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PROSTATE CANCER: RISK FACTORS, SCREENING, DIAGNOSIS AND TREATMENT

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ABSTRACT: Prostate cancer is one of the most important cancer in men. In most cases, prostate cancer confirmed by histological and transrectal biopsy for the examination of prostatic tissue. Metastatic prostate cancer is second leading cause of death from cancer. Androgen deprivation therapy is common treatment in men with prostate cancer that may cause fatigue, increased body fatness, and loss of lean body tissue. Abiraterone acetate improved overall survival in Metastatic Castration-Resistant Prostate Cancer. Enzalutamide is a novel anti-androgen that is approved for the treatment of Metastatic Castration-Resistance Prostate Cancer after taxane-based chemotherapy. The management options include surveillance, radiotherapy, and radical prostatectomy, but there is no evidence base to evaluate the benefits of each approach. Advanced prostate cancer is managed by hormonal therapy. Active surveillance is a novel and fascinating approach to distinguish between patients who are at higher risk and need active therapy and patients who are at low risk for disease progression. This review provides a short overview of the various approaches of prostate cancer.

INTRODUCTION: Cancer is a major human health problem worldwide and is the second leading cause of death. Over the past thirty years, significant progress has been achieved in understanding the molecular basis of cancer. The accumulation of this basic data has established that cancer may be a style of distinct diseases in which defective genes cause these diseases. Further, gene defects are diverse in nature and can involve either loss or gain of gene functions. A number of inherited syndromes associated with increased risk of cancer have been identified.

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While cancer is clearly associated with an increase in cell number, alterations in mechanisms regulating new cell birth, or cell proliferation, are only one facet of the mechanisms of cancer. Decreased rates of cell death, Cancer is distinctive from other tumor-forming processes because of its ability to invade surrounding tissue. Cancer can occur in all types of body tissue. It is found in many forms, including solid tissue formations (tumors or neoplasm), leukemia's (blood cancer), and lymphomas (cancer of the lymphoid cells).

Cancers are due to a reduction in control or loss of control of the growth of cells. This leads to a proliferation of cell growth. In its early stages, the cells formed by this growth resemble the parent, but as the cancer progresses, they lose the appearance and function of the parent cell. This loss of function, if left unchecked, will become life-threatening. For example, growing tumors will

obstruct, block, and generally affect adjacent organs. If these are nerves, it will cause pain. Furthermore, cancer cells are invasive. As cancer grows, the cells lose their adhesion, and the malignant cells are carried in the blood to other parts of the body. These cells lodge in different parts of the body and grow into so-called secondary cancers. Malignant tumors can attack and destroy neighboring tissue and organs. Cancer cells can spread to other parts of the body and form a secondary tumor. Cancer is classified according to the cell or organ in which they start.

Prostate: Prostate is a walnut size small gland only found in man. It's below the bladder, near nerves, blood vessels, and muscles that control erections and bladder function. In response to sex, the prostate produces seminal fluid, the liquid that carries the sperms. The male sex hormone, testosterone, is made by the testicles and control the growth of the prostate.

It is normal for the prostate to become as large as men get older. Sometimes this can cause problems, especially with urination. Prostate cancer begins when abnormal cells are growing in the prostate in an uncontrolled way. Prostate cancer grows more slowly than other types of cancer. The risk of prostate cancer increases with age.

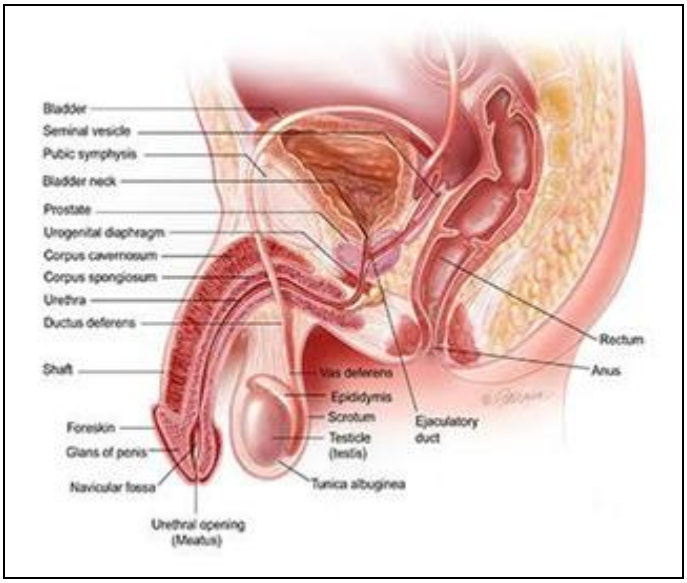

FIG. 1: PROSTATE

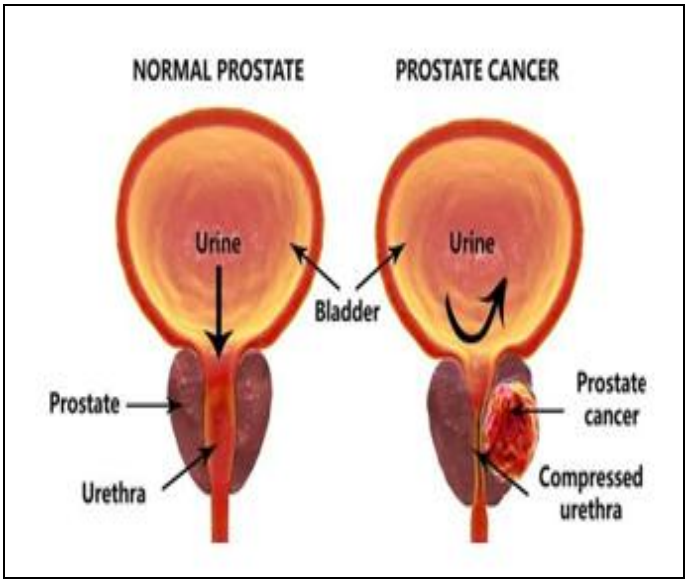

FIG. 2: PROSTATE CANCER

Signs and Symptoms: There are no symptoms in the earlier stage of prostate cancer.

- Poor urinary flow.
- Urinary frequency, particularly at night.
- Urinary hesitancy.
- Felling of incomplete bladder emptying.
- Urinary urgency.
- Incontinence.
- Urinary tract infection.
- Blood or pus may be passed in urine or semen.
- Aches and pain in the back and hips.
- Weight loss and fatigue.

Risk Factors: Clinically, prostate cancer is a heterogeneous disease. According to clinical features of the disease, the factors and prostate cancer risk may differ. The age and high-fat diet increase risk, and family history may increase men's risk. Recently, the genetic predisposition to prostate cancer is provided additional evidence by genome-wide-association study (GWAS). Age and taller height are strongly associated with risk of total prostate cancer. The men younger than 40 year of age prostate cancer is rare, after 55 years of age prostate cancer incidence rate increase dramatically. In 2012, 10% of US men diagnosed with prostate cancer. The implementation of PSA screening in US prostate cancer diagnosis age shifted earlier and currently 66 years of age.

Obesity, leading a higher level of insulin, estradiol, and inflammatory cytokines and lower level of adiponectin, testosterone, and sex hormone-binding globulin, is caused by dysregulation of the hormonal pathway. Change obesity and weight is a

need for prostate cancer strategies. Cigarette smoking, alcohol consumption, cadmium exposure, occupation infectious agent, ionizing radiation, ultraviolet light, physical activity, body mass, and dietary factor are an environmental risk factor. One study found number of female sexual partners and prior infection with gonorrhea supporting influence of infectious agents increase the risk of prostate cancer. Higher serum testosterone levels and higher cholesterol levels increase risk of prostate cancer.

TABLE 1: SUMMARY HAS BEEN GIVEN BELOW WITH RESPECT TO EVIDENCE FOR SELECTED RISK FACTOR OF PROSTATE CANCER

S. no.	Risk Factor Increased Risk	Strength of evidence
1	Older Age	Strong
2	African Descent	Strong
3	Family History	Strong
4	Genetic Risk Loci	Strong
5	Taller Height	Probable

Hormones: The hypothalamus stimulates the hormones from anterior pituitary gland, *i.e*., The Luteinizing hormones and follicle-stimulating hormones. The hormones are released due to luteinizing hormones. The luteinizing hormones produce testosterone because of stimulation occurs in leydig cells of testicles. Stromal and epithelial cella present in prostate glands under the androgen influence. The testosterone enters into anderogen cells of organs and canuerted into dihydro-testosterone (DHT) by enzyme. The active metabolites are responsible for prostatic develop-ment estrogen and prolactin responsible for the growth of the prostate gland directly or indirectly by negative feedback inhibition.

Screening and Diagnosis: In most cases, prostate cancer confirmed by histological and transrectal biopsy for the examination of prostatic tissue. In prostate cancer tumor marker is PSA, MRI is the most sensitive technique for detecting bone metastases in prostate cancer.

Prostate-specific antigen: Prostate-specific antigen (PSA) is a protein made by both normal and cancerous prostate cells. The blood test used to measures the PSA level. PSA level up to 2 ng/ml.

Prostate-specific membrane antigen (PSMA) is an excellent target for prostate cancer PSMA expression level enhanced in high grade, metastatic, and castration-resistant prostate cancer cells and also expressed other cells.

Digital Rectal Examination (DRE): The estimation of prostate size in DRE, and identify abnormality of prostate cancer. In DRE, the specialist inserts a gloved finger into the rectum to feel back of the prostate; it is uncomfortable but rarely painful. Hardened area or odd shape during testing, then further testing may be done.

MRI Scan: Magnetic resonance imaging scan uses a powerful magnet and radio waves to build details of the inside of the body. Multi-parametric magnetic resonance imaging (mpMRI) is used for prostate cancer. The abnormal area show in MRI and also help to show cancer can spread from the prostate to nearby areas.

Serum and Urine Markers: It utilizes non-invasive prostate cancer detection and investigated improvements in PSA assay. In the biological fluid measure, the molecular isoform of free PSA by using prostate health index (PHI). The urinary markers detection methods are complicated and require trained personal to run the assay.

Two methods are PCA3 markers that are more specific than PSA and measure mRNA selectively, and it also provided information about total prostate volume, and PCA3 identifies cancer effectively, but it does not differentiate between low-risk and aggressive form of prostate cancer. The second urinary marker is spots fusion of TMPRSS2 with ERG is under development and able to efficiently differentiate between the aggressive and low risk of prostate cancer forms.

The 4 markers Kallikrein panel and PCA3 provided more accurate information than the PSA detection method. The easy diagnosis and prognosis of prostate cancer the DNA methylation markers are used.

Biopsy: Biopsy is the second test performed after the PSA, and DER shows abnormality. In a biopsy, the small amount of tissue taken from different parts of the prostate using a special needle. With the help of transrectal ultrasound (TRUS), the biopsy is done. A small probe inserted into the rectum and send out sound waves. A computer creates an image when sound waves meet the

prostate. Using the TRUS image, the doctor inserts a thin, hollow needle into the prostate.

- Baseline biopsy
- Repeat biopsy
- Saturation biopsy
- Sampling sites and number of cores
- Diagnostic transurethral resection of the prostate (TURP)
- Seminal vesicle biopsy
- Transition zone biopsy
- Antibiotic prior to biopsy
- Local anesthesia prior to biopsy
- Fine-needle aspiration biopsy

Markers in Needle Biopsies: In the advanced stage of the disease the needle biopsy is done. The unnecessary radiation treatment or other painful management of the disease is avoided by using the identified marker.

The most recognized marker and differentiation between early-stage and aggressive stage prostate cancer detection by Ki-67 immunohistochemistry. The detection of PTEN the immunohistochemistry and FISH (Fluorescent *in-situ* Hybridisation) assay are developed.

Men with Elevated PSA but Negative Biopsies: Some patients show a negative signature in biopsy but a high level of PSA. After a negative biopsy, some patient shows a high incidence of development of prostate cancer after a few years.

Further Tests: Prostate cancer shows in a biopsy, other tests done, and also regular blood tests to check PSA, prostate cancer activity, and general health.

Bone Scan: The bone scan shows cancer spread to bones. For the bone scanning, the small amount of the radioactive substance injected into a vein and waits for the 1-2 h; the substance moves bloodstream to bone.

The whole body scanned with a machine that detects radioactivity. Lager amount of radioactivity shows up in an area of bone with cancer cells.

CT Scan: Computerised tomography scan used x-ray to create a detailed image of the inside of the body. CT scan show cancer spread to lymph odes in that area.

PET Scan: Positron emission tomography scan is a sensitive scan that helps detect cancer that has come back or spreads. The small amount of radioactive solution was injected, the cancer cells take up this solution and show up brighter on the scan.

Clinical Staging: Staging is the process of working out how cancer and whether has spread to another part of body. The TNM system is use for staging prostate cancer. T is for the size of tumour, N is for the cancer spread to nearby lymph nodes, and M is for whether cancer spread to bones or other organ or metastasized. The TNM score combined with working out the overall cancer staging, stage 1 to stage 4 the stage 3, and stage 4 is advanced stages.

TABLE 2: PROSTATE CANCER STAGING

Stage 1-2	The cancer is contained inside the prostate.	Localized/ early
Stage 3	The cancer is larger and has spread outside the prostate to nearby tissues of nearby organs such as the bladder, rectum or pelvic wall.	Locally advanced
Stage 4	Cancer has spread to distant parts of the body such as lymph glands or bone. This is called prostate cancer, even if the tumor is in a different sort of tissue.	Metastatic

American Joint Committee on Cancer (AJCC) TNM Staging: The Size and Extent of the Primary Tumour (T Stage):

1. T1 the tumor is not detectable with a digital rectal exam (DER) and biopsy or surgical treatment.

A. T1a cancer is found in 5% or less.

B. T1b cancer is found in more than 5%.

C. T1c tumors are found by needle biopsy done for a high PSA.

2. T2 the tumor is detectable with a DRE or imaging but is confined to the prostate.

A. T2a cancer is in no more than on half of one side of the prostate.

B. T2b cancer is in more than half of one side of the prostate.

C. T2c cancer is in both sides of the prostate.

3. T3 cancer has grown outside the prostate and may have grown into the seminal vesicles.

A. T3a cancer has spread outside the prostate but not to the seminal vesicles.

B. T3b cancer has spread to the seminal vesicles.

4. T4 cancer has grown into other nearby tissue, such as the urethral sphincter, rectum, bladder or wall of the pelvis.

2. Whether the cancer has spread to nearby lymph nodes (N stage)

A. NX the lymph nodes have not been assessed for cancer.

B. NO, there is no cancer in nearby lymph node.

C. N1 cancer has spread to nearby lymph nodes.

3. The absence or presence of cancer outside the prostate, or Metastasis (M stage)

A. MX it is unknown if cancer has spread to distant sites.

B. MO the cancer has not spread to distant sites.

C. M1 cancer has spread to distant sites.

I. M1a cancer has spread to distant lymph nodes.

II. M1b cancer has spread to bones.

III. M1c cancer has spread to a distant organ.

4. The PSA level at the time of diagnosis prostate-specific antigen or PSA is a protein produced by cells of the prostate gland. The PSA test measures the level of PSA in a man's blood. PSA is present in small quantities in the serum of men with healthy prostates but is often elevated in the presence of prostate cancer or other prostate disorders.

Gleason Score: The Gleason Score is the grading system used to determine the aggressiveness of prostate cancer. This grading system can be used to choose appropriate treatment options. The Gleason Score ranges from 1-5 and describes how much cancer from a biopsy looks like healthy tissue or abnormal tissue.

Most cancer score a grade of 3 or higher. If the Gleason Score is written as 3+4=7, it means most of the tumor is grade 3, and the next largest section of tumor is grade 4, together they make up the total Gleason Score. If the cancer is almost entirely made up of cells with the same score, the grade for that area is counted twice to calculate the total Gleason Score.

- A score of 6 or less describes cancer cells that look similar to normal cells and suggest that the cancer is likely to grow slowly.
- A score of 7 suggests an intermediate risk for aggressive cancer. Scoring a 7 means that the primary score 3 and 4. Tumours with a primary score of 3 and a secondary score of 4 have a fairly good outlook, whereas cancers with a primary Gleason Score of 4 and a secondary score of 3, are more likely to grow and spread.
- Scores of 8 or higher describe cancers that are likely to spread more rapidly; these cancers are often referred to as poorly differentiated or high grade.

Important of Gleason Score: The Gleason Score is very useful for predicting the behavior of prostate cancer. However, other factors also contribute to determining the stage of prostate cancer, including:

1. The PSA level.

2. Finding from a rectal exam.

3. The number of biopsy core samples that contain cancer.

4. The percentage of cancer making up each biopsy core sample.

5. If cancer is found in one or both sides of the prostate.

6. If the cancer has spread outside the prostate.

Treatment: Prostate cancer is typically slow-growing, giving men time to make the decision about their management or treatment options. Sometimes it is difficult to decide on the type of management or treatment that is right for the patient.

Active Surveillance: Active surveillance is used for monitoring prostate cancer that isn't causing any symptoms or problems. It may give an idea about the cancer is small and slow-growing and is unlikely to spread or cause symptoms.

Active surveillance involves PSA tests every 3 months, DRE every six months, mp MRI scans, and biopsies at 12 months and three years. If cancer is faster and more aggressive growth, start treatment with the aim of curing cancer.

Watchful Waiting: Another way to monitoring prostate cancer. This involves regular PSA tests and clinic check-ups. The process is less strict than the active surveillance and biopsy is not required. The treatment can be considered if the cancer spreads or causes symptoms. The aim of treatment will be to treat symptoms that may be causing problems, rather than cure the prostate cancer.

Surgery: The surgery aims to remove the cancer completely by removing the prostate, part of urethra, and seminal vesicles. For the more aggressive cancer, nearby lymph glands may also be removed.

Type of Radical Prostatectomy: The different surgical techniques used in radical prostatectomy. The extra cost involved for options, but they are not available at every hospital.

1. **Open Radical Prostatectomy:** usually cut in the lower abdomen.

2. **Laparoscopic Radical Prostatectomy:** the prostate can be removed via keyhole surgery.

3. **Robotic-Assisted Radical Prostatectomy:** the surgery can be performed using a robotic device. In this surgery, the surgeon sees the three-dimensional picture and use more advanced instruments than those used for conventional laparoscopic surgery. This is called robotic-assisted laparoscopic radical prostatectomy or RARP.

4. **Nerve-Sparing Radical Prostatectomy:** this involves the prostate, and seminal vesicles are removed and preserve the nerves that control erections. This procedure suitable for lower grade cancer but only possible if the cancer is not close to nerves.

Side Effects of Prostate Cancer Surgery:

- Nerve damage.
- Loss of bladder control.
- Erection problems.
- Infertility
- Penile shortening.

Radiation Therapy: The treatment offered to men with early prostate cancer. It is generally offered as an alternative to surgery and similar rates of success. Sometimes radiation therapy is used after prostatectomy for locally advanced or more aggressive cancers or signs the no total cancer removed by surgery.

External Beam Radiation Therapy (EBRT): In EBRT the targeted radiation to kill cancer cells or injure them so they cannot multiply. Radiation is generally x-ray beams.

Side Effect of EBRT:

- Erection problems
- Changes in ejaculation
- Infertility
- Skin irritation
- Tiredness
- Urinary problem
- Bowel problems

Brachytherapy: type of targeted internal radiation therapy, the radiation source is placed directly within the prostate. The doses of radiation given directly inside of prostate, and limits the effects on nearby tissue such as rectum and bladder. Permanent brachytherapy involves the radioactive seeds put into prostate. It is also called low-dose-rate (LDR) brachytherapy. The seeds slowly release radiation to kill cancer cells and lose radioactivity after about three months. Temporary brachytherapy is also called as high-dose-rate

(HDR) brachytherapy, the radiation delivered through hollow needles that are inserted into the prostate, usually under general anesthetic. With the help of needle, the high dose of radiation is delivering.

Androgen Deprivation Therapy (ADT): Androgen deprivation therapy is a common treatment in men with prostate cancer that may cause fatigue, functional decline, increased body fatness, and loss of lean body tissue. These physical changes can negatively affect health-related quality of life-resistance exercise may help to counter some of these side effects by reducing fatigue, elevating mood, building muscle mass and reducing body fat, the primary androgen deprivation therapy improve and reduce serum level of prostate-specific antigen (PSA) symptomatically and induced symptomatic care with narcotic analgesics, radiotherapy to dominant sites of bone pain, treatment with bone-seeking isotopes such as strontium-89 and cytotoxic chemotherapy.

ADT injections are often used before, during, and after radiation therapy. The main treatment for advanced prostate cancer, often combined with chemotherapy. The injection given in cycles, with treatment continuing until the PSA level is low and stopped for a period of time. It can be restarted if PSA rises again; this is known as intermittent ADT.

Medicines used in ADT:

GnRH Agonists: Gonadotropin-releasing hormone agonists stopped the production of male hormones (androgen) and caused shrink the prostate. GnRH agonists are given every one to six months or 12 months, and it includes leuprolide and goserelin.

GnRH Antagonist: Degarelix is GnRH antagonist that temporarily stopped the production of male hormones (androgen), and it is more rapidly active than GnRH agonist.

Combined Androgen Blockade: Some time doctors recommended antiandrogen as second medicine with GnRH agonist. Antiandrogen, flutamide, bicalutamide.

Side Effect of ADT:

1. Decreased libido and difficulties with erestion.
2. Hot flashes.
3. Enlargement of breasts (Gynecomastia).
4. Loss of muscle and increase in body fat.
5. Thinning and weakening of bones (osteoporosis) which can increase the risk of bone fractures.
6. Increased risk of developing type 2 diabetes.
7. Increased risk of developing or worsening coronary heart disease and lead to heart attack.
8. Mood swings, depression, trouble with thinking and memory.

Castration-Resistant Prostate Cancer: Sometimes, the tumors do not require a response or have stopped responding to testosterone-lowering hormone treatment. This type of cancer is called castration-resistant prostate cancer. The most common malignancy in prostate cancer in Western societies. The second most common cause in the UK and USA is prostate cancer in males which has 12% of death. By using PSA for screening, 15-33% of men fail to local therapy, and that is responsible for developing incurable metastatic disease. Androgen receptor is activated by testosterone and more potent 5-alpha reduced metabolite, 5-alpha dihydrotestosterone. These are androgenic steroids. This regulates the transcription of a diverse range of target genes; this is involved in the proliferation of prostate cells along with its differentiation and apoptosis. Continued androgen-dependent activation is done that is given below.

- Hypersensitive androgen receptor
- Gene amplification
- Mutation in the androgen receptor gene
- Increased androgen receptor expression
- Alteration in androgen receptor co-repressor / co-activator function

This important mechanism was taken place in castration resistance.

Abiraterone: Abiraterone is medication drug blocks the production of androgens by prostate

cancer as well as testes and adrenal glands and abiraterone given in combination with ADT and improve survival. Abiraterone taken with a steroid to avoid serious complication blocked enzyme called CYP17. Abiraterone acetate significantly decreases intracellular testosterone levels by suppressing its synthesis at the adrenal level as inside cancer cells. The abiraterone acetate used along with prednisone. It's avoided during pregnancy; no food should be eaten 2 h before and 1 h after taking abiraterone acetate.

A side effect of abiraterone acetate is high blood pressure (hypertension), low blood potassium level (hypokalemia), fluid retention (edema), dizziness, fast heartbeats, muscle weakness, feeling faint or lightheaded, pain in legs, headache, swelling in legs or feet. Adrenal problems may stop taking prednisone.

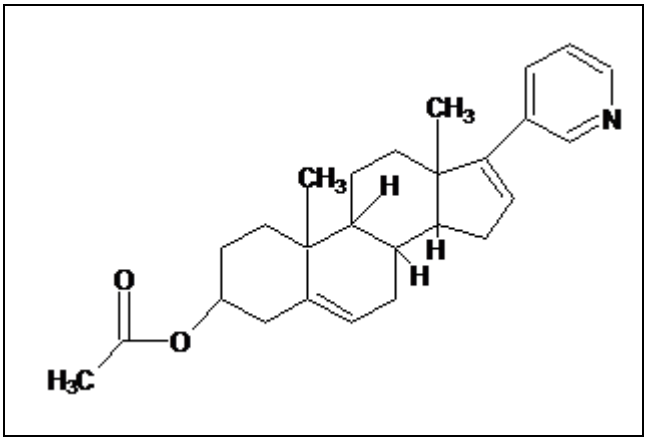

FIG. 3: ABIRATERONE

Enzalutamide: Enzalutamide is an agent that blocks the effect of androgens in stimulating the growth of prostate cancer cells and increase survival in men who have been treated with chemotherapy. After taxane-based chemotherapy, the enzalutamide is the novel antiandrogen approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Enzalutamide is said to be a novel androgen receptor inhibitor, it acts as antiandrogen agents, and that helps in the inhibition of nuclear translocation of androgen receptor and DNA binding. The binding of the androgen receptor to coactivator proteins is also prevented.

It gives agonistic effects, but it is not known again; it has a high affinity to the androgen receptor. In phase III, a randomized, placebo-controlled trial was performed on mCRPC patients, often the administration of Docetaxel chemotherapy is done.

A side effect of enzalutamide is a weakness or feeling more tired than usual, back pain, diarrhea, pain in joints, hot flashes, swelling in hands, arms, legs or feet, muscles or bone pain, headache, cold-like symptoms, muscles weakness dizziness, trouble falling or staying asleep, and breathing, back pain with nerve problems in the lower body, including leg numbness or weakness, pink or red urine, the sensation of tingling, burning, pricking, or numbness of skin, anxiety, high blood pressure.

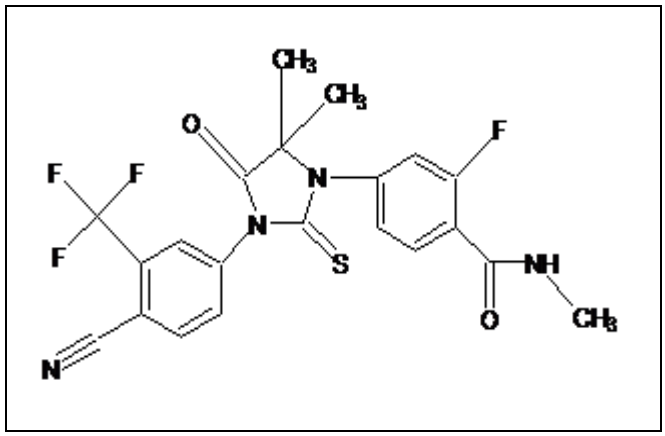

FIG. 4: ENZALUTAMIDE

American Urological Association (AUA) Guideline for Castration-Resistant Prostate Cancer:

1. Clinicians should recommend observation with continued androgen deprivation to patients with non-metastatic CRPC.
2. Clinicians may offer treatment with first-generation anti-androgens (flutamide, bicalutamide, and nilutamide) or first-generation androgen synthesis inhibitors (ketoconazole+ steroid) to select patient with non-metastatic CRPC who are unwilling to accept observation.
3. Clinicians should not offer systemic chemotherapy or immunotherapy to patients with non-metastatic CRPC outside the context of a clinical trial.
4. Clinicians should offer abiraterone + prednisone, enzalutamide, docetaxel, or sipuleucel-T to the patient with asymptomatic or minimally symptomatic mCRPC with good

performance status and no prior docetaxel chemotherapy.

5. Clinicians may offer first-generation anti-androgen therapy, ketoconazole + steroid or observation to the patient with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy who do not want or cannot have one of the standard therapies.

6. Clinicians should offer abiraterone + prednisone, enzalutamide or docetaxel to the patient with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy.

7. Clinicians may offer ketoconazole + steroid, mitoxantrone or radionuclide therapy to patients with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy who do not want or cannot have one of the standard therapies.

8. Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC with good performance status and no prior docetaxel chemotherapy and without the known visceral disease.

9. Clinicians should not offer treatment with either estramustine or sipuleucel-T to the patient with symptomatic, mCRPC with good performance status, and no prior docetaxel chemotherapy.

10. Clinicians may offer treatment with abiraterone + prednisone or enzalutamide to patients with symptomatic, mCRPC with poor performance status, and no prior docetaxel chemotherapy.

11. Clinicians may offer treatment with ketoconazole + steroid or radionuclide therapy to a patient with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy who are unable or unwilling to receive abiraterone + prednisone or enzalutamide.

12. Clinicians may offer docetaxel or mitoxantrone chemotherapy to patients with symptomatic mCRPC with poor performance status and no prior docetaxel chemotherapy in select cases, specifically when the performance status is directly related to cancer.

13. Clinicians may offer radium-223 to patients with symptoms from bony metastases from mCRPC with poor performance status and no prior docetaxel chemotherapy and without known visceral disease in select is directly related to symptoms related to bone metastases.

14. Clinicians should not offer sipuleucel-T to patients with symptomatic, mCRPC with poor performance status, and no prior docetaxel chemotherapy.

15. Clinicians should offer treatment with abiraterone + prednisone, cabazitaxel or enzalutamide to patients with mCRPC with good performance status who received prior docetaxel chemotherapy. If the patient received abiraterone + prednisone prior to docetaxel chemotherapy, they should be offered cabazitaxel or enzalutamide.

16. Clinicians may offer ketoconazole + steroid to patients with mCRPC with good performance status who received prior docetaxel if abiraterone + prednisone, cabazitaxel or enzalutamide is unavailable.

17. Clinicians may offer retreatment with docetaxel to patients with mCRPC with good performance status who were benefitting at the time of discontinuation (due to reversible side effects) of docetaxel chemotherapy.

18. Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC with good performance status who received prior docetaxel chemotherapy and without the known visceral disease.

19. Clinicians should offer palliative care to patients with mCRPC with poor performance status who received prior docetaxel chemotherapy. Alternatively, for selected patients, clinicians may offer treatment with abiraterone + prednisone, enzalutamide, ketoconazole + steroid, or radionuclide therapy.

20. Clinicians should not offer systemic chemotherapy or immunotherapy to patients with mCRPC with poor performance status who received prior docetaxel chemotherapy.

21. Clinicians should offer preventative treatment (*e.g.,* supplemental calcium, vitamin D) for fractures and skeletal-related events to CRPC patients.

22. Clinicians may choose either denosumab or zoledronic acid when selecting a preventative treatment for skeletal-related events for mCRPC patients with bony metastases.

Chemotherapy: Chemotherapy slow or stop the growth of cancer cells. The chemotherapy recommended in combination with ADT and also given to men with advanced prostate cancer who have stopped responding to initial therapy, including hormone therapy. Commonly used chemotherapy agents are docetaxel, cabazitaxel, mitoxantrone, and estramustine and administration by intravenous (IV) route. This therapy is not given every day but instead in cycles. The docetaxel and cabazitaxel cause severe allergic reactions and damage nerves. The mitoxantrone rarely causes leukemia, and estramustine increases the risk of blood clots.

Side Effect of Chemotherapy:

1. Temporary hair loss.
2. Nausea and vomiting.
3. Decrease in a number of blood cells that fight infection and increases risk of developing infection.
4. Loss of appetite.

For the safe use of docetaxel, the premedication is given with dexamethasone.

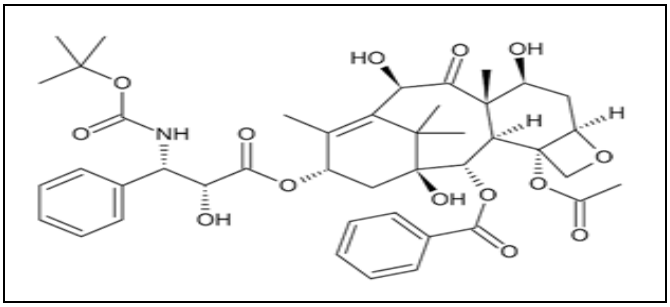

FIG. 5: DOCETAXEL

Radium-223: Radium-223 is localized in bone, and radioactive element for advanced prostate cancer for the effective relieving bone pain and complications prevention the treatment of radium-223 is given. In phase I and II with radium-223, the minimal myelotoxicity is reported in patients with bone metastases. Phase II show decrease pain and improves disease-related biomarkers.

To continue the treatment of patients with castration-resistant disease, maintenance is required. The radium-223 given by intravenously

Modern Treatment of Prostate Cancer:

Immunotherapy: Target to activate immune cells-PSA, PAP (prostatic acid posphatase), and PSMA.

1. Cell-based vaccines: Sipuleucel-T target PAP for the treatment of metastatic castration-resistant prostate cancer. Stimulate dendritic cells and activate T-cell and enhance the antitumor effect. i.e., GM-CSF Transduced tumor cell vaccine (Gvax) consists of two immortalized cell lines of prostate cancer and transfected to express granulocyte/macrophage colony-stimulating factor. Break immune tolerance and give a potential antitumor immune response.

2. Virus-based vaccines: The virus-based vaccine inserts plasmid-encoding for tumor proteins into a viral vector, and it infects host's epithelial cells and activates CD^{4+} and CD^{8+} T-cells.

3. DNA-based vaccines: The DNA-based vaccine is administered subcutaneously or intramuscularly. The DNA is taken up by host cells and proteins expressed. DNA vaccines are immunogenic.

Passive Immunotherapy: Passive immunotherapy is an attractive and most advanced strategy. The passive immunotherapy involves a general monoclonal antibody for desired therapeutic efficacy. *i.e.,* Cetuximab- inhibit signals for cellular growth. Bevacizumab- inhibit signals for pro-angiogenesis.

CONCLUSION: The prevention of prostate cancer is challenging. The diagnosis and treatment of prostate cancer based on cancer progression and patient preference. As compared to androgen

deprivation therapy, the initial chemotherapy is best. Patients with metastatic prostate cancer resistant to traditional hormonal therapy abiraterone, enzalutamide, and other agents improve the result. Enzalutamide significantly prolonged survival in men with metastatic castration-resistant prostate cancer after chemotherapy.

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