

## Prostate Cancer: Insights of Current Treatment, Prevention and Management

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### Review Article

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**Abstract:** The prostate is an exocrine gland of the male reproductive system, and exists directly under the bladder, in front of the rectum with approximately the size of a walnut. Male hormones affect the growth of the prostate, and also how much prostate specific antigen the prostate produces. Medications aimed at altering male hormone levels may affect prostate specific antigen blood levels. The tumor is graded with one of the most accurate ways of determining the aggressiveness of prostate cancer by the Gleason Scale. Factors like race, family history and life style influence the risk of the occurrence of the disease. Because of the slow progression of the disease, symptoms are rarely seen. However, the choice of treatment strategy is dependent on many factors, like patient preference, and quality of life aspects. It is expected that within a near future, the focal treatment approaches like surgery, radiation therapy, hormonal, and chemotherapy would be much more developed without minimal side effects. And most importantly, proper dietary management may keep away a person from prostate cancer risk.

**Keywords:** Prostate cancer, gleason score, prostate specific antigen, radiation therapy, focal treatment, chemotherapy.

### BACKGROUND

The prostate is an exocrine gland of the male reproductive system, and exists directly under the bladder, in front of the rectum with approximately the size of a walnut. The urethra - a tube that goes from the bladder to the end of the penis and carries urine and semen out of the body - goes through the prostate.

There are thousands of tiny glands in the prostate - they all produce a fluid that forms part of the semen. This fluid also protects and nourishes the sperm. When a male has an orgasm the seminal-vesicles secrete a milky liquid in which the semen travels. The liquid is produced in the prostate gland, while the sperm is kept and produced in the testicles. When a male climaxes (has an orgasm) contractions force the prostate to secrete this fluid into the urethra and leave the body through the penis.<sup>[1]</sup> As the urethra goes through the prostate: the prostate gland is also involved in urine control (continence) with the use of prostate muscle fibers which contract and release, controlling the flow of urine flowing through the urethra.<sup>[2]</sup> The current review details about factors responsible for prostate cancer, new insights of the diagnosis, treatment and management of prostate cancer.

### INTRODUCTION

#### Prostate cancer-etiology

Prostate cancer is a disease which only affects men. Cancer begins to grow in the prostate - a gland in the male reproductive system. The word "prostate" comes from Medieval Latin *prostate* and Medieval

French *prostate*. The ancient Greek word *prostates* means "one is standing in front", from *proistanai* meaning "set before".

The prostate is so called because of its position - it is at the base of the bladder. Prostate cancer is common, but it is not always dangerous. This is because it usually progresses very slowly. It affects older men; the average age at diagnosis is 70. And it's usually diagnosed before it causes any symptoms. When cells in the prostate become cancerous (malignant), they clump together, forming small "islands" of cancer in the prostate. In many cases, it takes years, even decades, for this localized cancer to spread beyond the prostate. And many of these cancers may never spread. It is said that prostate cancer starts with tiny alterations in the shape and size of the prostate gland cells - Prostatic intraepithelial neoplasia (PIN). The changes in these cells can be observed only under a microscope [1, 2].

It is estimated that 1 in 6 men will be diagnosed with prostate cancer but only 1 in 36 are expected to die because of it. The disease is the most common malignancy diagnosed in North American men (other

than skin cancer) and the sixth leading cause of cancer death among men worldwide. The rate of Prostate Cancer in western countries is 10–15 times higher than Asian countries [3].

### Role of PSA in prostate cancer

Prostate-specific antigen (PSA) is a protein produced by the epithelial cells in the prostate gland. The PSA helps maintain the semen in its liquid state. Some of the PSA escapes into the bloodstream. We can measure a man's PSA levels by checking his blood. If a man's levels of PSA are high, it might be an indication of either prostate cancer or some kind of prostate condition. It is a myth to think that a high blood-PSA level is harmful to you - it is not. High blood PSA levels are however an indication that something may be wrong in the prostate. Male hormones affect the growth of the prostate, and also the quantity of PSA the prostate produces. Medications aimed at altering male hormone levels may affect PSA blood levels.<sup>[3]</sup> If male hormones are low during a male's growth and during his adulthood, his prostate gland will not grow to full size [2,4].

### Prostate cancer-stages and grades

It is important to know the stage of the cancer, or how far it has spread. Knowing the cancer stage helps the doctor define prognosis - it also helps when selecting the therapies to use. The two stages that describe the cancer location also its spreading areas are the clinical stage and the pathologic stage. The former is based on the laboratory evidence which includes DRE, PSA, biopsy, Scans etc and the latter is based on the information found during surgery.

### TNM (tumor-node-metastasis) staging system

The most common system today for determining this is the TNM which involves defining the size of the [tumor](#), how many lymph nodes are involved, and whether there are any other metastases. When defining with the TNM system, it is crucial to distinguish between cancers that are still restricted just to the prostate, and those that have spread elsewhere. Clinical T1 and T2 cancers are found only in the prostate, and nowhere else, while T3 and T4 have spread outside the prostate. There are many ways to find out whether the cancer has spread. Computer tomography will check for spread inside the pelvis, bone scans will decide whether the cancer has spread to the bones, and endorectal coil magnetic resonance imaging will evaluate the prostatic capsule and the seminal vesicles[4].

### The gleason score-role in the diagnosis of prostate cancer

Once the cancer tissue is detected and confirmed, the tumor is graded with one of the most accurate ways of determining the aggressiveness of prostate cancer, Gleason Scale. It was developed by physician Donald Gleason in the 1960s. It provides a

score that helps predict the aggressiveness of prostate cancer. The score is based on how much the cancer looks like the healthy tissue. The Gleason System of grading goes from 2 to 10. The higher the number, the more abnormal the tissues are compared to normal prostate tissue. According to the National Cancer Institute (NCI) cancer tissue that looks most like normal tissue is grade 1. If the cancer tissue spreads through the prostate and deviates widely from the features of normal cells, it is grade 5.

- 2 to 4 means low-grade, nonaggressive cancer.
- 5 to 7 means intermediate-grade cancer.
- 8 to 10 (ten is the highest score) means high-grade, aggressive cancer.<sup>[2,5, 6, 7]</sup>

### Factors responsible for the prostate cancer

The exact cause of the disease is not known yet. But they have identified several factors that raise a man's risk of the disease.

#### Age:

The disease progresses slowly. So the degree of the cancer can be found at later ages. Autopsy studies of men who died of other causes have found that about three-quarters or more of them have some degree of prostate cancer by age 80. These men didn't know they had prostate cancer.

#### Race

African American men are more likely to get prostate cancer than other men—and to be diagnosed when the cancer is at a more advanced stage. They are also more than twice as likely to die of the disease as white men and about five times more likely to die of it than Asian Americans.

#### Family history

If a man's father or brother has been diagnosed with prostate cancer, his cancer risk is two to three times higher than a man who doesn't have family members with the disease. Researchers have identified several genetic defects that may be more common in men who develop prostate cancer. But overall, most experts say that inherited defects cause a relatively small number of cancers. Recent research also links a higher risk of developing prostate cancer in families whose female members are at higher than average risk to develop breast cancer. A common genetic abnormality may be responsible for an increased risk to both prostate and breast cancer.

#### Lifestyle

Men who eat a lot of red meat or high-fat dairy products seem to have a higher risk of prostate cancer. There is little evidence that being overweight increases the risk of prostate cancer. However, obese men are more likely to die of the disease than men at a healthy weight[1,2,8,10].

### Signs and symptoms

In its early stages, prostate cancer rarely causes symptoms. In fact, most men diagnosed with prostate cancer have no symptoms. Doctors suspect prostate cancer if a blood test shows high levels of prostate-specific antigen (PSA) [3,4]. However, if the cancer spreads to the bladder or presses on the urethra, the tube that carries urine out of the body, it can cause: a weak urine stream and micturition, an inability to urinate, pain or burning when during urination, blood in your urine or semen, erections that are less firm, a drop in the amount of semen ejaculated, Pain or stiffness in your lower back, hips, or upper thighs[5]. If prostate cancer spreads to the lymph nodes, bones, or other organs, it can cause bone pain, weight loss, anemia (a lack of red blood cells), shortness of breath, swelling in the scrotum, penis, legs, and feet and fatigue [6].

### Diagnosis [7, 14]

Digital rectal examination (DRE) is a test to check the size and shape of your prostate. Hard and knobby gland indicates cancer. Enlarged, firm and smooth gland is an indicative for Benign Prostatic Hyperplasia (BPH). Prostate-specific antigen (PSA) is a blood test to check PSA levels. It is a useful surrogate marker for the size of the prostate gland. Elevated PSA levels may indicate prostate cancer, a noncancerous condition such as prostatitis, or an enlarged prostate. This test is not always reliable because PSA levels are also raised during urinary infections, post biopsies, prostate or bladder surgery etc.

A Cystoscopy, also called a cystourethroscopy or bladder scope, is a test to measure the health of the urethra and bladder. Biopsy is used to take a sample of the prostate gland to be tested for cancer. The sample may also help healthcare providers determine the stage of the cancer<sup>13</sup>. Trans-rectal Ultrasound scan (TRUS) Biopsy is used if the prostate cancer is diagnosed by DRE and PSA. A CAT scan uses X-rays and computers to produce an image of a cross-section of the body. This image allows the doctor to check for swollen or enlarged lymph nodes, which might mean that cancer has spread. Genetic test (ProstaVysion): This is a panel of three prognostic molecular biomarkers (PTEN, ERG and HOXD3). Studies indicate that patients with PTEN deletions, ERG fusion/translocation and HOXD3 methylation typically have a less favorable prognosis. Testing is performed on prostate tissue sections [7].

### PCA3 (prostate cancer antigen 3 gene) gene testing

The PCA3 gene is over expressed in prostate cancer cells. This molecular test evaluates the ratio of mRNA transcripts of PCA3 to PSA. It is performed on a urine sample obtained after a digital rectal exam.

MRI plays an important role in cancer diagnosis, staging and treatment planning. With MRI, we can distinguish between normal and diseased tissue to precisely pinpoint cancerous cells within the body. It

is also useful for revealing metastases. MRI provides greater contrast within the soft tissues of the body than a CT scan. As a result, it is often used for imaging the brain, spine, muscle, connective tissue and the inside of bones. During an MRI, a patient rests on a table and slides into a large tunnel-shaped scanner. Some exams require a contrast dye to be injected into a vein before the procedure. This helps certain areas show up better on the images. The procedure is painless and typically takes 30-60 minutes. Unlike X-rays and CT scans, an MRI does not use radiation.

### ProstaScint Scan

Given by intravenous injection, ProstaScint circulates throughout the body and attaches to prostate cancer cells. The injection contains a small amount of radioactive material that is absorbed by cancer cells and shows up as "hot spots" using a special camera.

A bone scan is an imaging test that can detect cancerous cells, evaluate fractures in the bones, and monitor other bone conditions, such as infections and arthritis. During a bone scan, a small dose of radioactive material is injected into a vein, where it travels through the bloodstream. The material collects in the bones and is detected by a scanner using nuclear imaging to reveal cell activity and function in the bones. A bone scan can detect cancer that has metastasized to the bone from a different primary site, such as the breast, prostate or lungs. It may also be used to evaluate bone health before treatment.

### EXPECTED DURATION

Once prostate cancer develops, it usually grows slowly over many years. In a small number of men, prostate cancer grows and spreads quickly. Almost all prostate cancer will respond to some type of treatment. In some cases, prostate cancer might not need treatment right away, if at all. Doctors have developed criteria to determine which cancers need treatment and which ones can be watched. If a watched tumor worsens, it can be treated [8, 10, 13].

### TREATMENT

Choosing the treatment option is among the most important decisions when dealing with prostate cancer. Prostate cancer can be treated several ways but the medical and lifestyle issues before choosing a treatment are to be considered [15]. These include:

- the extent of cancer and the chance that cancer will grow and spread rapidly
- age and life span
- any health conditions that would make surgery or other treatments riskier
- Willingness to risk side effects.

If the cancer is confined to the prostate gland, several options exist which are as follows:

- Watchful waiting
- Active surveillance

- Surgery
- Chemotherapy
- External Beam Radiation Therapy
- Immunotherapy
- Brachytherapy
- Hormone therapy
- Stereotactic Radio surgery

#### **Watchful waiting**

This approach can be used only when symptoms are diagnosed. The cancer should be monitored with DREs and PSA tests from time to time. This strategy is a good option for elderly men who are too ill for radiation or surgery, or who are likely to die from another medical condition relatively soon[16,17].

#### **Active surveillance**

Men whose prostate cancer doesn't need treatment right away may opt for active surveillance. If this approach is chosen, the patient will be followed more closely than with watchful waiting. Every three to six months, a PSA test and a physical examination are conducted with a biopsy every year or two. If any of these show increased disease activity, the treatment can be started. This is advantageous with no hospitalization or surgery, accuracy in monitoring, other side effects associated with radio-therapy can be minimized or avoided. The method is less proactive and requires repeated biopsies and follow-ups and has potential for the cancer to spread. This may sometimes lead to anxiety or other psychological stress [16-19].

#### **Surgery**

Surgical treatment may be an option for men who qualified based on their overall health and other factors. The cancer is removed either through an open or traditional operation or with robotic equipment. Patients with localized cancer may need no further treatment and Simultaneous biopsy allows for more accurate staging. Post- surgical PSA levels reliably predict recurrence of cancer. Fewer bowel or rectal side effects and less risk of urinary incontinence than with radiation treatments. Surgery related risks include long term sexual changes like dry orgasms, shortened penis, chronic leakage of urine and psychological stress, urine and stool incontinence and Chronic Groin Hernia[20].

#### **Chemotherapy**

Chemotherapy uses drugs to kill cancer cells or restrict their growth, generally prescribed for recurrent cancer.

Chemotherapy can be designed to slowdown the growth of prostate cancer and may reduce cancer-related symptoms including pain, fatigue and loss of energy. But certain short term side effects hair loss,

mouth sores loss of appetite, nausea, vomiting, diarrhora, bruising and bleeding and fatigue are seen. Long term effects include allergic reactions, numbness, blood clots, nerve damage etc [21-24].

#### **External Beam Radiation Therapy**

The therapy utilizes high-energy beams outside the body to reduce or eliminate tumors. It requires short treatment periods each of 15-25 minutes and is advantageous in causing no urinary incontinence and pain. It has low risk of sexual dysfunction. Fatigue and abdominal cramping are certain. Few long term effects like fecal incontinence, rectal bleeding are seen[25-26].

#### **Immunotherapy**

It is designed to boost the body's immune system to fight cancer cells in late-stage cancers. It helps identify prostate cancer cells and is considered a minimally invasive procedure. Chances of toxicity are low compared to chemotherapy. It may be accompanied with fever, chill, hypertension, nausea, vomiting, fatigue, and sometimes anemia and apnoea[27-29].

#### **Brachytherapy**

It is also called seed implantation It is a type of radiation therapy used to treat prostate cancer. The two types of brachytherapy are low-dose rate and high-dose rate brachytherapy. It is beneficial with less radiation damage to the healthy tissue and low risk of urinary incontinence. But may be associated with haematuria and painful urination. Urethral stenosis and erectile dysfunction are also seen[30,31].

#### **Hormone Therapy**

It is otherwise called Androgen Deprivation Therapy (ADT) and is designed to stop testosterone from fueling cancer growth. This method also requires no hospitalization or surgery required. But hot flashes, fatigue, depression and mood swings, decreased muscle and bone mass, libido, nausea and diarrhea, decreased mental capacity are short term side effects noticed[32].

#### **Stereotactic Radiosurgery (SRS)**

It is a form of radiation that focuses high-power energy on a small area of the body. Despite its name, it is a treatment, not a surgical procedure. When SRS is used for the treatment of body tumors, it is called Stereotactic Body Radiotherapy (SBRT). This type of treatment requires little recovery time with no hospitalization and is typically recommended for men with low-risk to intermediate risk prostate cancer. Pain, mild fatigue and nausea and temporary urinary frequency, burning during urination and urinary retention are diagnosed as short term side effects. Very rare urinary incontinence is seen[33].

**Table-1: Drugs approved for the treatment of Prostate cancer**

Sl no	Drug	Mechanism	Uses	Brand name/ Dosage form/dose
1	Abarelix	gonadotropin releasing-hormone (GnRH) antagonist,	Reduces testosterone (hormone) level in your body, which involves in the growth of most prostate cancers.	Plenaxis injectable Suspension (this brand is now unavailable in US) Generic versions are available)
2	Abiraterone Acetate	Interrupts the androgen production at the testes, adrenal glands and the tumor	To treat men with castration-resistant prostate cancer that is resistant to medical or surgical treatments that lower testosterone that has metasized	Zytiga 1000mg (4x250mg) tablets for oral use.
2	Bicalutamide	non-steroidal androgen inhibitor. Used with luteinizing hormone- release hormone agonist	Prostate cancer that has metasized	Casodex Tablets 50 mg for oral use.
3	Cabazitaxel	Microtubule inhibitor in combination with prednisone	To treat metasized cancer in men with prednisone whose cancer is hormone-refractory and whose cancer have been treated with other chemotherapeutic agents	Jevtana Injection 60mg/1.5 mL
4	Degarelix	gonadotropin releasing-hormone (GnRH) antagonist,	Advanced prostate cancer	Firmagon Injection 240 mg subcutaneous injection
5	Docetaxel	Disrupting the microtubular network in cells that is essential for mitotic and in terphase cellular functions.	Adrenocarcinoma, Breast Cancer, Non-small cell lung cancer, Prostate cancer, Squamous cell carcinoma of the Head and Neck	Docetaxel, 20mg, 40 mg vial for IV infusion, Taxotere Injection Concentrate, 20mg/mL, 80 mg/4mL
6	Enzalutamide	Androgen receptor inhibitor	Metastatic castration-resistant prostate cancer	Xtandi Capsules, 40mg
7	Flutamide	Androgen receptor inhibitor	Locally advanced or metalized carcinoma	Eulexin capsules, 125mg
8	Goserelin Acetate	Pituitary gonatropin secretion inhibitor	Breast and Prostate cancer	Zoladex implant 10.8mg-3 month Depot.
9	Leuprolide Acetate	gonadotropin releasing-hormone (GnRH) antagonist	Palliative treatment of advanced Prostate cancer	Leupron Depot-Ped.2.8MI Vial, Eligard suspension for subcutaneous injection. 7.5mg, 22.5 mg, 30 mg, 45mg
10	Mitoxantrone Hydrochloride	intercalates into DNA through hydrogen bonding, causes crosslinks and strand breaks and also Topoisomerase-II inhibitor	Advanced prostate cancer that is hormone-refractory	Novantrone 20 mg/10 mL/multidose vial (2 mg/mL) injection concentrate
11	Nilutamide	antiandrogenic	Metasized prostate cancer and who have had Orchiectomy	Nilandron 150mg tablets for oral use.
12	Sipuleucel-T	induce an immune response targeted against PAP, an antigen expressed in most prostate cancers	Metasized and hormone-refractory Prostate cancer	Provenge (250mL) suspension for IV infusion
13	Radium 223 Dichloride	alpha particle-emitting isotope radium-223 which mimics calcium and forms complexes with the bone mineral hydroxyapatite-leading to high frequency DNA breaks in adjacent tumor cells.	Castration-resistant and metasized prostate cancer	Xofigo (55 KBq) by slow IV infusion for one minute

## New treatments

### Cryoablation

This treatment, also called cryotherapy, kills cancer cells by freezing and then thawing them. It isn't offered at many hospitals, so finding an expert to perform the procedure in your area may be difficult. Additional research is needed to determine the long-term effects of cryoablation. Cryotherapy was approved as treatment for primary prostate cancer by the Centers for Medicare and Medicaid Services. The type of treatment an individual chooses depends on clinical stage, Gleason Grade, and patient preference. There are several mechanisms of action by which cryotherapy works to destroy prostate cancer cells. The first mechanism is the cells' response to freezing that induces cell death. 'Freeze rupture' is the term used to describe the method by which the extracellular fluid freezes and forms ice crystals. The extracellular fluid then becomes hyperosmotic, which causes the cells to lose water, followed by cell shrinkage and damage to the intracellular proteins. The extracellular osmolality can get as high as 8,000 mOsm by  $-15^{\circ}\text{C}$ . Another mechanism is that at temperatures less than  $-15^{\circ}\text{C}$ , intracellular ice begins to form, and cell metabolism fails, causing cell destruction. After such a thermal injury the cells begin to die by programmed cell death, or apoptosis. Also, once ice crystals form in the cell, they disrupt the cell membrane. As temperatures rise, vasodilatation occurs, causing increased cellular permeability and edema. This leads to endothelial damage and platelet aggregation. Cell fragments resulting from freeze rupture are responsible for initiating the inflammation cascade. Another mechanism of cell death is through vascular cells, which are injured by the freeze cycle and cause vascular stasis. Vascular stasis causes local hypoxia and secondary necrosis of the tissue[34].

High intensity focused ultrasound. This treatment destroys prostate cancer with high energy sound waves that heat cells to high temperatures. It is not currently an approved treatment for prostate cancer. Ongoing studies should help doctors determine if this procedure is safe and effective. If your prostate cancer has grown through the prostate capsule but has not spread (metastasized) to other organs, watchful waiting or radiation therapy (with or without hormone therapy) are usually recommended[35].

### Prevention

Although the evidence is mixed, men who eat a low-fat diet rich in fruits and vegetables may reduce their risk of prostate cancer. Older studies suggested that eating tomatoes, which contain the antioxidant lycopene, might reduce risk. Recent studies have questioned lycopene's value.

Some medications have been tested to see if they prevent prostate cancer. These include finasteride and dutasteride, drugs normally prescribed for benign

prostate enlargement. One study showed that men who took finasteride reduced their prostate cancer risk by 25 percent. But it also found that the risk of aggressive cancer went up in some men. Later studies found that the drug doesn't increase aggressive tumors. Given the contradictory findings, experts don't agree about whether to offer finasteride to men with a higher risk of prostate cancer than normal.<sup>[34,35]</sup>

### Manage your prostate cancer

- Do not smoke. Smoking increases your risk for new or returning cancer. Smoking can also delay healing after treatment. Ask your healthcare provider for information if you currently smoke and need help quitting.
- Limit or do not drink alcohol as directed. Limit alcohol to 2 drinks per day. A drink is 12 ounces of beer, 1½ ounces of liquor, or 5 ounces of wine.
- Eat a variety of healthy foods. Healthy foods include fruits, vegetables, whole-grain breads, low-fat dairy products, beans, lean meats, and fish. Your healthcare provider may also recommend changes to the amounts of calcium and vitamin D you have each day.
- Manage your weight. Obesity may increase your risk for problems from prostate cancer. Limit or do not have high-calorie foods or drinks.
- Exercise as directed. Exercise may help you recover after treatment and may help prevent your prostate cancer from returning. Exercise can also help you manage your weight. Try to get at least 30 minutes of exercise 5 days a week, such as walking.
- Ask about sexual activity. Ask your healthcare provider when it is safe for you to start having sex after your treatment. Medicines may be given if you have trouble getting or maintaining an erection.
- Manage incontinence. You may have incontinence (trouble controlling when you urinate) after treatment. Ask your healthcare provider for information on managing urinary incontinence. You may be able to gain control over your urination with techniques or medicines.
- Drink liquids as directed. Ask how much liquid to drink each day and which liquids are best for you. Drink extra liquids to prevent dehydration. You will also need to replace fluid if you are vomiting or have diarrhea from cancer treatments.

### CONCLUSION

As prostate cancer is one of the life threatening and most frequent case of disorders, proper treatment and other control strategies are of specific goals of many biomedical researchers. An integrated treatment strategy, which combines the local and systemic therapies, can be beneficial in the management of prostate cancer. However, the choice of treatment strategy is dependent on many factors, like patient

preference, and quality of life aspects. It is expected that within a near future, the treatment approaches like surgery, radiation therapy, hormonal, and chemotherapy would be much more developed without minimal side effects. And most importantly, proper dietary management may keep away a person from prostate cancer risk.

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