint" proteins on immune cells, which act like switches that need to be turned on or off to start an immune response.

Cancer cells sometimes use these checkpoints to keep from being attacked by the immune system. But drugs that target these checkpoints, called **checkpoint inhibitors**, can help restore the immune response against cancer cells.

PD-1 and PD-L1 inhibitors

Avelumab (Bavencio) targets PD-L1, a protein on cells (including some cancer cells) that helps keep the immune system from attacking them. By blocking PD-L1, this drug boosts the immune system's response against the cancer cells. This can shrink some tumors or slow their growth.

Nivolumab (Opdivo) and **pembrolizumab (Keytruda)** target PD-1, a protein on certain immune cells (called T cells) that normally helps keep these cells from attacking other cells in the body. Blocking PD-1 can allow the immune system to attack the cancer cells, which can shrink some tumors or slow their growth.

These drugs can be used in different situations to treat bladder cancer. For example:

- Pembrolizumab can be used with enfortumab vedotin (see below), to treat advanced bladder cancer.
- Nivolumab can be used along with chemotherapy to treat advanced bladder cancer.
- Avelumab can be used as an additional (maintenance) treatment in people with advanced bladder cancer that did not get worse during their initial chemotherapy treatments.
- Any of these checkpoint inhibitors can be used in people with advanced bladder cancer that starts growing again after chemotherapy.
- Pembrolizumab can be used to treat certain bladder cancers that are not growing into the muscle wall of the bladder, are not getting smaller with intravesical BCG, and are not being treated with a cystectomy.
- Nivolumab might be offered to people with muscle-invasive bladder cancer (cancer that has invaded the muscle wall of the bladder) that has been removed with surgery but is at high risk of recurring (coming back). In this situation, it is given for one year.

These drugs are given as intravenous (IV) infusions, usually every 2 to 6 weeks, depending on the drug.

Possible side effects

Side effects of checkpoint inhibitors can include:

- Fatigue
- Nausea
- Loss of appetite
- Fever
- Urinary tract infections (UTIs)
- Rash
- Diarrhea
- Constipation

Less often, more serious side effects can occur:

Infusion reactions: Some people might have an infusion reaction while getting one of these drugs. This is like an allergic reaction, and can include fever, chills, flushing of the face, rash, itchy skin, feeling dizzy, wheezing, and trouble breathing. It's important to tell your doctor or nurse right away if you have any of these symptoms while getting one of

these drugs.

Autoimmune reactions: These drugs work by basically removing one of the safeguards on the body's immune system. Sometimes the immune system starts attacking other parts of the body, which can cause serious or even life-threatening problems in the lungs, intestines, liver, hormone-making glands, or other organs.

It's very important to report any new side effects to your health care team right away. If serious side effects do occur, treatment may need to be stopped and you may get high doses of steroids to suppress your immune system.

Antibody-drug conjugates

Antibodies are proteins made by your immune system to help fight infections. Manmade versions, called **monoclonal antibodies**, can be designed to attach to a specific target, such as a protein on the surface of bladder cancer cells.

Antibody-drug conjugates (ADCs) are monoclonal antibodies that are linked to a chemo drug. Once inside the body, the antibody part of the ADC acts like a homing device, bringing the chemo directly to the cancer cells.

Enfortumab vedotin (Padcev)

Bladder cancer cells usually have the Nectin-4 protein on their surface. Enfortumab vedotin is an anti-Nectin-4 antibody attached to a chemo drug. The antibody part acts like a magnet to bring the chemo drug to the bladder cancer cells with Nectin-4 on them. The chemo enters the cancer cells and kills them.

This drug can be used **along with the immunotherapy drug pembrolizumab** (see above) in people with advanced bladder cancer.

It can also be used **by itself** to treat people with advanced bladder cancer who:

- Have already been treated with a platinum-based chemo drug (such as cisplatin) and immunotherapy (specifically, a PD-1 or PD-L1 inhibitor), OR
- Can't be treated with cisplatin for some reason, and who have already had at least one type of drug treatment

Enfortumab vedotin is infused into a vein (IV), typically once a week for 2 or 3 weeks, followed by a week off.

Common side effects include fatigue, peripheral neuropathy (a type of nerve damage that can lead to numbness or tingling in the hands or feet), nausea, taste changes, decreased appetite, diarrhea, rash, hair loss, dry eyes or vision changes, dry skin, itching, and high blood sugar levels.

Less common but **more serious side effects** can include severe skin reactions, inflammation (swelling) in the lungs, and very high blood sugar levels.

Sacituzumab govitecan (Trodelvy)

In this ADC, the monoclonal antibody part attaches to the Trop-2 protein on bladder cancer cells and brings the chemo directly to them like a magnet. Some bladder cancer cells have too much Trop-2, which helps them grow and spread.

This ADC can be used in people with advanced bladder cancer who have already been treated with a platinum-based chemo drug (such as cisplatin) and immunotherapy (specifically, a PD-1 or PD-L1 inhibitor).

This drug is infused into a vein (IV) once a week for two weeks, followed by one week off, then restarted.

Some **common side effects** of this drug include nausea, vomiting, diarrhea, constipation, feeling tired, rash, loss of appetite, hair loss, low red blood cell counts, and belly pain.

More serious side effects can include very low white blood cell counts, with an increased risk of infection, and severe diarrhea, as well as reactions when the drug is infused. Medicines are normally given before treatment with this drug to lower the chances of having a reaction.

More information about immunotherapy

To learn more about how drugs that work on the immune system are used to treat cancer, see <u>Cancer Immunotherapy</u>¹.

To learn about some of the side effects listed here and how to manage them, see <u>Managing Cancer-related Side Effects</u>².

Hyperlinks

- 1. www.cancer.org/cancer/managing-cancer/treatment-types/immunotherapy.html
- 2. <u>www.cancer.org/cancer/managing-cancer/side-effects.html</u>

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Targeted Therapy Drugs for Bladder Cancer

As researchers have learned more about the changes inside cells that cause them to become cancer cells, they have developed newer drugs that target some of these changes. These targeted drugs work differently from other types of treatment, such as chemotherapy (chemo). They may work in some cases when other treatments don't. Targeted drugs also often have different types of side effects.

- FGFR inhibitor
- Antibody-drug conjugates
- More information about targeted therapy

FGFR inhibitor

Fibroblast growth factor receptors (FGFRs) are a group of proteins on bladder cancer cells that can help them grow. In some bladder cancers, the cells have changes in *FGFR* genes, which are the genes that control how much of the FGFR proteins are made. Drugs that target cells with *FGFR* gene changes (called **FGFR inhibitors**) can help treat some people with bladder cancer.

Erdafitinib (Balversa)

This FGFR inhibitor can be used to treat advanced bladder cancer that has certain changes detected in the *FGFR3* gene, and that is still growing despite treatment with other drugs, such as chemo. This drug isn't usually given to people who are eligible for but haven't yet received an immune checkpoint inhibitor.

Erdafitinib is taken by mouth as tablets, typically once a day.

Common side effects of erdafitinib include mouth sores, feeling tired, changes in kidney or liver function, diarrhea, dry mouth, changes in fingernails or toenails, changes in mineral levels in the blood (such as phosphate and sodium), loss of appetite, changes in how things taste, low red blood cell counts (anemia), dry skin, dry eyes, and hair loss.

Other side effects can include hand-foot syndrome (redness, swelling, peeling or tenderness on the hands or feet), constipation, belly pain, nausea, and muscle pain.

This drug can also cause **eye problems**, which can sometimes be serious, so people taking this drug need to have regular eye exams and should tell their health care provider right away if they have blurred vision, loss of vision, or other visual changes.

Antibody-drug conjugates

Antibody-drug conjugates (ADCs) might also be considered a form of targeted therapy. These medicines are made up of a chemo drug linked to a monoclonal antibody, which is a lab-made version of an immune system protein that's designed to attach to a specific target on cancer cells. Once inside the body, the antibody part of the ADC acts like a homing device, bringing the chemo directly to the cancer cells.

ADCs that can be used to treat bladder cancer include:

- Enfortumab vedotin (Padcev)
- Sacituzumab govitecan (Trodelvy)

For more on these drugs, see Immunotherapy for Bladder Cancer.

More information about targeted therapy

To learn more about how targeted drugs are used to treat cancer, see <u>Targeted Cancer</u> <u>Therapy</u>¹.

To learn about some of the side effects listed here and how to manage them, see <u>Managing Cancer-related Side Effects</u>².

Hyperlinks

- 1. www.cancer.org/cancer/managing-cancer/treatment-types/targeted-therapy.html
- 2. <u>www.cancer.org/cancer/managing-cancer/side-effects.html</u>

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Treatment of Bladder Cancer, Based on the Stage and Other Factors

The treatment of bladder cancer is based mainly on the <u>clinical stage</u>¹ of the cancer when it's first diagnosed. This is your doctor's best estimate of how far the cancer has grown, based on the exams and tests done so far. The stage takes into account how deeply the cancer is thought to have grown into the bladder wall and if it has spread beyond the bladder.

Other factors, such as the size of the tumor, how fast the cancer cells are growing (the <u>grade of the cancer</u>²), and how many tumors there are, are also important, especially for non-muscle invasive bladder cancers (NMIBCs), which are earlier-stage cancers that haven't yet invaded the muscle layer of the bladder wall. These factors can be used to determine the <u>risk group of the cancer</u>³, which, in turn, can affect treatment options.

Still other factors, such as your overall health and preferences, can also affect your treatment options.

- Treating non-muscle invasive (stage 0 and stage I) bladder cancers
- Treating stage II bladder cancer
- Treating stage III bladder cancer
- Treating stage IV bladder cancer
- Treating bladder cancer that progresses or recurs

Treating non-muscle invasive (stage 0 and stage I) bladder cancers

Non-muscle invasive bladder cancers (NMIBCs) have not yet grown deep enough to reach the muscle layer of the bladder wall. They include:

- Stage 0a: Non-invasive papillary carcinoma (Ta)
- Stage 0is: Non-invasive flat carcinoma (Tis), also known as carcinoma in situ (CIS)
- **Stage I:** Cancer that has grown into the connective tissue layer of the bladder wall (T1), but that hasn't reached the muscle layer

Most often, the stage of these cancers is determined when a transurethral resection of the bladder tumor (TURBT) (also known as a transurethral resection, or TUR) is done to remove the tumor(s). **Fulguration** (using an electrical current to burn the area where the tumor was) might be done during the TURBT. This is typically followed by a dose of intravesical chemotherapy within 24 hours.

Sometimes, a second, more extensive TURBT is done (usually a few weeks later) to help ensure that all the cancer has been removed.

Whether any further treatment is needed mainly depends on which **risk group** the cancer falls into. This is a measure of how likely the NMIBC is to come back after treatment or to progress to a more invasive cancer.

Low-risk NMIBC

These are single, small, low-grade, papillary (Ta) tumors.

Usually, no further treatment is needed for these tumors.

<u>Cystoscopy</u>⁴ is then done regularly to watch for any signs that the cancer might have come back and to look for new tumors. This is usually about every 3 months to start with, but the time between exams can be extended if no new tumors are found.

In some situations, <u>imaging tests</u>⁵ of the rest of the urinary tract might also be done to check for new tumors.

Intermediate-risk NMIBC

These NMIBCs typically have one concerning feature, such as the tumor being larger or high grade, or growing into the connective tissue layer (T1); there being more than one tumor; or a tumor that has recurred (come back).

Most often, intravesical therapy (either BCG or chemotherapy) is recommended after

the TURBT. It is typically started a few weeks later and is given once a week for about 6 weeks. Sometimes intravesical therapy is continued as **maintenance therapy** over the next year to try to keep the cancer from coming back.

Another option after TURBT might be close follow-up with regular cystoscopies and other tests, without further treatment.

High-risk NMIBC

These NMIBCs typically have more than one concerning feature, such as the tumor being both high grade and either flat (CIS) or growing into the connective tissue layer (T1).

A second TURBT might be done (usually a few weeks after the first one) to help ensure that the cancer hasn't reached the muscle layer of the bladder wall. The main treatment options after TURBT include:

- Intravesical therapy with BCG, weekly for 6 weeks, then less frequently for up to 3 years
- Radical cystectomy (surgery to remove the bladder), especially for tumors with very high-risk features

If BCG isn't effective, other treatment options might include:

- Cystectomy
- Intravesical immunotherapy with nadofaragene firadenovec (Adstiladrin) or nogapendekin alfa inbakicept (Anktiva)
- Intravesical chemotherapy
- Treatment with the immunotherapy drug pembrolizumab (Keytruda)

Follow-up and outlook after treatment of NMIBC

After treatment for NMIBC, close follow-up is needed (especially if the bladder hasn't been removed), with cystoscopy about every 3 months for a least a couple of years to look for signs of the cancer coming back or new bladder tumors.

The outlook for people with **low-risk NMIBC** tends to be very good. These cancers can almost always be cured with treatment. During long-term follow-up care, more superficial cancers might be found in the bladder or in other parts of the urinary system.

Although these new cancers do need to be treated, they rarely are deeply invasive or life-threatening.

The long-term outlook for **intermediate- or high-risk NMIBC** is not quite as good as for low-risk cancers. These cancers have a higher risk of coming back, and they may return as a more serious cancer that's growing into deeper layers of the bladder or has spread to other parts of the body.

Treating stage II bladder cancer

These cancers have invaded the muscle layer of the bladder wall (T2a and T2b), but they have not grown any farther.

Transurethral resection (TURBT) is typically the first treatment for these cancers, but it's done to help determine the extent (stage) of the cancer rather than to try to cure it.

Treatment options after the TURBT might include:

- Neoadjuvant chemotherapy that includes the drug cisplatin, followed by radical cystectomy (removal of the bladder)
- Neoadjuvant chemotherapy that includes cisplatin, followed by partial cystectomy (removal of the part of the bladder wall that contains the tumor). This is only likely to be an option for certain tumors that are only in one part of the bladder.
- Cystectomy alone, for people who can't get cisplatin
- A more extensive TURBT, followed by chemoradiation, for people who can't have or don't want a radical cystectomy. This is known as bladder-preserving **trimodality therapy**.
- Radiation therapy or TURBT alone, for people who can't have a cystectomy or get chemoradiation.

For people getting a cystectomy, chemo is usually given before surgery because it's been shown to help people live longer than surgery alone.

If cancer is found in nearby lymph nodes that were removed during surgery, or if there's reason to think there's a high risk that the cancer might come back, radiation therapy may be given after surgery. Other options might include chemo, if it wasn't given before surgery or an immunotherapy drug such as nivolumab (Opdivo).

For people who have not had their bladder removed, frequent and careful follow-up exams are very important. Cystoscopy exams and biopsies are often done during the

chemo and radiation treatments. If cancer is still found in the biopsy samples, a cystectomy will likely be needed.

Treating stage III bladder cancer

These cancers have reached the outside of the bladder (T3) and might have grown into nearby tissues or organs (T4) and/or lymph nodes (N1, N2, or N3). They have not spread to distant parts of the body.

Transurethral resection (TURBT) is typically the first treatment for these cancers, but it's done to help determine the extent (stage) of the cancer rather than to try to cure it.

Treatment options after the TURBT might include:

- Neoadjuvant chemotherapy that usually includes the drug cisplatin, followed by radical cystectomy (removal of the bladder)
- Cystectomy alone, for people who can't get cisplatin
- A more extensive TURBT, followed by chemoradiation, for people who can't have or don't want a radical cystectomy. This is known as bladder-preserving **trimodality therapy**.
- Other medicines, such as the immunotherapy drug pembrolizumab (Keytruda), with or without the antibody-drug conjugate enfortumab vedotin (Padcev), especially for people who can't get cisplatin. This might shrink the cancer and allow a person to get other treatments such as a cystectomy or chemoradiation.
- Radiation therapy or TURBT alone, for people who can't have a cystectomy or get chemoradiation.

Chemotherapy (chemo) or other medicines given before surgery (with or without radiation) can often shrink the cancer, which may make surgery easier. These treatments might also kill any cancer cells that have already spread to other areas of the body.

If cancer is found in nearby lymph nodes that were removed during surgery, or if there's reason to think there's a high risk that the cancer might come back, radiation therapy may be given to these areas after surgery. Other treatment options might include chemo, if it wasn't given before surgery, or an immunotherapy drug such as nivolumab (Opdivo).

For people who have not had their bladder removed, frequent and careful follow-up exams are very important. Repeat cystoscopy exams and biopsies might be

recommended during chemo and radiation treatments. If cancer is still found in the biopsy samples, a cystectomy will likely be needed.

Treating stage IV bladder cancer

These cancers have reached the pelvic or abdominal wall (T4b) and/or have spread to distant lymph nodes (M1a) or other parts of the body (M1b). Stage IV cancers are very hard to get rid of completely.

If the cancer **has** *not* **spread to distant parts of the body (M0):** It's very unlikely these cancers could be removed completely with surgery, so medicines are usually the first treatment. Treatment options might include:

- The immunotherapy drug pembrolizumab (Keytruda) plus the antibody-drug conjugate enfortumab vedotin (Padcev)
- The immunotherapy drug nivolumab (Opdivo) plus chemotherapy
- Chemotherapy, which usually includes the drug cisplatin, if a person can tolerate it. If not, other chemo drugs might be used.
- Chemotherapy, followed by the immunotherapy drug avelumab (Bavencio)
- Pembrolizumab alone
- Chemoradiation (radiation therapy plus a chemo drug to help it work better)

After a few cycles of treatment, the cancer is typically rechecked with <u>tests</u>⁶ such as cystoscopy, TURBT, and imaging tests. Further treatment at this point might include chemotherapy and/or immunotherapy, chemoradiation, or <u>cystectomy</u> (removal of the bladder), if it can be done.

If the cancer *has spread to distant parts of the body (M1):* It's very unlikely these cancers could be removed completely with surgery, so medicines are usually the first treatment. Treatment options might include:

- The immunotherapy drug pembrolizumab (Keytruda) plus the antibody-drug conjugate enfortumab vedotin (Padcev)
- The immunotherapy drug nivolumab (Opdivo) plus chemotherapy
- Chemotherapy, which usually includes the drug cisplatin, if a person can tolerate it. If not, other chemo drugs might be used.
- Chemotherapy, followed by the immunotherapy drug avelumab (Bavencio)
- Pembrolizumab alone

After a few cycles of treatment, the cancer will probably be rechecked with tests such as cystoscopy, TURBT, and imaging tests.

If there are no signs of cancer or if it has shrunk significantly, chemoradiation or cystectomy (removal of the bladder) might be an option in some cases. If surgery is an option, it's important to understand the goal of the operation – whether it's to try to cure the cancer, to help a person live longer, or to help prevent or relieve symptoms from the cancer.

If the first treatment doesn't shrink the cancer or if it stops working (or if it does shrink the cancer and cystectomy isn't an option for some reason), further treatment with medicines (chemo and/or immunotherapy) might still be helpful. Another option might be a targeted therapy drug. (See below for more on further treatment options.)

Because these cancers are hard to cure with current treatments, many experts recommend considering taking part in a <u>clinical trial</u>⁷ that's testing a newer treatment. Talk to your doctor if this is something you think you might be interested in.

Treating bladder cancer that progresses or recurs

If the cancer continues to grow during treatment (progresses) or if it comes back after treatment (recurs), treatment options will depend on where and how much the cancer has spread, what treatments you've already had, and your overall health and desire for more treatment. It's important to understand the goal of any further treatment, such as trying to cure the cancer, slow its growth, or relieve symptoms, as well as the likely benefits and risks.

For instance, **non-muscle invasive bladder cancer** often comes back in the bladder. A new cancer may be found either in the same place as the original cancer or in other parts of the bladder. These tumors are often treated the same way as the first tumor. But if the cancer keeps coming back, a cystectomy (removal of the bladder) may be needed. For some non-invasive tumors that keep growing even with BCG treatment, other options might include immunotherapy with pembrolizumab (Keytruda) or intravesical therapy either with chemotherapy or with an immunotherapy drug such as nadofaragene firadenovec (Adstiladrin) or nogapendekin alfa inbakicept (Anktiva).

Cancers that spread or recur in distant parts of the body can be harder to remove with surgery, so other treatments, such as chemotherapy, immunotherapy, targeted therapy, or radiation therapy, might be needed. (See "Treating stage IV bladder cancer" above for an idea of what your treatment options might be.)

For more on dealing with a recurrence, see <u>Understanding Recurrence</u>⁸.

At some point, it may become clear that standard treatments are no longer controlling the cancer. If you want to continue getting treatment, your doctor may recommend taking part in a <u>clinical trial</u>⁹ of a newer bladder cancer treatment. While clinical trials might not always be the best option for everyone, they can benefit some people with bladder cancer, as well as helping other people in the future.

Even if medicines are no longer controlling the cancer, there might still be other treatments that can be helpful. For example, some treatment options that focus more on preventing or relieving problems the cancer might cause:

- Radiation therapy (or chemoradiation) might shrink or slow the growth of tumors and help relieve symptoms.
- A <u>urinary diversion</u> without cystectomy (making another path for urine to leave the body, without removing the bladder) might be an option to prevent or relieve a blockage of urine that could cause kidney damage.

It's very important to let your treatment team know about any symptoms you're having, as there are often ways to help with them.

Hyperlinks

- 1. <u>www.cancer.org/cancer/types/bladder-cancer/detection-diagnosis-</u> staging/staging.html
- 2. <u>www.cancer.org/cancer/types/bladder-cancer/detection-diagnosis-staging/how-diagnosed.html</u>
- 3. <u>www.cancer.org/cancer/types/bladder-cancer/detection-diagnosis-</u> staging/staging.html
- 4. <u>www.cancer.org/cancer/diagnosis-staging/tests/endoscopy/cystoscopy.html</u>
- 5. <u>www.cancer.org/cancer/types/bladder-cancer/detection-diagnosis-staging/how-diagnosed.html</u>
- 6. <u>www.cancer.org/cancer/types/bladder-cancer/detection-diagnosis-staging/how-diagnosed.html</u>
- 7. <u>www.cancer.org/cancer/managing-cancer/making-treatment-decisions/clinical-</u> <u>trials.html</u>

- 8. www.cancer.org/cancer/survivorship/long-term-health-concerns/recurrence.html
- 9. <u>www.cancer.org/cancer/managing-cancer/making-treatment-decisions/clinical-</u> <u>trials.html</u>

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