Advanced Prostate Cancer

Us TOO International
Prostate Cancer Education and Support Network
Advanced Prostate Cancer

Prostate cancer is called localized or early stage disease when no cancer cells have spread outside of the prostate gland. Prostate cancer is advanced when cancer cells have spread outside the prostate gland to the seminal vesicles or nearby lymph nodes* or to other parts of the body such as the bones, bladder, lungs, liver or brain. This may have occurred prior to the initial prostate cancer diagnosis, or after a man’s initial treatment for prostate cancer. When the cancer has moved from the prostate to another part of the body it has metastasized and is referred to as metastatic prostate cancer. While prostate cancer cannot be cured once it has advanced, there are several treatment options and combinations for effectively managing advanced prostate cancer.

*Lymph nodes are small glands located in many parts of the body that help defend against harmful foreign particles. Lymph nodes in the pelvic region are usually the first place to which cancer spreads outside the prostate.

PSA Tests

Once diagnosed with prostate cancer, a man must continue with regular PSA (prostate specific antigen) blood tests throughout his life to detect the possibility of a rise in the PSA, which can indicate the potential recurrence of prostate cancer. The following tests can determine the cause of the rise in PSA:

- Bone scan to detect whether the cancer has spread to the bones
- Computerized tomography (CT) scan to identify general signs of disease, such as enlarged lymph nodes or organ abnormalities that may be related to prostate cancer
- Magnetic resonance imaging (MRI) to detect spread of cancer to lymph nodes or tissues near the prostate
- The positron emission tomography (PET) scan detects cancer in the bones and is being used increasingly in place of the bone scan because it is more sensitive
- Molecular imaging (C11-choline, F18-sodium fluoride, PSMA-PET)
Treatments

Once prostate cancer has advanced, further treatment specific to the prostate gland (such as surgical removal of the prostate following initial radiation, or follow up radiation or cryosurgery) is uncommon since no studies have demonstrated that it will improve survival. Treatment options for men with metastatic disease have increased in the past several years and provide men with a significantly longer survival compared to 5-10 years ago. The challenge today is to determine the right timing and sequencing of the treatment options.

Hormone (Androgen Deprivation) Therapies

Hormone therapy, androgen deprivation therapy (ADT), or castration are directed at lowering the male sex hormone, testosterone, which stimulates the growth of prostate cancer cells wherever they are in the body. For men with locally advanced stage T3 and T4 (larger tumors with possible spread into other areas) prostate cancer, studies show that combining ADT with radiation can improve survival.

Treatments are also available that block the ability of testosterone to stimulate cancer cells. Over the last several years, other new treatments have been FDA approved giving men more options for managing and minimizing the growth of metastatic disease.

Physical Castration: Orchiectomy

Bilateral orchiectomy is an operation to remove both testicles, which produce 95% of the body’s testosterone.

Advantages of Orchiectomy
• One-time procedure
• Effective, permanent reduction in testosterone
• Minimal or no hospitalization
• Low Cost

Disadvantages of Orchiectomy
• Side effects, such as reduced or absent sexual desire, impotence, and hot flashes and emotional impact make this procedure difficult for some patients to accept, although side effects are the same as with medical castration
• Irreversible surgical procedure
• May require hospitalization in some patients
• Will not allow for intermittent androgen deprivation (IAD) therapy

Chemical Castration with Hormone Therapy: LHRH Therapy

The administration of an injectable luteinizing hormone-releasing hormone (LHRH) agonist or antagonist causes a drop in testosterone levels in the body, lowering the ability to produce testosterone.

Advantages of LHRH
• Antiandrogen therapy is not needed to prevent possible flare symptoms
• Easy subcutaneous (just under the abdomen skin) injections

Disadvantages of LHRH
• Side effects of hormone therapy, including bone weakening, hot flashes, low libido, and impotence, may be difficult to treat and hard for some people to accept
• Overall rate of adverse reactions is similar to LHRH agonists
• Injection site discomfort
• Currently only monthly injection available
LHRH agonists and antagonists are drugs that stop the body from producing LHRH, which leads to a drop in the level of testosterone in the body. Since doctors are not sure whether one is better than the other, both are reasonable choices when ADT is the treatment of choice and men wish to avoid removing the testicles.

LHRH agonists initially cause a short-term rise in the testosterone level in the body and after a few weeks it drops very low.

**Advantages of LHRH Agonists**
- Easy administration of injections every 1, 3, 4, 6 or 12 months
- Treatment with LHRH agonists is almost always as effective as orchiectomy in reducing testosterone levels
- Side effects may be reversible upon termination of the treatment so as to allow intermittent androgen deprivation (IAD) therapy

**Disadvantages of LHRH Agonists**
- Side effects of hormone therapy may be difficult to treat and hard for some people to accept
- Testosterone level rises during first two weeks of initiating therapy (flare response), which may cause increase in cancer symptoms in some men
- Requires injections every 1, 3, 4, 6, or 12 months
- May need short-term anti-androgen to reduce risk of flare response

LHRH antagonists drop the testosterone immediately, without causing any rise in the testosterone level.

**Advantages of LHRH Antagonist**
- Reduces testosterone levels quickly without the initial “testosterone surge” seen with an LHRH agonist
- Antiandrogen therapy is not needed to prevent possible flare symptoms
- Easy subcutaneous (just under the abdomen skin) injections

**Disadvantages of LHRH Antagonist**
- Side effects of hormone therapy may be difficult to treat and hard for some people to accept
- Overall rate of adverse reactions is similar to LHRH agonists
- Injection site discomfort
- Currently only monthly injection available

See [www.ustoo.org/Prostate-Cancer-Drugs](http://www.ustoo.org/Prostate-Cancer-Drugs) for the latest treatment options.

**Antiandrogen Therapy**
Antiandrogen therapy includes orally administered drugs that block the action of male hormones. This includes testosterone and androgens released by the adrenal glands or produced by prostate cancer cells. First generation anti-androgens were often used in combination with LHRH agonist therapy in a strategy called maximal androgen blockade (MAB) or combined androgen blockade (CAB). Some studies
showed longer survival with MAB compared to ADT alone. The anti-androgen is continued until the PSA rises. When the PSA rises, stopping the anti-androgen can result in a short-term benefit.

Second generation anti-androgens have been approved which improve survival and are being tested in combination with castration. With approval of the newer anti-androgens, first generation drugs are no longer used as early in the management of advanced disease. Prostate cancer that has recurred but has not yet metastasized is non-metastatic prostate cancer. Prostate cancer is castration resistant when it no longer responds to chemical castration. The newer anti-androgens have been FDA-approved to treat non-metastatic castration resistant prostate cancer (nmCRPC), and metastatic castration resistant prostate cancer (mCRPC). In both cases survival is improved.

Prostate cancer is castration sensitive when it responds to chemical castration. Treatments are available for metastatic castration-sensitive prostate cancer (mCSPC) in combination with androgen deprivation and for non-metastatic castration resistant prostate cancer (nmCRPC).

**Advantages of First Generation Antiandrogen Therapy**
- Fewer side effects than LHRH therapy
- Administered by mouth

**Disadvantages of First Generation Antiandrogen Therapy**
- Breast pain or enlargement
- Diarrhea
- Gastrointestinal pain
- Adverse effects on liver function (possible elevation of liver enzymes that must be monitored)
- Night blindness (niutamide)

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Estrogen Therapy
Administration of estrogen hormones lowers testosterone production and has some direct apoptotic effects (normal death of cells) on both androgen-dependent and androgen-independent prostate cancer cells.

Advantages of Estrogen Therapy
- Does not cause bone loss
- Does not induce androgen-independent cancer growth
- Can dramatically slow the growth of some prostate cancer cell types
- Inexpensive

Disadvantages of Estrogen Therapy
- Will cause gynecomastia (enlarged breasts in men), unless prevented by breast irradiation
- Depending on the route of administration, it may promote hypercoagulation of blood, causing blood clots in the legs, lungs, heart, and brain
- May cause heart attacks in some cases (discuss this with your doctor)
- No evidence that blood thinners significantly reduce risk of clots
- Causes decreased libido and impotence
- Risk of cardiovascular side effects is reduced when treatment is given as patch or injectable drug rather than by mouth

See www.ustoo.org/Prostate-Cancer-Drugs for the latest treatment options.

Genetic Testing
Genetics looks at specific genes responsible for inherited traits, such as hair or eye color or the risk for certain cancers. The study of genetics in prostate cancer is important. A family history increases a man’s risk for prostate cancer by 60% but a man with prostate cancer may not know his complete family history. The presence of the BRCA gene can be a high-risk indicator for prostate cancer in men as it is for breast cancer in women. These genes have a 50% chance of being passed on to children. Inherited genetic mutations, which are present in approximately 12% of men with metastatic prostate cancer, can help direct the most effective treatment regimen.

Talk to your doctor about this test and visit www.ustoo.org/genetics-and-genomic-testing for more information.
Autologous Cellular Immunotherapy
The goal of this therapy is to stimulate the body’s immune system to attack cancer cells. As of early 2020, the only approved immunotherapy for prostate cancer is sipuleucel-T. It is indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. Sipuleucel-T is given by intravenous (IV) infusion in three doses, approximately two weeks apart over the span of a month. Blood is collected a few days prior to each infusion, processed at an outside laboratory and then returned to the patient by intravenous infusion. Total course of therapy is generally completed in four to six weeks.

Advantages
• Minimal typical side effects compared to other treatment options
• Prolongs survival of men with CRPC
• Does not interfere with effectiveness of other therapies
• Therapy completed quickly

Disadvantages
• The most common side effects reported with sipuleucel-T treatment (usually occurring within the first few days of treatment) are: chills, fatigue, fever, back pain, nausea, joint ache and headache; other side effects are also possible
• In a very small number of men, sipuleucel-T can cause severe acute reactions resulting from the infusion, which typically occur within one day of infusion
• Does not lower PSA or produce measurable objective response
• Costly, but covered by most insurance companies, including Medicare

Other Drugs: P450 Enzyme Inhibitors
The P450 enzymes are involved in the synthesis of several hormones, including testosterone, that stimulate prostate cancer cell growth. Inhibitors of these enzymes can decrease the levels of testosterone and adrenal androgens, and have direct cytotoxic (toxic to living cells) effects on prostate cancer cells. Although not specifically approved for men with prostate cancer, they were used for men progressing on castration therapy but are seldom used today.

See www.ustoo.org/Prostate-Cancer-Drugs for the latest treatment options.
Advantages of P450 Enzyme Inhibitors
- May still be useful in men for whom CAB has failed (who are androgen resistant)
- Reduces both testicular testosterone and adrenal androgen production
- Additional cytotoxic effect on prostate cancer cells

Disadvantages of P450 Enzyme Inhibitors
- Not approved in U.S. for treatment of prostate cancer
- Requires continued use of LHRH agonists or estrogen therapy to block pituitary stimulation of testicular hormone production (unless the patient had an orchiectomy)
- Non-selective effects on other cells may cause discomfort (nausea, gastric irritation)
- May have significant adverse effects on liver function (must measure liver enzymes)

5-Alpha Reductase (5-AR) Inhibitors
Block conversion of testosterone to DHT, a more potent stimulator of prostate cell growth than testosterone. May delay rise in PSA. Not currently approved for use in men with prostate cancer.

Advantages of 5-AR Inhibitors
- Reduces the normal prostate cell growth and prostate size
- May reduce the risk of recurrence following surgery

Disadvantages of 5-AR Inhibitors
- Not approved as a treatment for prostate cancer
- No evidence it influences survival of men
- Causes only modest reductions in PSA levels (15-20%) when used alone

See www.ustoo.org/Prostate-Cancer-Drugs for the latest treatment options.
Systemic Radiation Therapy
Agents are injected intravenously and are taken up by cancer cells that have invaded the bones. Only radium-223 has been shown to significantly improve survival.

Advantages
• Treatment administered as a one-time injection
• Significantly improves survival in men with symptomatic bone metastases
• Patients still eligible for chemotherapy

Disadvantages
• Side effects include nausea, vomiting, diarrhea, low blood counts
• See the sections on radiation therapy and treating pain associated with advanced prostate cancer for more details

See www.ustoo.org/Prostate-Cancer-Drugs for the latest treatment options.

Chemotherapy
Chemotherapy treatment (chemo) for advanced prostate cancer is the use of chemicals that kill cells that grow and divide quickly such as cancer cells. Since chemo can work throughout the body it can also affect some fast-growing healthy cells. Chemo is a pivotal treatment option for many men with advanced or aggressive prostate cancer. It is critical to learn about the potential benefits of chemotherapy, debunk the myths and learn the facts to ensure treatments are received at the time they are the most beneficial.

Typical Side Effects
• Fatigue
• Nausea / decreased appetite (occurring in 20% of patients)
• Mouth sores
• Diarrhea (32%)
• Hair loss (65%)
• Low white blood cell count
• Increased risk of infection
• Weakness/numbness in fingers and toes

For information on chemotherapy, visit www.ustoo.org/chemotherapy.
Hormone-Resistant Prostate Cancer
Prostate cancer that is no longer responsive to hormone therapy is referred to as hormone-resistant prostate cancer, hormone refractory prostate cancer (HRPC), castrate resistant prostate cancer (CRPC) or androgen-independent prostate cancer. Several new therapies have been approved in the past several years to treat CRPC. More studies are needed to determine the optimal sequencing of these new treatments.

Advantages
- Oral agent
- Prolongs survival in men with CRPC

Disadvantages
- Must be given with prednisone
- Must be taken on an empty stomach
- Costly
- Various side effects

Clinical Trial Finder
A clinical trial is a scientific study to determine how a new medicine or treatment works in people. Through clinical trials, doctors find new and better ways to prevent, detect, diagnose, control, and treat illnesses. FDA approval of drug therapies requires a series of clinical trials.

Quick, Free, Easy Access to info on all available Prostate Cancer Clinical Trials

For more information on clinical trials or to find one as a potential treatment, visit www.ustoo.org/HCP-Clinical-Trials.
Management of Treatment Side Effects

Bone Health
It’s important to begin using a bone-building agent at the point that a man begins hormone therapy. There are many ways to help maintain bone health throughout the course of treatment. These include: diet management, exercise, vitamin D and calcium supplements, limiting salt and protein, and eliminating smoking and drinking. Talk to your doctor about the specifics of managing these changes.

Fatigue
A heart-healthy/prostate-healthy diet, regular exercise, proper rest, and stress reduction (using meditation, spirituality, and open communication with others) can all help to address fatigue. Talk to your doctor about these options.

Anxiety & Depression
Anxiety and depression are very common and affect many men with prostate cancer, at various points along their journeys. Consulting a medical health clinician (psychiatrist, social worker, or psychiatric nurse) can be invaluable. There should be no stigma in seeking help with any cancer side effect. For ways to address anxiety and depression, visit www.ustoo.org/anxiety-and-depression.

Urinary Incontinence
To address incontinence, including pelvic floor health before and after treatment, visit www.ustoo.org/incontinence.

Erectile Dysfunction
Many prostate cancer treatments have side effects that include erectile dysfunction (ED). For more information, visit www.ustoo.org/intimacy.

End-of-Life Plan
While most of the information in this brochure has been dedicated to enhancing the quality of life and empowering individuals and their loved ones through the treatment process, there are concerns that need to be addressed for those who have reached the end of their journey. Available resources that can help with the process include: pain management, hospice care, grief counseling, creating a will, and end-of-life decisions.

For more information visit www.ustoo.org/Access-Additional-Resources#end-of-life and www.prostatecancercareteam.org/Additional-Resources.
Us TOO helps men with prostate cancer learn to **fight** this disease.

The power of Us TOO is in helping men, and those who love them, by transforming resignation into **determination** and fear into **Hope**.

Find a Support Group at:  

Join an Online Support Community on Inspire at:  
[www.inspire.com/groups/us-too-prostate-cancer](http://www.inspire.com/groups/us-too-prostate-cancer)

For a Call-In Support Group Through the Answer Cancer Foundation, Visit:  
[www.ustoo.org/Join-a-Phone-Conversation](http://www.ustoo.org/Join-a-Phone-Conversation)

Call Our Toll-Free HelpLine at:  
800-808-7866 or email [ustoo@ustoo.org](mailto:ustoo@ustoo.org)

**Additional Nonprofit Prostate Cancer Organizations/Resources**
- Prostate Cancer Foundation ([www.pcf.org](http://www.pcf.org))
- Prostate Cancer Research Institute ([www.pcri.org](http://www.pcri.org))
- Prostate Conditions Education Council ([www.prostateconditions.org](http://www.prostateconditions.org))
- Prostate Health Education Network ([www.prostatehealthed.org](http://www.prostatehealthed.org))

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