Prostate Cancer
Patient's Guide to Hormone Therapy
This is an up-date to the very first brochure created by Us TOO and is meant to provide current information on one of the most common therapies for prostate cancer.

In this document you will find information on:

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Background: You Are Not Alone

When dealing with prostate cancer you are not alone. After skin cancer, prostate cancer is the number one diagnosed cancer in men. It is the second leading cause of cancer-related death in men (behind lung cancer). In 2005, it is estimated by the American Cancer Society that 232,090 men in the United States will be diagnosed with this disease and 30,350 men will die as a result of it.

Today, greater numbers of men are being diagnosed and diagnosed earlier. This has happened since the late 1980s when the prostate specific antigen (PSA) test became available. Also, today, fewer men are diagnosed with advanced or metastatic prostate cancer and the number of annual deaths has been declining.

Tracking the changes in PSA levels over time has helped patients and their physicians respond earlier. A doubling of PSA over time is a firm indication of advancement of prostate cancer.

With today’s early detection, many feel that there is no reason why any man should be diagnosed with anything other than “localized” early stage prostate cancer. In today’s environment, many more men are opting for therapy that changes the hormonal environment of their body. This therapy is selected because the continued growth of prostate cancer cells depends on male hormones.
What are Hormones and Androgens?

Hormones are chemical messengers. They are produced by the body’s glands or organs and they cause or control a bodily function. The human body has many hormones. They help our bodies grow and carry out its many activities. Some examples include thyroid hormone, growth hormone, and estrogens (the predominant hormone class in females).

In men, a critical class of hormones called “androgens” has a wide range of functions. Androgens are responsible for many uniquely male features including lower voice, male hair patterns and the male libido, or sexual drive.

In addition, androgens are extremely important in building muscle mass, increasing bone formation and stimulating red blood cell production. In essence, androgens affect every major tissue in the male body. The two major androgens involved in prostate cancer are testosterone and dihydrotestosterone (DHT). Testosterone, which is produced in the testicles and in the adrenal glands, is often referred to as “the male sex hormone.”
What is Hormonal Therapy/Androgen Deprivation Therapy (ADT) for Prostate Cancer and When is it Used?

Due to the finding that almost 100% of newly diagnosed prostate cancer will grow as a result of stimulation by androgens, some doctors refer to testosterone as the “fertilizer for prostate cancer growth.”

Actually, it would be more correct to state that any androgen will stimulate prostate cancer growth. In fact, DHT, the androgen that is created due to the metabolism of testosterone, is five times as potent a growth stimulator of prostate cancer when compared to testosterone.

With this in mind, hormonal therapy for prostate cancer, more properly termed androgen deprivation therapy (ADT), refers to any treatment that lowers the body’s amount of androgen. Hormonal therapy or ADT is simply any method to deprive the man’s body of testosterone as a way to treat his prostate cancer.

Traditionally, hormonal/ADT therapy has been used to treat men with prostate cancer that has spread beyond the confines of the prostate or for prostate cancer that is in an advanced (metastatic) stage.

Because of the availability of injections to lower the level of testosterone and pills to block the use of any androgens, ADT use has become more common in earlier stages of prostate cancer and used as intermittent (on-again, off-again) therapy.
Patients to be treated with ADT include men with regional spread of prostate cancer, men with early recurrence of prostate cancer (after prior treatments such as surgery or radiation), and men with metastatic prostate cancer.

Why Use ADT for Prostate Cancer?

Removing testosterone from the body usually causes the prostate cancer to shrink or grow more slowly. Furthermore, recent study suggests that ADT started at the time of diagnosis of stage D prostate cancer (when it has spread or metastasized to lymph nodes, the bones or to other tissues) provides longer survival.

The rationale for ADT in earlier stage prostate cancer may be to shrink the local tumor to allow for more effective radiation or cryosurgery and to theoretically kill any cancer cells that could have escaped the prostate prior to, or during, other treatments.
What are the Side Effects of ADT?

ADT does have side effects. They are not life threatening, but they often detract from a man’s quality of life. Most prominent is their effect on sexual desire, or libido.

Most men lose their desire for sexual relations and lose the ability to obtain or maintain an erection. Men, however, maintain their ability to foster loving and nurturing relationships with their spouses or significant others.

Your doctor can provide treatments that may restore the ability to have an erection that is satisfactory for sexual intercourse. Studies are underway testing lower dose hormonal therapies (such as anti-androgen pills alone) which may not affect sexual function as much as traditional hormonal therapy.

Most men also experience “hot flushes” from time-to-time. For the vast majority of men, these are a minor nuisance. For men who experience frequent or bothersome flushes, their doctor can provide medications that lessen or eliminate the symptoms.

Men are also concerned that ADT will affect their other male characteristics such as deepness of their voice, hair growth, or breast growth. Fortunately, these side effects are rare. Men should not notice any change in their voice or significant alteration in hair growth.

Although in the past, estrogen pills were used and did cause breast enlargement (gynecomastia) and tenderness, current hormonal therapies do not commonly cause this side effect. Low dose
hormonal therapy with anti-androgens alone or with other oral drugs can cause breast nipple tenderness or some breast enlargement. To prevent such side effects, options should be discussed with your physician.

Long term ADT often results in anemia, which is often mild but on occasion may be moderate to severe. Periodic monitoring of the routine blood count (CBC) while on ADT is advised. Other side effects of ADT include decreased muscle mass and strength, and bone loss that can result in osteoporosis. Studies have been published that indicate that bone loss is common in men with prostate cancer, even prior to starting ADT.

Since androgen deprivation will increase bone loss, attention should be given to approaches that focus on bone health (bone integrity). Low dose or intermittent hormonal therapy use may lessen these side effects. Weight gain is common in men on ADT. Therefore, caloric restriction, attention to carbohydrate intake and the need for a realistic exercise program are part of the supportive care for men on ADT.

Anti-androgens may also have unique side effects. For example, all three FDA-approved anti-androgens may cause liver dysfunction. Typically, your doctor will monitor your liver with blood tests periodically and will discontinue the anti-androgen if liver abnormalities occur. The liver problem is almost always reversible upon discontinuation of the drug.
Some physicians prescribe supplements that help protect the liver cells from damage due to these agents. Such supplements include silybinin, curcumin, d-alpha tocopherol succinate and allicin (from garlic). The anti-androgen flutamide may cause diarrhea in approximately 7-10% of men who take it. A lower dose or switching to another anti-androgen may eliminate the problem. Nilutamide may cause a delayed adaptation to darkness which may affect nighttime driving. It may rarely cause lung fibrosis, which is reversible. All anti-androgens can cause interactions with alcohol, although this is not common.

**What are the Specifics of Hormone Therapy/ADT (androgen deprivation therapy)?**

1) **Luteinizing Hormone-Releasing Hormone (LH-RH) Agonists**

The LH-RH agonists (LHRH-A) are intramuscular injections of medications that are given monthly, or alternatively every 84 days, 112 days, or even every six or 12 months. The LHRH-A shuts down the production of LH and thus causes the testicles to stop producing testosterone.

These agents are often referred to as a “medical orchiectomy” or as “medical castration” because they are equivalent to the effect produced by orchiectomy (removal of the testicles). Similar to an orchiectomy, there are advantages and disadvantages to the use of LHRH-A.
Some men find the need for periodic visits to their doctor an advantage because they get to “check-in” regularly and feel they are under more active treatment. Indeed, men receiving ADT (androgen deprivation therapy) should be seen at intervals not only to be monitored for potential adverse effects of this therapy (as well as anti-androgen therapy), but also because the reduction of testosterone in general leads to a multitude of possible side effects. Some physicians have termed this the Androgen Deprivation Syndrome (ADS) since it reflects a spectrum of signs and symptoms that may or may not occur in men on ADT.

Other men find the very same visits a disadvantage because of time and schedule requirements. However, the fine tuning of ADT absolutely requires communication between the patient and the physician with refinements of such therapy based on the patient’s personal biologic responses. This is a required ingredient of optimal ADT.

Intermittent Androgen Deprivation (IAD) is often employed. It means starting and stopping treatment for periods of time. It can be used following a protocol or guide that determines if and when a man can discontinue LHRH-A therapy (and/or anti-androgens or other anti-prostate cancer agents).

Considering that this is a life-threatening illness, the time expenditure is certainly worth it to reach an excellent outcome. The other obvious advantage of LHRH-A therapy is the elimination of the need for an orchiectomy in those men preferring not to have the surgery. Furthermore, as noted earlier, a key advantage to LHRH-A therapy is that it is reversible.
The main disadvantage to LHRH-A are their costs. The injections are cumulatively more expensive than a one-time surgical procedure. This cost factor becomes a major financial burden if a man’s health insurance does not cover the cost of such medications. Fortunately, most, if not all, insurance companies, including Medicare, cover the cost of LHRH-A injections.

Some important points are crucial to the success of LHRH-A therapy. One is the need to receive such injections on schedule. The goal of this therapy is reduction of testosterone. Therefore measurements of serum testosterone are essential to confirm that the biological endpoint of AD (androgen deprivation) be achieved. This is defined by most physicians well versed in the use of ADT as a testosterone level of less than 20 nanograms per 100 milliliters of blood (< 20ng/dl) or less than 0.69 nanomoles per liter (< 0.69 nM/L). If sufficient lowering of testosterone is not attained, tests can tell the doctor which androgens are not being suitably reduced, i.e. testicular and/or adrenal androgens.
In some men, with a particularly strong pituitary-testicular axis, initial LHRH-A therapy should be carried out with monthly LHRH-A. Only after documentation of testosterone reduction to less than 20ng/dl or equivalent should longer acting LHRH-A be used. In this way, the maximal effect of adequate testosterone lowering can be realized in regard to how far the PSA can be lowered.

2) Surgical Orchiectomy

Commonly used in the past, surgical orchiectomy, when a surgeon removes both testicles where most testosterone is produced, is described as a minor surgical procedure. However, in general, studies have shown that most men prefer not to undergo this surgery, despite it being a very effective treatment for those who make that choice.

Choice is the key element. Men have options and are able to select this surgery or the LH-RH agonist (LH-RH - luteinizing hormone-releasing hormone injections described above. The LH-RH agonists block a hormone that is produced in the pituitary gland that triggers the testicles to produce testosterone).

There are some misconceptions about this surgery. Some men mistakenly believe that during an orchiectomy the surgeon removes the testicles and the scrotum, and/or the penis. In actuality, an orchiectomy only involves removing the testicles (“balls”) from the scrotum and only with a small incision in the mid-area of the scrotum.
If a man desires, he can have the testicles replaced with testicular prostheses, silicon implants of similar size to actual testicles and the patient can select a prosthesis size comfortable for him. A “sub-capsular” orchiectomy procedure may also be performed. The inside glandular tissue of the testicles is removed and the outer shells of the testicles are left in place.

The advantage to an orchiectomy is that it is a one-time minor surgical procedure and there is no need for repeated LH-RH agonist injections. The major disadvantage is the psychological effects of such a surgical procedure involving removing a man’s testicles. Also, an orchiectomy is not reversible.

Because some men and their physician team prefer the intermittent use of androgen deprivation, the use of LH-RH agonist therapy is the preferred treatment. Some physicians have considered the use of androgen replacement therapy in men who have undergone an orchiectomy and who have had a complete remission of all manifestations of prostate cancer. This approach is worthy of further investigation in specialty practices of prostate cancer.

3) Anti-Androgen Therapy

An additional medical therapy to inhibit the adrenal androgen derived testosterone involves a blocking maneuver at the site of interaction of testosterone with cells normally stimulated by testosterone. This medical therapy involves drugs called “anti-androgens”.

Examples of anti-androgens are flutamide (Eulexin®), bicalutamide (Casodex)®, and nilutamide (Nilandron)®. Your doctor may prescribe the LH-RH agent or an orchiectomy alone or they may
prescribe “combination hormonal therapy” which is an LH-RH agent or an orchiectomy plus daily anti-androgen pills.

Anti-Androgens are part of the “complete” testosterone blockade therapy referred to in many ways such as: combination hormonal therapy (CHT), total androgen blockade (TAB), or maximal androgen blockade (MAB).

Anti-androgens are also being tested for their effectiveness when used alone (monotherapy) or as combination therapy with other oral drugs, such as finasteride (Proscar®) or dutasteride (Avodart®).

The main advantage of anti-androgens is that they do indeed block testosterone contributed by the adrenal glands, as well as any residual testosterone that may not be blocked by LHRH-A therapy. In many publications, the use of anti-androgens is shown to provide a modest treatment advantage for most men with metastatic prostate cancer.

The main disadvantages include cost and compliance as well as drug-related side effects. Some of these medicines must be taken several times per day and men may forget to take all the needed medicine. It is important to take all the prescribed doses of these medicines so that they have their maximal benefit. Like the LH-RH agents, these medicines are expensive and may be a burden for those men whose insurance does not cover oral anti-cancer medicines. Some drug manufacturers have created programs for needy patients to receive anti-androgens.
4) **5 Alpha Reductase Inhibitors**

The discussion above has focused on reducing the production of testosterone from the testicles 1) by use of medicines that reduce the hormone that stimulates the testicles to make testosterone or 2) by surgical removal of the testicles.

In addition, the anti-androgens work to block the effect of testosterone (that is either produced by the adrenals, or that has escaped suppression by medical or surgical orchiectomy). None of these therapies are absolute in their ability to stop the interaction from androgens with the androgen receptor.

An additional hormonal maneuver that has been used to provide further blockade involves inhibiting the enzyme called 5-alpha reductase (5AR or 5-a reductase). Two drugs that have been approved by the FDA to inhibit 5AR are Proscar® (finasteride) and Avodart® (dutasteride).

Both agents are potent inhibitors and quickly reduce levels of the androgen called dihydrotestosterone (DHT) to extremely low values. Either of these agents added to an LHRH-agonist and to an anti-androgen, results in a 3-drug combination. This has been referred to as ADT3 or Triple Therapy. The general academic community has not adopted ADT3 as a major therapeutic option, but a significant number of medical oncologists who are specializing in prostate cancer management use ADT3 as their treatment of choice.
What is the History? Finding the Source of Androgens and Therapeutic Responses

Over sixty years ago, Huggins & Hodges documented the vital importance of androgens on prostate cancer growth. Their research, conducted at the University of Chicago in the 1940’s, led to a Nobel Prize in Medicine in 1966.

Their initial work showed that prostate cancer growth was under the influence of testosterone, and that the removal of a man’s testicles (where most testosterone is produced) could result in dramatic remissions in men with metastatic prostate cancer. This surgical procedure orchiectomy became the predominant form of therapy for men with advanced prostate cancer until the late 1980’s.

Not long after the pioneering work described above, the same physicians documented that approximately 30% of men with evidence of progressive prostate cancer after an initial response to orchiectomy showed a secondary remission if both adrenal glands were removed.

The responses obtained with this surgical procedure called “bilateral adrenalectomy” provided evidence that the adrenal glands were contributing hormones that also affected prostate cancer growth and spread.
It was subsequently shown that a man’s body is able to convert these adrenal androgens to testosterone. The adrenal glands are small crescent-shaped organs that are located above both kidneys and produce 5-10% of a man’s testosterone by this conversion. Even though these glands are responsible for a relatively small amount of testosterone, many doctors believe that it is important to block or eliminate this additional source of male hormone. ADT therefore reflects any therapeutic approach to minimize these two sources of testosterone—the testicles and adrenal glands.

Years ago, the same medical pioneers that initiated orchiectomy in the treatment of prostate cancer, also showed that estrogens (the predominant hormone class in females) resulted in the same anti-cancer effects on prostate cancer as orchiectomy.

Currently, estrogens such as diethylstilbestrol (DES) are seldom used in the United States. There are many explanations for this, but essentially this occurred because of the cardiovascular side effects such as heart attacks and stroke associated with the use of estrogens.
The medical therapy that replaced DES and other estrogens in the treatment of prostate cancer involved the injection of a new drug class called LH-RH agonists (LH-RH - luteinizing hormone-releasing hormone). The LH-RH agonists block a hormone that is produced in the pituitary gland.

The pituitary gland, lying at the base of the brain, produces many hormones to regulate other target sites. LH (luteinizing hormone) is one of these regulators that is sent from the pituitary to the testicles to turn on testosterone production. The continued use of an LH-RH agonist drug (e.g. Lupron, Zoladex, Eligard, Trelstar, Viadur, etc) shuts down LH production and in turn dramatically decreases the testicles ability to make testosterone.

The androgens produced by the adrenal glands—called adrenal androgen precursors—are converted within prostate cells to active testosterone. In other words, prostate cells including prostate cancer cells, contain the enzymatic machinery to convert the two major adrenal androgen precursors (DHEA-S and androstenedione) into testosterone.

Therefore, two major sources of male hormone or androgen are the testicles, producing testosterone, and the adrenal glands, producing adrenal androgen precursors (DHEA-S and androstenedione) which are in turn converted to testosterone within prostate cells. Surgical or medical orchiectomy (or the use of LH-RH-agonist drug therapy) affects only the production of testosterone from the testicles. It does not inhibit the testosterone produced via the adrenals.
The above discussion describes what is called the hormonal axis involved in prostate cancer. It includes the pituitary-testicular axis and the pituitary-adrenal axis. However, there is another aspect of the endocrinology of prostate cancer that is often ignored involving hormonal changes that occur within the prostate cell. This is often referred to as the intra-crinology of prostate cancer.

The adrenal androgen precursors are not only converted to testosterone within the prostate cell but also further conversion of testosterone takes place as well. This conversion involves an enzyme called 5-alpha reductase, which metabolizes testosterone to dihydrotestosterone (DHT). DHT is 5 times as potent as testosterone in stimulating prostate cancer cell growth. DHT also stimulates normal prostate cell growth and is implicated in prostate glandular enlargement that occurs as men get older.

**What are the Common Reasons Doctors Recommend ADT for Various Stages of Prostate Cancer?**

**Clinical Stages T1 & T2**

These stages of prostate cancer are considered confined to the prostate and, by conventional wisdom, curable by surgery, radiation, or other local treatment. Traditionally, ADT was not usually used to treat men with such stages of disease. There are exceptions, however.
In elderly men, or in men with poor overall health who are not candidates for surgery or radiation, ADT can be very effective. Also, for patients with significant tumor volumes such as clinical stage T2b or T2c, ADT is often used for variable periods of time prior to, during, and after radiation treatment or cryosurgery. ADT will shrink the prostate gland and decrease PC volume. This has been shown in randomized clinical trials to provide better overall treatment results in patients treated with radiation.

Another setting for the use of ADT is with men who choose brachytherapy. This approach results in a decrease in size of the prostate gland, thus requiring fewer numbers of seeds to be placed. It also decreases the tumor volume, which may allow for a better cell-killing effect by the RT delivered by the permanent seeds or temporarily implanted wires. ADT in this setting is usually reserved for men with prostate glands 40 cubic centimeters or larger.

**Clinical Stage T3**

Typically, treatments recommended for stage T3 included surgery, radiation, or ADT. It is now clear the combination treatment of ADT and external beam radiation is preferred for most men with clinical stage T3 disease.

A currently popular approach is to start ADT for a variable number of months (typically 2 or 3) prior to radiation. Therapy with ADT is continued during the radiation. After radiation, ADT may be continued for two to three months or longer, depending upon the characteristics of the cancer such as Gleason grade and PSA level.
Medical studies have shown that the combination of ADT and external beam radiation has improved the outcomes for men with stage T3 prostate cancer. However, what is not known is the optimal duration of ADT prior to and after radiation therapy completion. Three major studies have shown benefit related to four months, three years, and indefinite use of ADT, respectively. A recent study has suggested that six months of ADT after radiation may be sufficient.

**Stage D (N1 or M1)**

Stage D2 patients, with clinical apparent metastatic prostate cancer, have traditionally been treated with ADT. At the present time, there has been a shift to treat all stage D patients as well as patients with PSA recurrence using ADT. Past studies suggested that ADT was only palliative for stage D2 prostate cancer. In other words, it helped symptoms but did not prolong a man’s survival.

However, recent studies show that starting ADT as soon as a man is diagnosed with this stage does prolong life. Stage D1 patients (lymph node spread only) have often been treated with surgery, radiation, ADT and combinations of therapy. Research data over the last number of years point to the necessity of ADT for providing the best cancer control for this group of patients. In men who have been treated by radical prostatectomy or with radiation, and who are discovered to have D1 disease, the best results appear to be for men who were continued on ADT.
Stage D0

ADT has traditionally been restricted to prostate cancer patients who are without evidence of cancer spread on radiologic tests but who demonstrate an abnormal level of an enzyme in the blood called PAP (Prostatic Acid Phosphatase).

This finding was correlated with the probability that microscopic cancer spread had occurred. In the current era, doctors are very suspicious about microscopic cancer spread when the prostate specific antigen (PSA) is also elevated in the blood. Different doctors have different threshold values when they consider the PSA test to signify D0 disease. The D0 category, like the other stage D categories, may occur when men are first diagnosed with prostate cancer, or may occur when the cancer recurs after prior treatments such as surgery, radiation, or cryosurgery. A very common current scenario is the man who has a rising PSA, also called PSA recurrence, with negative X-ray tests after prior radiation or surgery. Men in this category are commonly started on ADT.

In summary, the “when” of ADT runs the spectrum from early PSA elevation after prior treatments to advanced metastatic disease to variable duration ADT before, during or after other treatments such as radiation or cryosurgery.
Clinical Stages of Prostate Cancer

**T1:** Prostate cancer believed to be confined within the prostate gland but no tumor can be felt by the doctor on digital rectal examination (DRE).

**T2:** Prostate cancer believed to be confined within the prostate gland and with an abnormality that the doctor feels on DRE.

**T3:** Prostate cancer that has spread outside of the prostate into adjacent local tissues but is believed not to have spread further. Some patients with clinical stages T1 and T2 are upstaged to T3 or beyond at the time of surgery.

**Stage D:** D0 – Called “D-Zero” disease by many doctors. This refers to significantly elevated blood tests such as PSA or acid phosphatase that suggest the cancer has spread despite negative X-ray tests such as CT-scans and bone scans. A rising PSA after prior surgery or radiation treatment could also be classified as stage D0. Stage D can be further classified. Prostate cancer that has spread or metastasized to lymph nodes is called (D1) or the bony skeleton or other organs or tissues away from the prostate gland (D2).
About Us TOO

Us TOO International Prostate Cancer Education and Support Network is a nonprofit, grassroots organization started in 1990 by prostate cancer survivors for prostate cancer patients, survivors, their spouses/partners and families. Us TOO, through its more than 320 chapters throughout the United States and internationally, helps men and their families learn more about prostate cancer so they can make better decisions on treatment options and cope with emotional and quality of life issues following treatment. Us TOO and its chapters reach more than 50,000 men per month through discussion groups, lectures, publications and presentations by medical professionals. Visit www.ustoo.org or call 800-80-UsTOO (800-808-7866) for more information.

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For more detailed information on Hormone Therapy and Prostate Cancer you can read “A Primer on Prostate Cancer” by Stephen Strum and Donna Pogliano.

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