MANAGING ADVANCED PROSTATE CANCER
Whether you’ve been living with prostate cancer for years or newly diagnosed, you have advanced prostate cancer when cancer cells have:

1. Spread outside the capsule of the prostate gland to the tissue around the prostate but not the lymph nodes (Stage III: localized advanced prostate cancer)

2. Prostate cancer cells have spread to the lymph nodes and/or organs and tissue distant from the prostate such as bones, liver, or lungs (Stage IV: metastatic prostate cancer)

3. Prostate-Specific Antigen, or PSA, has risen at least three consecutive times after completion of primary treatment or while on androgen deprivation therapy or hormone reduction. At this point, the disease becomes castration-resistant.

This brochure focuses primarily on Stage IV and castrate resistant prostate cancer.
There is no cure for Stage IV prostate cancer. But there is hope as many men are able to effectively manage the disease through treatments that were not available five years ago. Through these options, a patient is able to slow the progression and sometimes halt the growth of the cancer. Currently, understanding the progression of advanced prostate cancer is gauged by a rise in the PSA level.

An important and typical sign of advanced disease is a rapid rise in the PSA level during a short period of time following initial treatment such as a radical prostatectomy. Be sure to talk to your doctor to confirm because there are circumstances that may cause a temporary escalation in PSA levels.

In addition to PSA, your doctor should evaluate the testosterone level that acts as an accelerant to prostate cancer. Further, a circulating tumor test (CTC), a type of blood test, should be administered to determine if and how many prostate cancer cells have broken away from the existing tumors and entered the bloodstream. The CTC test is used together with the PSA test to effectively determine the impact a treatment is having on a patient’s cancer.

In addition to monitoring blood test results, it’s critical to know where the cancer is located. In recent years, there have been great advances in body imaging to detect prostate cancer. Talk to your doctor about your options for imaging as some may be more effective than others. Depending on the situation, your insurance may cover some imaging options, but may not cover other emerging methods.
<table>
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<tr>
<th>DETERMINING YOUR DISEASE STATE</th>
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<tr>
<td><strong>RESULT</strong></td>
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<tr>
<td>Initial Diagnosis</td>
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<tr>
<td>Initial Treatment (surgery and/or radiation)</td>
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<tr>
<td>Treatment Failure</td>
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<tr>
<td>Hormone Therapy (injections)</td>
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<tr>
<td>Treatment Failure</td>
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<tr>
<td>Secondary Hormone Therapy (emerging treatments, taken in addition to hormone shots, or clinical trials)</td>
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<tr>
<td>Treatment Failure</td>
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<tr>
<td>Treatment (radiation, immunotherapy, chemotherapy, or clinical trials)</td>
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<tr>
<td>Treatment Failure</td>
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<tr>
<td>Treatment (options not tried in previous steps or possible clinical trials)</td>
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<tr>
<td>Treatment Failure</td>
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HORMONE THERAPY

Hormone therapy, also called androgen deprivation therapy, is a prostate cancer treatment that alters the body’s hormone balance to prevent cancer from growing. Hormone therapies can’t kill prostate cancer but they can improve the quality of life and extend survival.

Hormone therapy is most often used when surgery is not an option, in conjunction with primary treatment if the cancer is labeled aggressive, or if the cancer returns after surgery or front-line radiation therapy.

Orchiectomy, where the testicles (which make 90 percent of the body’s testosterone) are removed, is an option for men who prefer a one-time, low-cost procedure. However, the operation is permanent and irreversible.

LHRH Agonists

Luteinizing-hormone releasing hormone is a key hormone released into the body prior to producing testosterone. Blocking the release of LHRH with the use of LHRH therapies is the most common hormone therapy used on prostate cancer patients. Drugs in this class include Lupron, Viadur, Zoladex, Trelstar and Eligard. They are administered as regular shots ranging from once per month to once per year. LHRH agonists cause what is known as a “flare” reaction of a rise in testosterone during the first several weeks following a shot before the drug starts to take action.

LHRH Antagonists

Antagonist medications are a newer class of drugs that can block LHRH from stimulating testosterone production without causing a surge of testosterone (which can cause a temporary additional rise in PSA). This class includes Firmagon and it’s given as a monthly shot.

ADVANCED PROSTATE CANCER
IDENTIFYING TREATMENT OPTIONS
Anti-Androgens
The “flare” or rise in testosterone associated with LHRH drugs can be prevented with anti-androgens such as Casodex, Eulexin and Nilandron. They can help block the action of testosterone in prostate cancer cells and are used in conjunction with LHRH agonists.

These drugs come with positives and negatives. Anti-androgens can cause less sexual side effects than agonists but are not as effective as an orchiectomy or LHRH agonists in treating the disease, leaving it a poor choice for many men with metastatic prostate cancer.

These initial hormone therapies are effective for only a few years. Inevitably, cells become castrate resistant and grow strong enough that hormone therapies have a lessening effect on the cancer. However, a number of “secondary” or inhibitor and blocker hormone therapies can be used to slow the spread of disease.

Inhibitors and Blockers
Even with hormone injections, your cancer may progress to the point where the adrenal glands or prostate cancer cells themselves may produce androgens that fuel the cancer’s growth. This is when the disease becomes castration-resistant and stronger treatments need to be added to a regimen of injected hormone therapies. New hormonal medications that inhibit the synthesis of androgen, Zytiga, and block androgen receptor signaling, Xtandi, are now FDA-approved with the help of ZERO – The End of Prostate Cancer supported federal funding for research. Each of these drugs is for men with metastatic disease.

About 10 percent of the body’s testosterone is created by the adrenal glands and few therapies focus on shutting down this production until it becomes absolutely necessary to rid the body of all testosterone. Zytiga is used with steroids to shut down the adrenal glands while avoiding the adverse effects of chemotherapy.
Xtandi is able to block androgen receptors to slow the production of testosterone without the use of a steroid.

There are other treatments in the pipeline for castrate resistant prostate cancer patients.

Custirsen is an experimental drug designed to block proteins in cancer cells that enable prostate cancer to become hormone resistant. Currently, clinical trials are enrolling for use with first and second line chemotherapy drugs.

Side effects of hormone therapies include:

- Breast pain or enlargement
- Cardiovascular events
- Cholesterol level changes
- Erectile dysfunction/lower libido
- Diarrhea and/or constipation
- Increase in belly fat
- Increased risk of osteoporosis
## Identifying Treatment Options

<table>
<thead>
<tr>
<th>Type of Hormone Therapy</th>
<th>What It Does</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Anti-Androgens</td>
<td>Disrupts the interaction of testosterone with cancer cells</td>
<td>Flutamide, Casodex, Nilandron</td>
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<tr>
<td>Luteinizing Hormone Treatment</td>
<td>Shuts down luteinizing hormones that signal the production of testosterone</td>
<td>Lupron, Zoladex, Eligard, Firmagon</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>Blocks enzymes and/or proteins from making testosterone</td>
<td>Zytiga, Xtendi and others in clinical trials</td>
</tr>
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</table>

No prostate cancer is the same from one case to the next. There are many different hormone treatments. Talk to your doctor about which one may be best for you.
RADIATION

Radiation targets the prostate and specific sites where the cancer has metastasized. It can be used alone or in combination with hormone therapy, chemotherapy, and immunotherapy.

It is common for cancer to metastasize to the bones when it progresses. There are several types of radiation therapies including intensity modulated radiation therapy (IMRT), external beam radiation therapy or EBRT, 3D conformal radiation, proton beam therapy, CyberKnife, and brachytherapy. Although these types of therapies will not eliminate all cancer cells, they do relieve bone pain and can slow the growth of cancer.

External radiation can be given to the affected bone, or single area of treatment and can be used as a series of treatments. It can take up to several weeks for pain to lessen.

If several areas of the skeletal system are affected and are causing pain, radiation can be administered in the blood stream by injection. Some forms of radiation work like calcium and are absorbed by the bones, most often where there is high bone density. Xofigo, a new treatment in radioactive medicine for patients with castration-resistant prostate cancer, works through an intravenous injection to bring small doses of radiation to the cancer cells in the bone while operating on a short-wave alpha stream that causes less damage to healthy tissue during treatment while slowing progression and giving some relief to bone pain for a certain length of time.

Targeted radiotherapy is improving its ability to hit the cancer while leaving healthy tissue alone every day. See our “Learn” section of the zeroancer.org website for more details about the types of radiotherapy.
Immunotherapy
Unlike vaccines against infections like measles or mumps, immunotherapy is designed not to prevent but to treat prostate cancer by using the patient’s own immune system to fight the disease when other therapies have failed.

To date, there is only one FDA-approved immunotherapy - Provenge. It is designed to activate a man’s immune cells to best identify prostate cancer cells as abnormal or invader cells in the body. Most prostate cancer cells contain phosphates which the immunotherapy recognizes and commands the body to attack. The process involves extracting white blood cells from the body and “training” them in a lab to destroy prostate cancer cells. The newly “trained” cells are then injected back into the body a few days later. Since the original cells are from the patient, there is little chance of the body rejecting the therapy.

There is a prostate cancer vaccine that is currently in clinical trials - PROSTVAC. It uses a virus that has been genetically modified to contain PSA. The theory is the patient’s immune system responds to the virus and begins to recognize and destroy cancer cells containing PSA.
Chemotherapy
Chemotherapy is employed only after all other treatments have failed to manage the progression of the disease. Recent advancements offer new drugs for extending life of patients with advanced prostate cancer.

The most widely used and most effective chemotherapy option for advanced prostate cancer patients is Taxotere. It is administered as an infusion every three weeks over 10 days. Some patients report results within the first three treatments. The newest chemotherapy drug, Jevtana, can be used in combination with prednisone which can be used following Taxotere.

Chemotherapy treatments are often administered as part of a regimen to help make the best impact on the cancer while leaving the body time to recover from side effects, which sometimes can be significant.

Angiogenesis Inhibitors
Growth of prostate cancer tumors depends on growth of new blood vessels (a process called angiogenesis) to nourish the cancer cells. Cancers that stimulate many new blood vessels to grow are difficult to treat.

New drugs that have already been approved for other cancers are being studied in the hopes that they may be useful in stopping prostate cancer growth by keeping new blood vessels from forming. Talk to your doctor about potential clinical trial options regarding this method.
Bone Health
There are developments to fight prostate cancer progression to the skeletal system that were not available even three years ago. Once prostate cancer spreads to the bone, it becomes a painful process but there is hope through treatment.

Xgeva and Zometa are treatments that stop proteins from signaling bone removal within the skeletal system for use in patients with bone metastases from solid prostate cancer tumors. The body naturally destroys old bone material while making new bone material. The drugs slow the process of destroying bone and interrupt skeletal damage to the bones by spreading prostate cancer cells.

Cabozantinib is a new drug in clinical trials that targets certain proteins in the skeletal system that could shrink bone tumors in men with castration-resistant prostate cancer.

Xofigo, as previously addressed under the radiation section, delivers small doses of radiation to impacted areas in the skeletal system to relieve pain and slow disease progression.
Thousands of men across the U.S. suffer from the difficult effects of prostate cancer and often undergo treatment that does not produce optimal results. If you have prostate cancer, you may feel that your treatment options are limited and you may not know what to do next.

Joining a clinical trial may offer a new avenue of hope. It could prolong your life, improve your health, and enable you to enjoy more quality time with your loved ones.

Here are some current open clinical trials for men with advanced prostate cancer:

- **Apatorsen (Pacific Trial)** – Rising PSA with metastatic prostate cancer. OrcaTrials.com
- **ARN-509 (Spartan Study)** – Study for ARN-509 with castration-resistant prostate cancer.
- **Enzalutamide (PROSPER Trial)** – For men with non-metastatic castration-resistant prostate cancer.
- **Radium 223 (ERA 223 Study)** – Treatment for men with bone metastases.

Visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as a resource for all approved clinical trials.
# MANAGING SIDE EFFECTS

<table>
<thead>
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<th>TREATMENT</th>
<th>WHAT IT DOES</th>
<th>POSSIBLE SIDE EFFECTS</th>
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<tbody>
<tr>
<td>Hormone Therapy</td>
<td>Minimizes presence of androgens which fuels prostate cancer growth</td>
<td>Erectile dysfunction (ED), hot flashes, and bone loss</td>
</tr>
<tr>
<td>Radiation</td>
<td>Slows prostate cancer cell growth by targeting cells externally or by injection</td>
<td>ED, incontinence, diarrhea, rectal bleeding and discomfort during urination and bowel movement</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Changes the body’s immune system to kill cancer cells</td>
<td>Fever</td>
</tr>
<tr>
<td>Bone-related Treatments</td>
<td>Inhibits bone loss and fractures and relieves pain from prostate cancer in the bone</td>
<td>Tiredness, diarrhea, nausea, and weakness</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Targets cancer cells that grow quickly including cancer cells metastasized to the bone</td>
<td>Hair loss, fragile bones and nervous system disorders like confusion, depression, headaches, and nausea</td>
</tr>
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Minimizing Pain
Fighting cancer is best supported when steps are taken to minimize pain. Reducing pain levels makes it easier to think clearly, and reduces stress especially when taking a treatment regimen. It also reduces the burden on loved ones. Talk to your doctor about pain management that can include medications, physical therapy, and alternative means like acupuncture.

Managing Incontinence
Some patients may already have experience with incontinence as a result from primary treatment like surgery. Incontinence associated with advanced prostate cancer is fairly common with radiation treatment. Kegel exercises help strengthen the muscles in the pelvic floor.

Additionally, absorbent products, penile clamps, and catheter devices can be useful responses to the side effect. Another solution is a device called a “male sling” that can be used to support the urethra through minimally invasive surgery. Finally, surgically implanting a urinary sphincter that permits voiding to empty the bladder is a solution for moderate to high incontinence.

Gaining Intimacy
A loss of libido is a common side effect to hormone therapy. For many, a healthy sex life is important. Depending on the treatments undertaken to attack prostate cancer, solving this issue may be difficult. Using medications such as erectile dysfunction (ED) drugs help relax the penis enabling blood to rush in and an erection to occur.

For difficult cases of ED, a penile implant can be inserted by surgical procedure that puts the penis in a permanent semi-rigid state. Another option is an inflatable prosthesis that consists of a squeeze-activated pump.
Studies continue to show a link between prostate cancer and diet. These studies indicate that men who wish to reduce their risk of prostate cancer, as well as men who have already been diagnosed with prostate cancer, may benefit from changing their diet as part of their treatment regimen.
Specifically, following these dietary principles may be helpful:

1. If it’s heart healthy, chances are it’s also prostate healthy.
2. Reduce animal fat. Studies show that excess fat, primarily red meat and high-fat dairy, stimulates prostate cancer growth.
3. Avoid trans fatty acids in foods like margarines, and fried and baked foods.
4. Increase fresh fish intake with omega-3 fatty acids especially cold-water fish like salmon, sardines and trout. Avoid fried fish.
5. Significantly increase fresh fruits and vegetables. Studies show colorful fruits and vegetables as well as some nuts and seeds contain powerful anticancer nutrients. Cruciferous vegetables are protective against cancer (cabbage, broccoli and cauliflower). Also, red grapes and products from red grapes contain flavonoids that inhibit cancer cells.
6. Consume the recommended amounts of calcium. Talk to your doctor about the correct amount for you.
7. Add pomegranate juice to your diet. Studies show it may directly reduce PSA.
8. If you take dietary supplements, choose wisely. Discuss all supplements you take with your doctor.
9. Tomatoes, especially tomato products, are rich in lycopene that is a powerful anticancer substance.
10. Drink green tea several times per week.
1. What is the result of my blood work, biopsy, and imaging?
2. What do my current PSA and testosterone levels indicate about my current treatment? How often should we recheck these levels?
3. What criteria do you use to determine treatments?
4. What treatment are you recommending?
5. When do you recommend we start treatment?
6. What kind of results can I expect from this treatment?
7. What are the chances the cancer responds to this treatment?
8. How much time does it take before I can start to see results from the treatment?
9. What are the risks and side effects?
10. What is recommended to deal with side effects?
11. Do you recommend any lifestyle changes? Changes in diet? Exercise?
12. Do you recommend any supplements?
13. How can my loved ones help?
14. Are there any clinical trials that may also be options to consider?
15. What other doctors should I include in getting opinions? Is it time to talk to oncologist or get an opinion from a second oncologist?

STAY INFORMED

To find out more about prostate cancer, please go to our website at www.zerocancer.org and click on “Learn.” ZERO has online videos, links, and news items about advanced prostate cancer. We also distribute a free electronic newsletter to get up-to-the-minute news on treatments, clinical trials, and breakthrough research.
ZERO - The End of Prostate Cancer is a national nonprofit organization with the mission to end prostate cancer. As a leader in the fight against prostate cancer, ZERO advances research, encourages action, and provides education and support to men and their families. ZERO’s premier programs include the ZERO Prostate Cancer Challenge, the largest men’s health event series in America. ZERO is a 501c3 charity, a Better Business Bureau member and 89 cents of every dollar donated goes to research and programs. For more information, visit www.zerocancer.org.

The Patient Access Network (PAN) Foundation is dedicated to providing help and hope to patients who would otherwise be unable to afford high-cost specialty medications. PAN envisions a society in which every individual can access needed medical care, offering hope for a healthy tomorrow. PAN provides assistance through nearly 50 disease-specific programs designed to help patients being treated for certain cancers, chronic illnesses, and rare diseases. Through a streamlined application process and state of the art online tools, the PAN Foundation is able to ensure that patients are put on the fast track to therapy. For more information about the PAN Foundation, please visit www.PANFoundation.org.