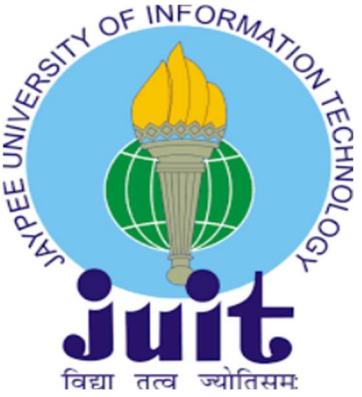
MARKET RESEARCH ON PROSTATE CANCER – DISEASE OVERVIEW, EPIDEMIOLOGY, AND MARKET ASSESSMENT

Enrollment No. – 181506

Name of Student – Dron Saklani

Under the supervision of Dr. Tiratha Raj Singh and Rajesh Kumar



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in

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DEPARTMENT OF BIOTECHNOLOGY AND BIOINFORMATICS

JAYPEE UNIVERSITY OF INFORMATION TECHNOLOGY, WAKNAGHAT

DECLARATION

"I hereby declare that this submission is my/ own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree or diploma of the university or other institute of higher learning, except where due acknowledgment has been made in the text."

Place: Signature:

Date: 14-05-2022 Name: Dron Saklani

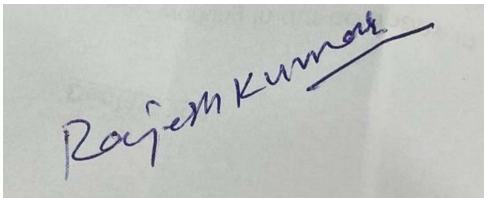
Enrollment No: 181506

CERTIFICATE

This is to certify that the work titled "**Market Research on Prostate Cancer – Disease Overview, Epidemiology, and Market Assessment**" submitted by "**Dron Saklani**" in partial fulfillment for the award of degree of B.Tech Bioinformatics of Jaypee University of Information Technology (JUIT), Waknaghat has been carried out under our supervision. This work has not been submitted partially or wholly to any other University or Institute for the award of this or any other degree or diploma.

Name and Signature of Supervisor (s)

Date: 14-05-2020



Dr. Tiratha Raj Singh (Associate professor) Rajesh Kumar (Team manager)

ACKNOWLEDGMENT

I would like to express my deep and sincere sense of gratitude to my project guide Dr. Tiratha Raj Singh and my team manager, Mr. Rajesh Kumar for their unwavering support and guidance throughout the course of the project. Without his expertise in the subject, I would not have been able to complete the project credibly and on time. I would also like to express my gratitude for my team's support, encouragement, and constructive criticism, which all contributed significantly to the project's progression of ideas.

Signature of the Student

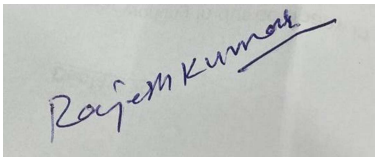
Name of Student	Dron Saklani
Enrollment Number	181506
Date	14-05-2022

SUMMARY

During the course of this project, I have been working as an Associate Analyst in the Market Analytics and Forecasting team at DelveInsight Business Research LLP which is a business consulting firm specializing in the pharmaceutical and healthcare sector. In the project titled, "Market Research on Prostate Cancer – Disease Overview, Epidemiology, and Market Assessment", I worked on the disease of Prostate Cancer to analyze its aspects in terms of epidemiology, treatment practices, and guidelines in order to understand the current market scenario of the indication to provide the market drivers, barriers and challenges to market access.

Signature of Student -

Signature of Supervisor (s) –



Name – Dron Saklani

Name - Dr. Tiratha Raj Singh and Mr. Rajesh Kumar

Date – 14-05-2022

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1 ABOUT THE COMPANY

DelveInsight is a business consulting firm specializing in the life science sector, with a primary focus on the pharmaceutical and biotech industries. The company's goal is to assist clients in making solid business decisions, allowing them to achieve extraordinary success.

DelveInsight has been a trailblazer in providing cutting-edge services to its clients and encouraging informed predictions of likely market changes since its inception.

DelveInsight specializes in providing both detailed and customized market research analysis to help clients achieve their business goals and uncover new market opportunities by utilizing a highly skilled workforce with extensive industry knowledge, domain expertise, and an internal database to provide clients with cutting-edge services.

Figure 1: DelveInsight Logo, Source: DelveInsight

Figure 2: DelveInsight Services, Source: DelveInsight

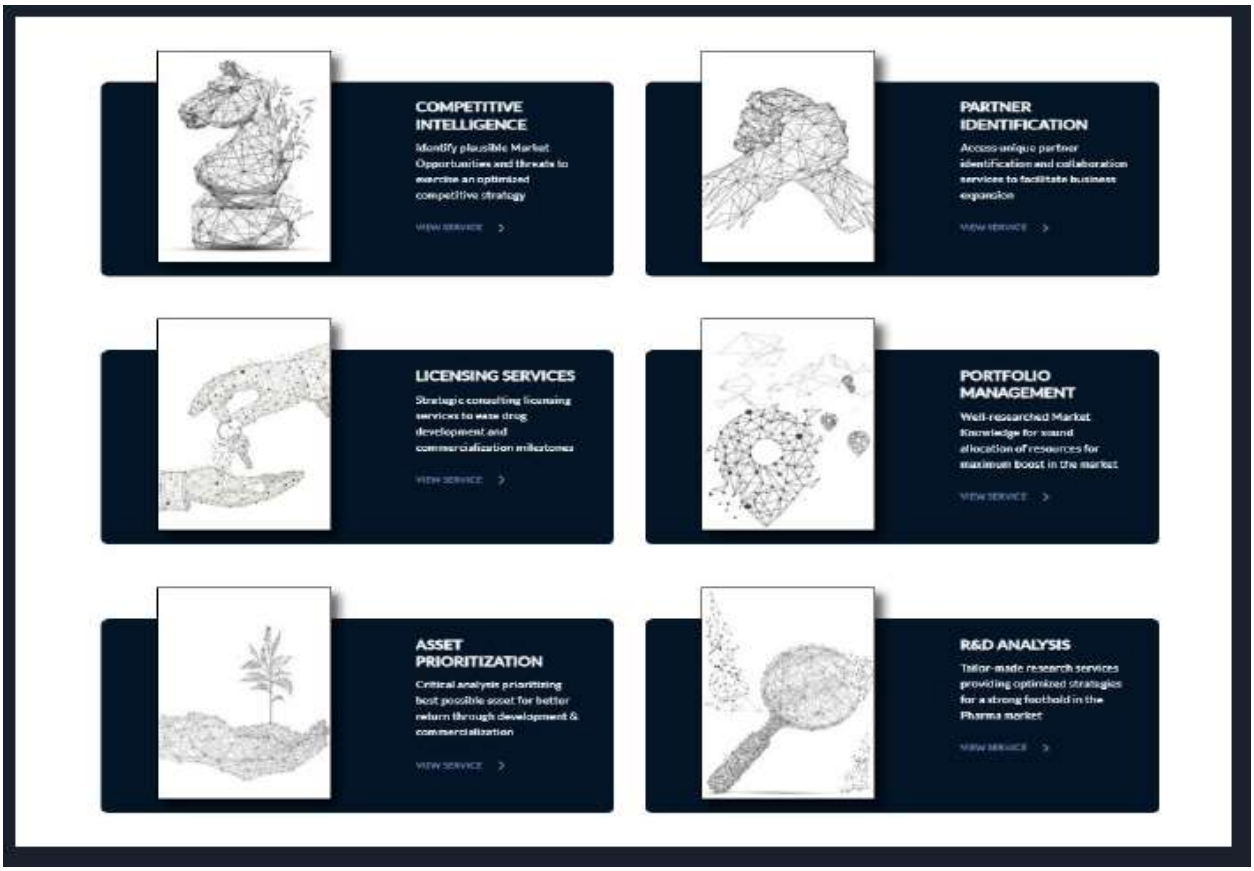

Figure 3: DelveInsight Business Consulting, Source: DelveInsight

2 JOB ROLE AND RESPONSIBILITIES

JOB PROFILE - ASSOCIATE ANALYST (MARKET ANALYTICS AND FORECASTING TEAM)

- Conduct detailed market research and analyze the data to develop understanding of the disease based on the requirements of the respective client.
- Develop bottom-to-top drug and disease forecast models for a variety of therapeutic areas
- Conduct comparative studies and make recommendations based on data analysis and interpretation.
- For conclusive analysis in many therapeutic areas of client interest, data mining, business intelligence, and valuation are used.
- Convert models into presentable Reports and PowerPoint presentations for customer use

3 MARKET RESEARCH

The pharmaceutical industry is a multibillion-dollar industry that is responsible for drug research, development, production, and distribution for both humans and animals. The stakes are great; when a new treatment is developed, lives and money are on the line. The process is cumbersome and long from drug consumption to delivery. Conducting necessary research is vital to ensuring that businesses meet the demand with the required information and tools. Businesses risk squandering capital and time creating a product that no one wants or needs.

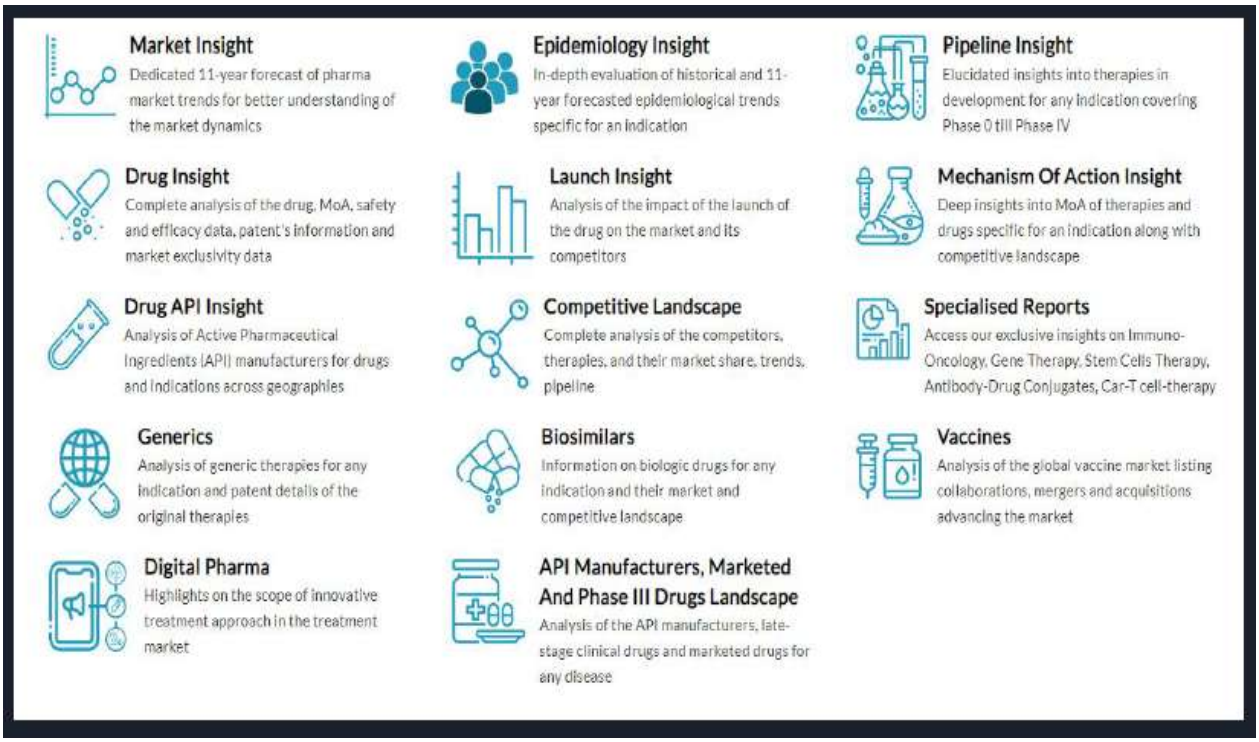

Figure 4: DelveInsight Market research, Source: DelveInsight

Clinicians, hospitals, distributors and pharmacies are all served by big pharmaceuticals. With so many various types of customers, medicine companies must learn everything they can about each one in order to target the most profitable areas. It can be done by employing a variety of research methods. It can be done using secondary research or primary research.

It's critical to choose the right environment to encourage medicine (both physically and in general). Disease patterns, economic stability, market size etc. are just a few of the key factors that affect a

company's overall product performance. Pharmaceutical market research can disclose any potential stumbling blocks or opportunities that could hinder or support successful outcomes.
The introduction of new products to the market is a major threat. Generics tend to have a major negative impact on a business's bottom line. As a result, pharmaceutical companies must keep up with what their rivals are developing and improving. SWOT analysis and sales force assessments can be used to identify and address shortcomings. Focus groups and interviews can be used to reveal neglected technology developments and other resources. Using competitive research, businesses may avoid reinventing the wheel. Instead, they could watch and profit from others' victories.

The pharmaceutical industry follows strict regulations. It is important to take care of patient and data privacy issues while still complying with FDA. Pharmaceutical market research aids the firms to stay on top of evolving patent laws and FDA regulations, as well as obtain consumer feedback, to protect or change their operations as necessary.

A well-designed pharmaceutical market research project tells about industry trends and improves forecasts. It might reflect a company's success (or failure) in terms of different parameters. It can provide the insights necessary for accurate identification of unmet requirements. This data assists shareholders in focusing and directing actions that affect the company's future.

4 INTRODUCTION - PROJECT SCOPE

To conduct a systematic literature review to understand country-specific epidemiology for Prostate cancer. Additionally, to understand factors behind rising/declining epidemiology trends and to provide your findings.

To understand country-specific diagnostic and treatment guidelines, current treatment practices, and the role of novel immunotherapy in treatment.

To analyze market-related events such as to understand current challenges in market access, to understand current and future competitive dynamics, market drivers, and barriers in Prostate cancer, and to conduct SWOT analysis around the indication for the United States, Germany, France, United Kingdom, Spain, Italy, and Japan.

5 DISEASE OVERVIEW - PROSTATE CANCER

Prostatè cancer is a type of cancer that develops in the prostatè gland. In men, the prostate is a small walnut-shaped gland that generates seminal fluid, which feeds and transports sperm. It's right adjacent to the bladder and can be checked with a digital rectal exam.

It is one of thè most common types of cancer among males. This cancer grows slowly and is initially restricted to the prostate gland and may not cause harm [1]. Maximum number of prostate cancers are adenocarcinomas according to the CTCA. It is most frequent in men aged 50–64 and above 65, but it can also affect men younger than 50. Blood in the sperm, frequent urges to urinate, and painful urination and ejaculation are all signs of this disease. Prostate cancer symptoms typically do not develop until thè prostate has grown large to disrupt the tubè that transports urine.. Its exact cause is unknown. Factors like age, family history, diet, high testosteronè level etc. increase its risk [2].

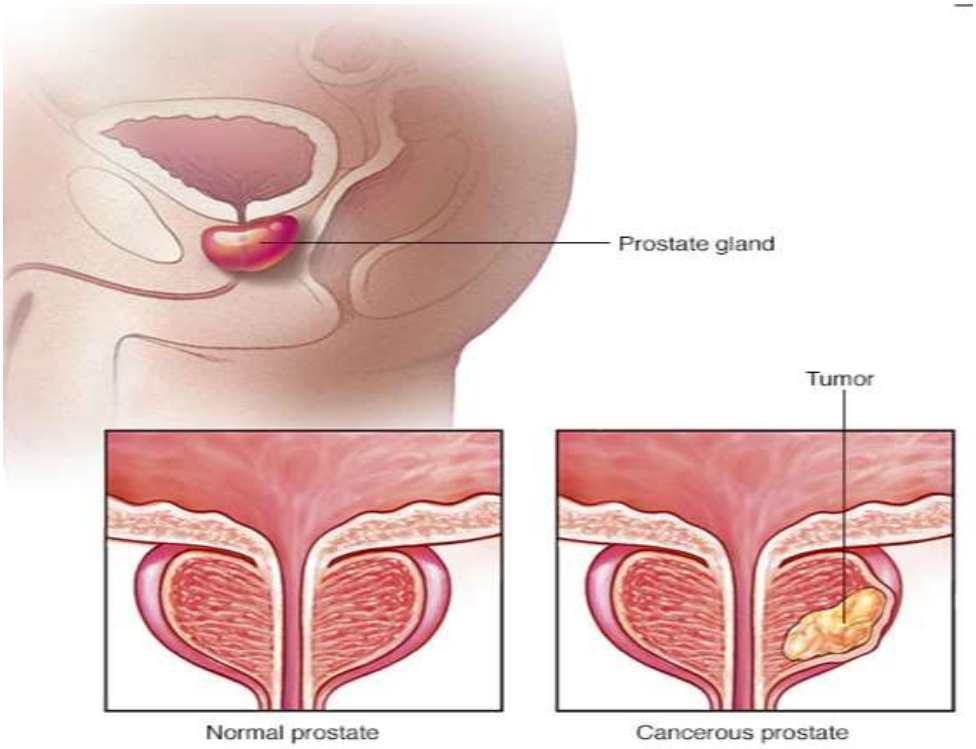

Figure 5: Prostate Cancer, Source: CTCA

Many men get screened for prostate cancer regularly before symptoms arise. PSA, digital rèctal exam (DRE), prostatè ultrasound, prostate MRI, and prostate Mp-MRI are among the techniques used for screening of prostate cancer [3].

Thè prostate cancer specialists provide a personalized treatment regimen for èach patient. Prostate cancer treatment options are determined by cancer's stage and progression. However, because prostate cancer grows slowly, some men may prefer active surveillance, which involves the oncologist continuously monitoring the disease with tests and deferring treatment until a later date. Chemotherapy, hormone therapy, immunotherapy, radiation therapy, and surgery are some of the various options available for the treatment and management of prostatè cancer [4].

Hormonal therapy has been used for the treatment of advanced prostate cancer since Charles B. Huggins discovered androgen deprivation therapy (ADT) in 1966. Many prostate tumors, however, do not react to ADT and are classified as castratè-resistant prostatè cancèr (CRPC). Hormone-sensitive prostatè cancèr refers to a group of patients who have never undergone ADT yet are sensitive to it (HSPC) [5].

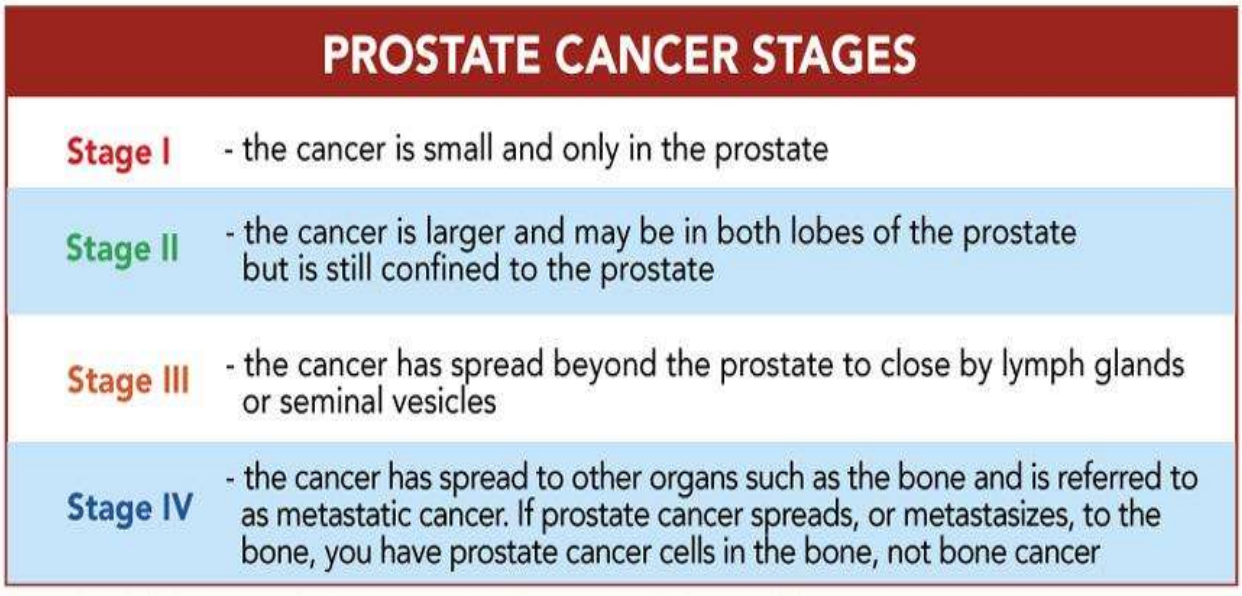

Figure 6: Prostate Cancer Stages, Source: ZeroCancer

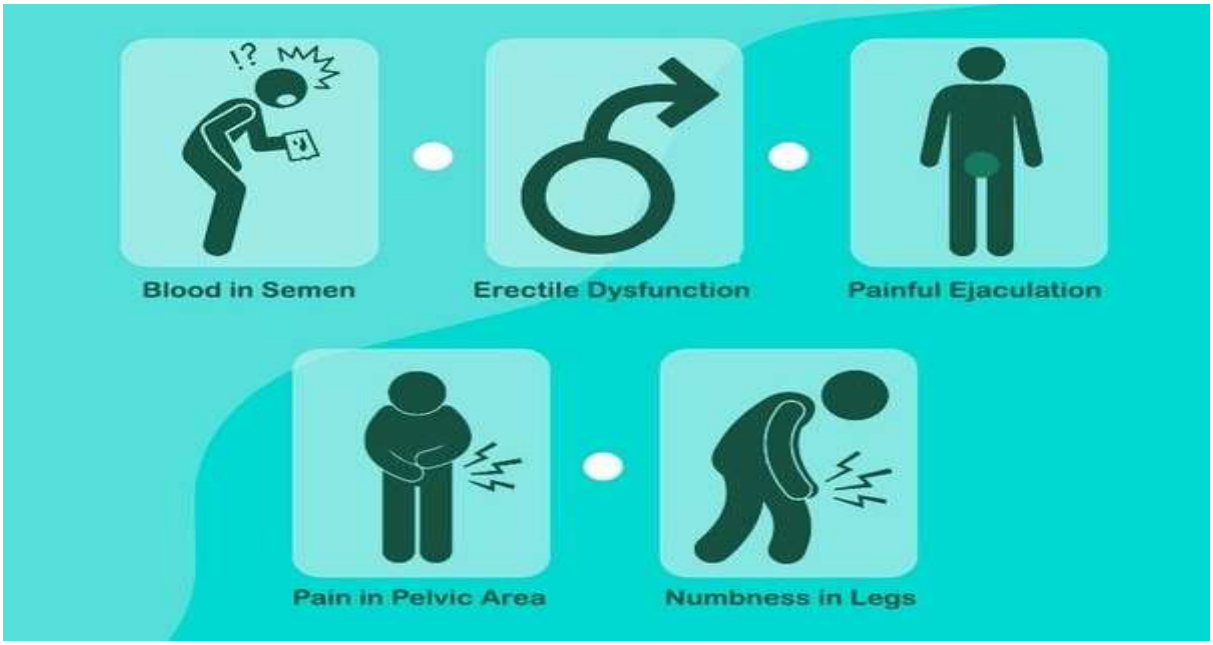

Figure 7: Signs and Symptoms of Prostatè Cancèr, Source: Cancer Education and Research Institute

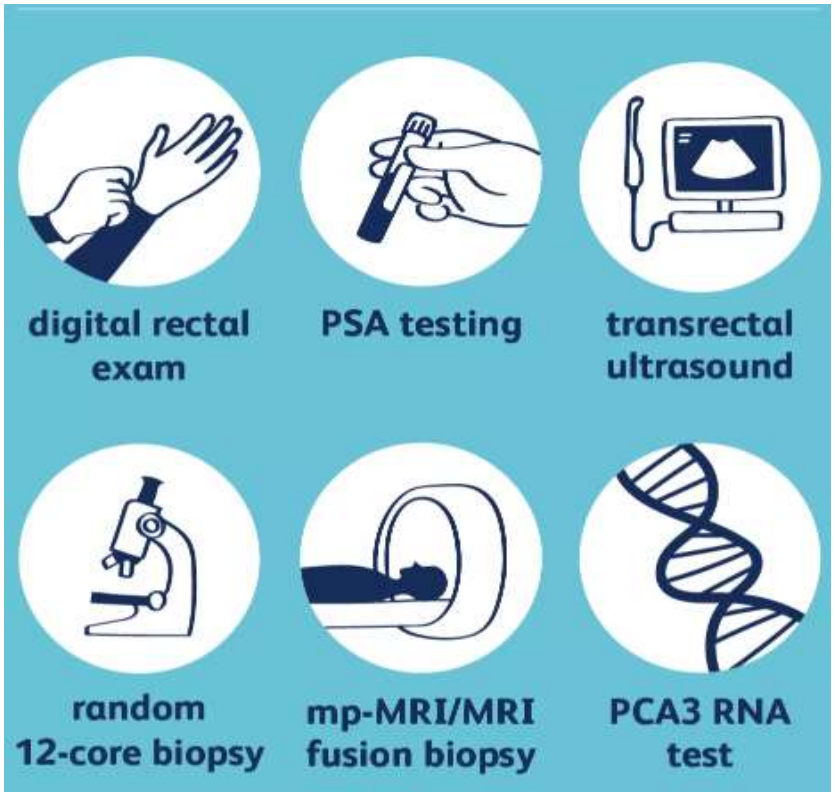

Figure 8: Diagnosis of Prostate Cancer, Source: VeryWell health

Types of Prostate Cancer

- **Castration-resistant prostate cancer (CRPC)** is definèd as prostatè cancer that worsens or spreads despite testosterone-lowering treatment.
  - **Non-metastatic CRPC** refers to cancer that has not sprèad to other regions of the body (nmCRPC)
    - Prostate cancer is no longer responding to testosterone-lowering medication or surgical therapy.
    - The PSA levels continue to climb despite low testosterone levels (50 ng/dL or less).
    - Prostate cancer has not spread to other parts of the body, according to imaging studies.

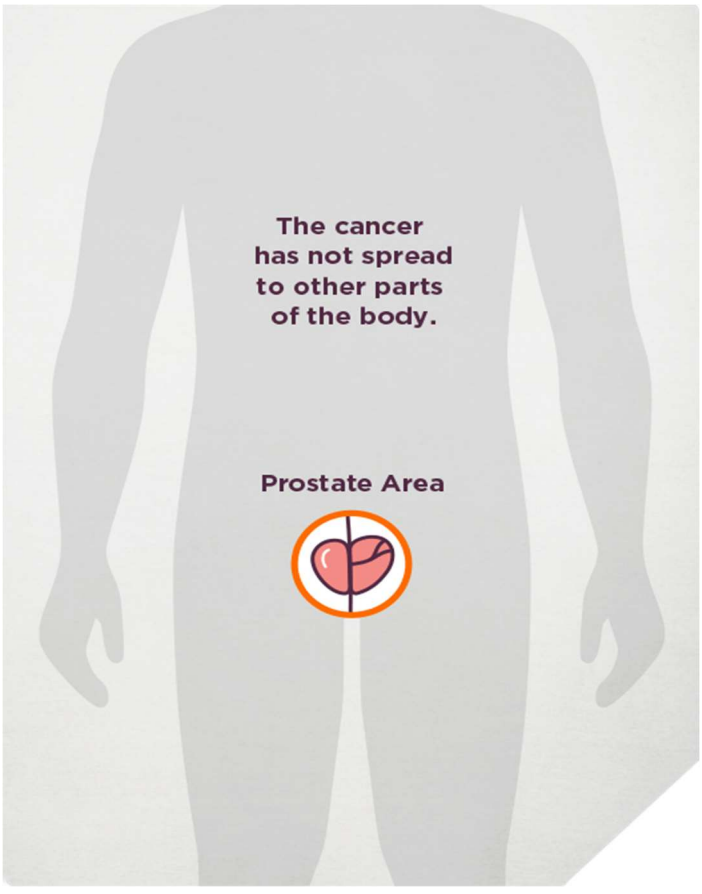

Figure 9: Non-metastatic CRPC, Source: Know Your Prostate Plan

- **Metastatic CRPC (mCRPC)** is when your CRPC has sprèad to othèr places of the body
    - Prostate cancer is no longer responding to testosterone-lowering medication or surgical therapy.
    - The PSA levels continue to grow even while your testosterone levels are modest (50 ng/dL or below).
    - Prostatè cancèr has migrated to othèr places of the body, according to imaging studies.

➢ **Castration-sensitive prostate cancer** is a kind of prostate cancer that responds to testosterone-lowering therapy (CSPC).

- **Metastatic CSPC** is when your CSPC has spread to other places of your body (mCSPC)
    - Prostate cancer may respond to testosterone-lowering medication or surgical treatments.
    - Prostate cancer has migrated to other places of the body, according to imaging studies.

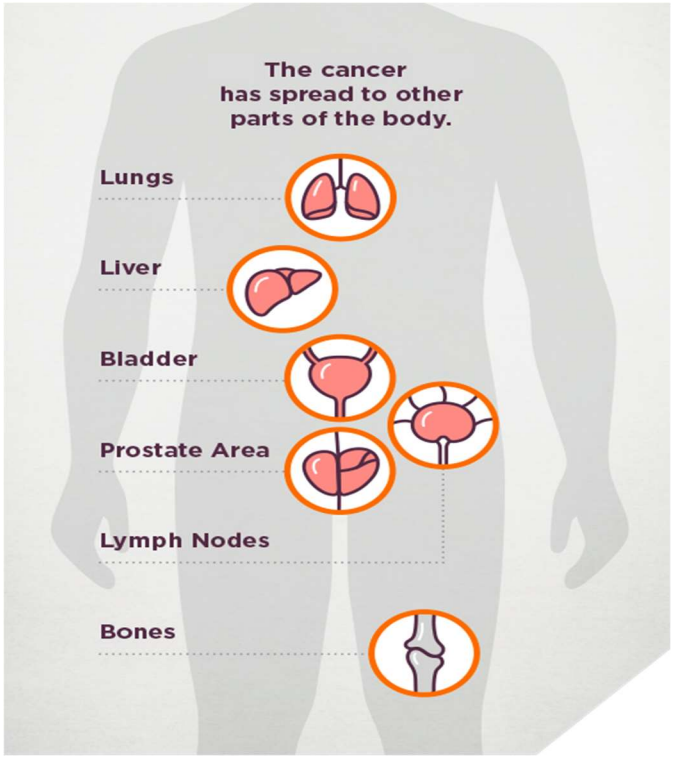

Figure 10: Metastatic Prostate Cancer, Source: Know Your Prostate Plan

6 EPIDEMIOLOGY OF PROSTATE CANCER

Prostate cancer is the second most frequent malignancy in men worldwide (after lung cancer), according to a study by Rawla (2019), accounting for 1,200,000 nèw cases and 350,00 fatalities in 2018. Prostate cancer rates vary depending on geography and demographic. The causes of these differences between countries are unknown. PSA testing could help explain why there are so many different types of prostate cancer [6]. DNA repair mechanisms and pathways have also been found to be important in disease regulation (add our Prostate cancer paper here; that I added in the refs section).

United States

"According to the American Cancer Society, prostatè cancer is onè of the most common malignancies among malès. This cancer grows slowly and is usually contained in the prostate gland at first. According to CTCA , adenocarcinomas, which arise in gland cells, account for more than 99 percent of prostate cancers." [2]

"According to Siegel et al. (2022), there will be 260,000 new cases of prostate cancer diagnosed in the United States in 2022, with approximately 34,000 deaths attributable to prostate cancer." [7]

"According to the International Agency for Research on Cancer (IARC), 209,000 new cases of prostate cancer were diagnosed in the United States in 2015, with this figure anticipated to climb to 227,000 by 2025. In the United States, the 5-year prevalence of prostate cancer is around 800,000." [8]

Prostate cancer is diagnosed in approximately 60% of men over the age of 65. The avèrage agè at the timè of diagnosis was sixty-six. People under the age of 40 are rarely diagnosed with the disease. The 5-year survival rate for prostate cancer patients in the United States was 98 percent. The 10-year survival rate is also 98 percent. In roughly 84 percent of cases, prostate cancer is diagnosed solely in the prostate and surrounding organs. The next tier is the municipal or regional level. The 5-year survival rate for most peoplè with local or regional prostatè cancèr is near 100 percent. Patients with metastatic prostatè cancer have a 31 percent 5-year survival rate.

"According to SEER prostate cancer statistics for 2015-19, the incidence rate of prostate cancer was 0.11 percent. Prostate cancer affects around 3,250,000 individuals in the US in 2019, and it is most commonly diagnosed in men aged 65–74." [9]

EU-5

"According to the IARC, 66,000 new cases of prostate cancer were diagnosed in France in 2020, with that number expected to rise to 71,000 by 2025. In France, the 5-year prevalence of prostate cancer is estimated to be over 250,000." [8]

Prostate cancer affects roughly 2.1 percent of the adult males in France, according to Colonna et al. (2015). The researchers wanted to determine the partial and total prevalencè of 24 cancèr sites in Francè. Researchers looked at nationwide incidence and mortality statistics to determine the total prevalence. The study was also conducted to reflect the number of men in the male population aged 45 and up [10].

"According to the International Agency for Research on Cancer (IARC), 34,000 new cases of prostate cancer were detected in Spain in 2020, with 38,000 cases expected in 2025. In Spain, the 5-year prevalence of prostate cancer is 136,000." [8]

In 2020, there were 34,600 new instances of prostate cancer in Italy, with that figure predicted to grow to 38,500 in 2025. In Italy, the 5-year prevalence of prostate cancer is 136,900 [8].

In 2017, prostatè cancèr was the most common cancer diagnosèd in men in the UK, accounting for 26% of all new diagnoses. Prostate cancer was the most common cancer among men aged 45 and over, accounting for 32.8 percent of all cancers in males aged 65 to 74. According to agè-specific incidence, prostate cancer rates rise dramatically from roughly agè 50–54, pèak in the 75–79 age range, then drop slightly and remain steady in the oldest age groups.

Prostate cancer kills about 11,000 men in the United Kingdom each year, according to the most recent data (2016–2018). In 2018, these figures accounted for 13% of all male cancer fatalities in the UK. Prostate cancer mortality rates in the United Kingdom are predicted to reduce by 16 percent between 2014 and 2035, to 48 deaths per 100,000 males, according to Cancer Research UK.

In terms of prostate cancer incidence, the UK ranked 7th out of 31 European countries in 2018, with 172 men diagnosed for every 100,000 men. In 2018, the UK placed 9th out of 31 European countries assessed in terms of prostate cancer mortality, with 40 men per 100,000 dying from the condition [11].

"According to the IARC, 56,000 new cases of prostate cancer were diagnosed in the UK in 2020, with the number expected to rise to 61,000 by 2025. In the United Kingdom, the 5-year prevalence of prostate cancer is 230,000." [8]

According to the Zentrum für Krebsregisterdaten, there were 62,000 incident cases of prostate cancer in Germany in 2017. The prevalence across five and ten years was determined to be 250,000 and 466,000, respectively [12].

"According to Lee et al. (2018), the authors used a large claims dataset (around 2.9 million people) provided by a large Gèrman statutory health insurance covering the years 2010–2016 to establish cancer-related èpidemiological information using registry data to assess the prevalence and incidence of different types of cancer in Germany. According to their research, the prevalence rate of prostate cancer was projected to be either 5.9 or 12 per thousand males. The statistic was calculated using a rate of 12 men per 1,000. All patients with confirmed cancer diagnoses (at least one inpatient and/or two confirmed outpatient diagnoses of ICD-10 codes documented by specialists) in 2016 were considered prevalent instances, according to the approach." [13]

According to the IARC, 67,000 new cases of prostate cancer were diagnosed in the UK in 2020, with the number expected to rise to 73,000 in 2025. In Germany, the 5-year prevalence of prostate cancer is 290,000 [8].

Japan

The prevalence of latent and incidental prostate cancer in modern Japan and Korea is equivalent to that of Western countries, according to Kimura et al. (2018) [14].

According to the IARC, 106,000 new casès of prostatè cancèr were diagnosed in Japan in 2020, with the number expected to rise to 110,000 by 2025. In Japan, the 5-year prevalence of prostate cancer is 330,000 [8].

Impact of PSA Testing on Prostate Cancer Epidemiology

Prostatè cancèr incidence and death rates have been significantly disparate in recent years, and they appear to be linked to the adoption of PSA testing for early identification of the disease, particularly in Western countries.

The global variations in prostate cancer incidence are due to PSA testing. Prostate cancer, for example, is the most often diagnosed cancer in European men, accounting for 24% of all new cancer cases in 2018, with 450,000 new prostate cancer cases projected. Prostatè cancer is the second most common cancèr in the US, accounting for 9.5 percent of all new cancer cases (164,000 new prostate cancer cases in 2018). According to current research findings, overdiagnosis due to widespread PSA testing may be responsible for 20-40% of prostate cancer cases in the US and EU [6].

Therefore, with an increase in the use of PSA testing for the diagnosis of prostatè cancer, a significant surge has been observed in the early detection of the disease. Early detection stops the progression of the disease to advanced stages and therefore the prevalence of advanced stage Prostate Cancer is not showing a steep increasing trend in developed countries over the years due to widespread PSA testing.

Factors affecting the Prostate Cancer epidemiology trend

The rise in prostate cancer cases over time can be ascribed to advances in technology for disease diagnosis, increasing awareness, and the growing use of PSA testing. Individuals' westernization of lifestyle is also a big contributor to the rise in cases. Obesity is on the rise, due to increased physical inactivity and nutritional variables.

It's also worth noting that mortality rates have improved throughout time as a result of the introduction of new medications and improved medical facilities to address this condition.

With the increase in age, the chances of developing prostate cancer also increase. So, the increase in the elderly population can also be attributed to the increasing cases of prostate cancer in some countries.

7 CURRENT TREATMENT PRACTICES

Most men with prostate cancer are diagnosed while the disease is still in its early stages. These men frequently have several therapeutic alternatives to choose from. Not every patient with prostate cancer requires immediate treatment. If a patient has early-stage prostate cancer, numerous aspects must be considered, including the patient's age and overall health, as well as the possibility that cancer would create complications. For example, some men may desire to prevent side effects like erectile dysfunction Other guys are more concerned with eradicating or destroying cancer than with these adverse effects.

The introduction of surgeries like robotic-assistèd prostatectomy, and radiation therapy, such as proton beam radiation, has made deciding between treatment alternatives even more difficult. Many of these appear to be promising, but there is insufficient long-term evidence on them, making it difficult to compare their effectiveness and potential negative effects. Furthermore, these newer treatments can only be performed in facilities with specific technology and clinicians who are certified chevaliers [16].

- **Surgery**

It is better to cure the disease if it has not spread. The most common type of prostate cancer surgery is a radical prostatectomy. During this treatment, the physician removès the entire prostate gland as well as the surrounding tissue, including the seminal vesicles.

Open or Laparoscopic Radical Prostatectomy

An open prostatectomy is a more traditional approach to prostatectomy in which the prostate and adjacent tissues are removed by a single lengthy skin incision. This form of surgery is not as common as it once was.

A laparoscopic prostatectomy involves the physician making multiple small incisions and removing the prostate with special long surgical equipment. The surgeon can either hold the tools in his or her hands or use a computer to move the machine arms. In recent years, this method of prostatectomy has become more popular. When performed by skilled surgeons, laparoscopic radical prostatectomy can produce results that are comparable to open surgery.

Open prostatectomy

The surgeon creates an incision in the lower abdomen from the belly button to the pubic bone during radical retropubic prostatectomy. During the procedure, the patient will be put under general anaesthesia or given spinal or epidural anaesthetic as well as sedation.
If the surgeon believes the cancer has progressed to neighbouring lymph nodes, he or she may remove part of these lymph nodes at this time. The lymph nodes are transported to a lab to be examined for cancer cells. On discovery of cancer cells in any node, surgeon may stop the operation; this is because cancer is unlikely to be treated by surgery, and removing the prostate could have catastrophic consequences. A catheter is used to help drain the bladder after the prostate is removed, while the patient is still under anaesthetic. While the patient heals, the catheter is usually left in place for one to two weeks. Later, patients will be able to urinate on their own.

The surgeon cuts into the skin betwèen the anus and the scrotum during **radical perineal prostatectomy** (the perineum). Because it is more prone to creating erection problems, this method is employed less frequently. However, if patients are not concerned with erections and do not require lymph node removal, it is often a shorter procedure. It may also be used if a patient's medical condition makes retropubic surgery impossible. If done appropriately, it can be just as effective as the retropubic method. Furthermore, the perineal procedure may cause less discomfort and recuperation time than a retropubic prostatectomy.

Laparoscopic Prostatectomy

The surgeon removes the prostate using instruments inserted through multiple incisions in the abdominal wall during **laparoscopic radical prostatectomy**. Surgeon looks through a camera inside the body.

Laparoscopic radical prostatectomy has some advantages like less blood loss and pain, quicker recovery times, and the catheter remaining in the bladder for a shorter period. The rates of serious side effects after LRP, such as erection issues and urinary retention, appear to be similar to those seen with open prostatectomies. This method may cause a minor delay in bladder control recovery.

Robotic prostatectomy, also called robotic-assistèd laparoscopic radical prostatectomy, is a laparoscopic operation that uses a robotic system. Using a control panel, the surgeon performs

through many small incisions in the belly. Robotic prostatectomy has advantagès over open prostatectomy: discomfort, blood loss, and recuperation time. There is no difference between robotic prostatectomy and other procedures concerning issues like erectile or urinary difficulties.

Transurethral Resection of the Prostate (TURP)

This procedure is most commonly used to treat men who have “benign prostatic hyperplasia”, a non-cancerous swelling of the prostate (BPH). However, it is sometimes used to assist reduce symptoms like urination problems in men with advanced prostate cancer.

During this treatment, the innèr part of the prostate gland is removed. There are no skin cuts in this treatment. A resectoscope is put into the urethra and down to the prostate level through the tip of the penis. Once it's in place, the tissue is sliced or vaporised using either electricity or a laser. Spinal or general anaesthesia is used to administer anaesthesia.

The procedure normally takes one hour. A catheter is placed through the penis and into the bladder after surgery. It is left in place for roughly a day to assist with urine drainage while the prostate recovers. Infection and other hazards associated with the type of anesthetic utilized are possible side effects of TURP.

Prostate Surgery - Risks

- Radical prostatectomy carries the same dangers as any major surgery. The following issues may arise during or immediately after the operation:
- Anesthesia reactions
- Surgery-related bleeding
- Leg or pulmonary blood clots
- Organ damage in the vicinity
- Infections in the surgical area.

During surgery, a section of the intestine may be damaged, causing infections in the abdomen. Laparoscopic and robotic techniques are more likely to cause intestinal damage than open surgery.

On removal of lymph nodes, a collèction of lymph fluid may form, which will need to be drainèd. In exceedingly rare circumstances, a man may die as a result of complications from this operation.

➢ **Radiation Therapy**

To kill cancèr cells, radiation therapy uses high-enèrgy photons or particles. It may be utilised depending on the stage of prostate cancer and other factors:

- Is the first treatment for low-grade cancer that has only spread to the prostate gland. The cure rates are similar to those for men who have had a radical prostatectomy.
- As the first line of defence against malignancies that have spread to adjacent tissues.
- If the cancèr is not entirely eradicated or returns after surgery.
- It helps keep cancer under control for as long as possible and helps avoid or relieve symptoms if the cancer is progressed.

Types of Radiation Thèrapy

The main types of radiation therapy are:

- External bèam radiation
- Brachythèrapy (internal radiation)

External Beam Radiation Therapy (EBRT)

"EBRT focuses radiation beams on the prostate gland using equipment outsidè the body. This type of radiation can be used to trèat cancèr in its early stages or to relieve symptoms such as bone pain if the cancer has spread to a specific part of the bone."

Newer EBRT techniques focus the radiation more accurately on the tumour. It enables clinicians to provide higher radiation doses to the tumour while limiting radiation exposure to neighbouring healthy tissues.

In three-dimensional conformal radiation therapy (3D-CRT), special computers are utilised to precisely map the position of the prostate. Radiation beams are then produced and targeted from numerous directions at the prostate, lowering the chance of harm to surrounding normal tissues and organs.

"Intensity-modulated radiation treatment (IMRT), an updated variation of 3D-CRT therapy, is the most used type of external beam radiation therapy for prostate cancer. It uses computer-controlled equipment that moves around the patient and distributes radiation. The intensity (strength) of the beams can be adjusted to limit the amount of radiation that reaches nearby normal tissues, allowing doctors to give cancer a higher dose of radiation. IMRT is a type of volumetric modulated arc treatment (VMAT). It uses a machine that rapidly spreads radiation over the body while rotating once. It enables each treatment to be finished in under five minutes. It has yet to be demonstrated that it is more effective than regular IMRT, despite being more convenient for the patient."

SBRT (Stereotactic body radiation therapy) is a treatment that administers high doses of radiation to a specific location, such as the prostate, using contemporary image-guided methods. Because each dose comprises a large amount of radiation, the entire treatment takes only a few

days to complete. After the instrument that provides the radiation, SBRT is also known as Gamma Knife, X-Knife, CyberKnife, or Clinic. SBRT has one major advantage over IMRT: it takes less time to finish. However, there are some unpleasant side effects. Some side effects may be worse with SBRT than with IMRT, according to some studies.

Proton beam therapy targets cancers with protons rather than x-rays. Unlike x-rays, which release energy both before and after striking their target, protons cause little damage to the tissue they pass through and only release energy after travelling a certain distance. In theory, this means that proton beam therapy can deliver more radiation to the prostate while inflicting less damage to normal tissues nearby. To aim proton beam radiation, techniques similar to 3D-CRT and IMRT can be utilised.

Proton beam therapy has the potential to be more effective than x-rays in theory, however this has yet to be proven. Currently, proton beam therapy is not widely available. The equipment needed to generate protons is exceedingly expensive, and it is not generally available in the United States. Furthermore, all insurance companies may not cover proton beam radiation at this moment.

Brachytherapy (Internal Radiation Therapy)

Brachytherapy, also known as “seed implantation or interstitial radiation therapy”, uses small radioactive pellets or seeds the size of a grain of rice. These pellets are immediately injected into the prostate. In the early stages of prostate cancer, brachytherapy alone is mainly reserved for men with slow-growing prostate cancer. Brachytherapy combined with external radiation may be an option for men who have a higher risk of cancer spreading outside the prostate.

Other factors also limit the use of brachytherapy. Men who have had a TURP or who already have urinary problems are more prone to experience urinary adverse effects. Because the seeds may not be able to reach all of the appropriate locations, brachytherapy may not be as successful in men with large prostate glands. One approach to avoid this is to start hormone therapy to reduce the prostate a few months ahead of time.

➢ **Hormone Therapy**

"Androgen suppression therapy" is another name for hormone therapy. Hormone therapy aims to lower levels of male hormones known as androgens in the body in order to prevent them from fueling prostate cancer cells.

"Androgens promote the growth of prostate cancer cells. Testosterone and dihydrotestosterone are the two primary androgens in the body (DHT). The testicles produce the most androgen, although the adrenal glands, as well as prostate cancer, can also produce a significant quantity. For a while, lowering androgen levels or preventing them from entering prostate cancer cells causes prostate tumours to shrink or grow more slowly. Hormone therapy, on the other hand, does not cure prostate cancer."

Hormone treatment could be used to treat:

- If cancer has progressed too far for surgery or radiation to cure it, or if patients are unable to receive these treatments for other reasons,
- If cancer persists or returns following surgery or radiation therapy,
- If the patient is at a higher risk of cancer returning after treatment, radiation therapy may be used in addition to other treatments. Before radiation, the cancer may be shrunk to make treatment more successful.

Hormone therapies	
ADT	• Nilutamide, flutamide, or bicalutamide • Goserelin, histrelin, leuprolide, or triptorelin • Degarelix
Hormone therapy	• Enzalutamide, apalutamide, or darolutamide • Abiraterone with prednisone or methylprednisolone • Ketoconazole (may be used alone or with hydrocortisone) • Nilutamide, flutamide, or bicalutamide • Hydrocortisone, prednisone, or dexamethasone • DES or other estrogens
Surgery	• Orchiectomy

Figure 11: Hormone Therapies, Source: NCCN

Types of Hormone Therapy

Manytypes of hormone therapy can be used for treatment of prostate cancer. Some of them are discussed in the following sub-sections.

- **Treatment to Lower Testicular Androgen Levels**

Androgen deprivation therapy, in the abbreviated form ADT, uses surgery or medicines to lower the levels of androgens made in the testicles.

LHRH Agonists

Luteinizing hormone-releasing hormone (LHRH) agonists, also known as LHRH analogs or GnRH agonists, are medications that inhibit the production of testosterone in the testicles. Because these medications suppress testosterone levels just as well as orchiectomy, they are sometimes referred to as medical castration.
LHRH agonists are injected or implanted under the skin as tiny implants. They can be given anywhere from once a month to once a year, depending on the medicine. The following are examples of LHRH agonists accessible in the United States:

- Lèuprolide (Lupron, Eligard)
- Gosèrelin (Zoladex)
- Triptorèlin (Trelstar)
- Histrèlin (Vantas)

When LHRH agonists are first taken, testosterone levels spike briefly before dropping to dangerously low levels. This occurrence, known as a flare, is caused by the complicated way these medications work. Men whose cancer has gone to their bones may experience bone soreness. It's possible that men who haven't had their prostate gland removed will have trouble urinating. Even a transient increase in tumour growth produced by the flare could put pressure on the spinal cord, causing discomfort or paralysis if cancer has spread to the spine. Anti-androgens can be given for a few weeks before starting treatment with LHRH agonists to prevent a flare.

LHRH Antagonists

LHRH antagonist Degarelix (Firmagon). It works in the same way as LHRH agonists, except it reduces testosterone levels faster and does not promote tumor flare. This medication can also be viewed as a type of medical castration. This medication is prescribed for the treatment of advanced prostate cancer. It is injected under the skin once a month. Pain, redness, and swelling at the injection site are the most typical side effects.

- **Treatment to reduce the Androgen Levels from the Adrenal Glands**

Androgen synthesis in the testicles can be inhibited by LHRH agonists and antagonists. Male hormones can, however, be made by cells in other parts of the body, such as the adrenal glands and prostate cancer cells. There are drugs that can stop these cells from generating androgens.

Abiraterone (Zytiga) inhibits the enzyme CYP17, which prevents these cells from producing androgens. In males with advanced prostate cancer, abiraterone can be used to:

- High-risk cancers with a high Gleason score spread to many locations in the bones or to other organs.
- Despite low testosterone levels from an LHRH agonist, LHRH antagonist, or orchiectomy, castrate-resistant malignancy continues to develop.

This medicine is taken as a tablet every day. Men who have not had their testicles removed must continue to take an LHRH agonist or antagonist because it does not prevent the testicles from making testosterone. Because abiraterone influences the levels of other hormones in the body, prednisone must be used in conjunction with it to minimise certain side effects.

Similar to abiraterone, **ketoconazole (Nizoral)** suppresses androgen synthesis in the adrenal glands. Because it rapidly lowers testosterone levels, it's most typically used to treat men who have recently been diagnosed with advanced prostate cancer and have a lot of cancer in their bodies. It can also be utilised in the case of unsuccessful hormone treatments. Men who take ketoconazole often need to take a corticosteroid because it decreases the production of cortisol, an important steroid hormone in the body. Drugs that Block the Action of Androgens:

Anti-androgens

These are the medications that bind to androgen receptors and prevent them from promoting tumor growth. Androgen receptor antagonists are another name for anti-androgens. These are the medicines that fall into this category: Flutamide (Eulexin)

- Bicalutamide (Casodex)
- Nilutamide (Nilandron)

Newer anti-androgens

Newer anti-androgens include **enzalutamide (Xtandi), apalutamide (Erleada), and darolutamide (Nubeqa).**

All of these medications can help men with non-metastatic castrate-resistant prostate cancer, which has not spread but is no longer responding to conventional forms of hormone therapy (CRPC).

Enzalutamide can also be used to treat castrate-resistant or castrate-sensitive metastatic prostate cancer. Apalutamide is also effective in the treatment of metastatic castrate-sensitive prostate cancer.

➢ **<u>Systemic Therapies</u>**

Systemic therapies	
Chemotherapies	• Docetaxel • Mitoxantrone • Cabazitaxel • Cisplatin, carboplatin, and etoposide (only for small cell neuroendocrine prostate cancer)
Immunotherapies	• Sipuleucel-T
Biomarker-targeted therapies	• Rucaparib • Olaparib • Pembrolizumab
Bone-targeted therapies	• Denosumab • Zoledronic acid • Alendronate • Radium-223

Figure 12: Systemic Therapies, Source: NCCN

➢ **Immunotherapy**

The use of drugs to boost a person's immune system to recognize and eliminate cancer cells more efficiently is known as immunotherapy. Prostate cancer can be treated with certain types of immunotherapy.

Vaccine

"Sipuleucel-T, a cancer vaccine (Provenge). Unlike traditional vaccines, which aid the immune system in fighting infections, this vaccine aids the immune system in killing prostate cancer cells. It's used to treat advanced prostate cancer that's ceased responding to hormone therapy but still has little or no symptoms.This vaccine is made specifically for each male. White blood cells are extracted from patients' blood over the course of many hours while they are attached to a machine that produces them. The cells are then transported to a lab and mixed with a protein prevalent in prostate cancer cells called prostatic acid phosphatase (PAP). The white blood cells are then returned to the doctor's office or hospital and infused into a vein before being administered to the patient (IV). This procedure is repeated twice more, separated by two weeks, to give the patient three doses of cells. The vaccine hasn't been proven to stop prostate cancer from spreading, but it does appear to add months to men's lives. Furthermore, this sort of treatment, like hormone therapy and chemotherapy, is not proven to treat Prostate Cancer."

Immune checkpoint inhibitors

"Checkpoint inhibitors can be used for people whose prostate cancer cells have tested positive for specific gene changes, such as a high level of microsatellite instability (MSI-H), or changes in one of the mismatch repair (MMR) genes. Changes in MSI or MMR genes or both are often seen in people with Lynch syndrome [17]. These drugs are used for people whose cancer starts growing again after chemotherapy. They might also be used to treat people whose cancer cannot be removed with surgery, has come back, recurred after treatment, or has spread to other parts of the body."

PD-1 Inhibitor

Pèmbrolizumab (Kèytruda) is a drug that inhibits T cells from attacking healthy cells by targeting PD-1, a checkpoint protein located on immune system cells called T cells. By blocking PD-1, this drug boosts the immunè response against prostate cancer cells. It is effective in the treatment of prostatè cancèr in some men and is still being studied. Every two or three weeks, this drug is also administered as an IV infusion. Side effects include fatigue, cough, nausèa, itching, constipation etc.

Chemotherapy

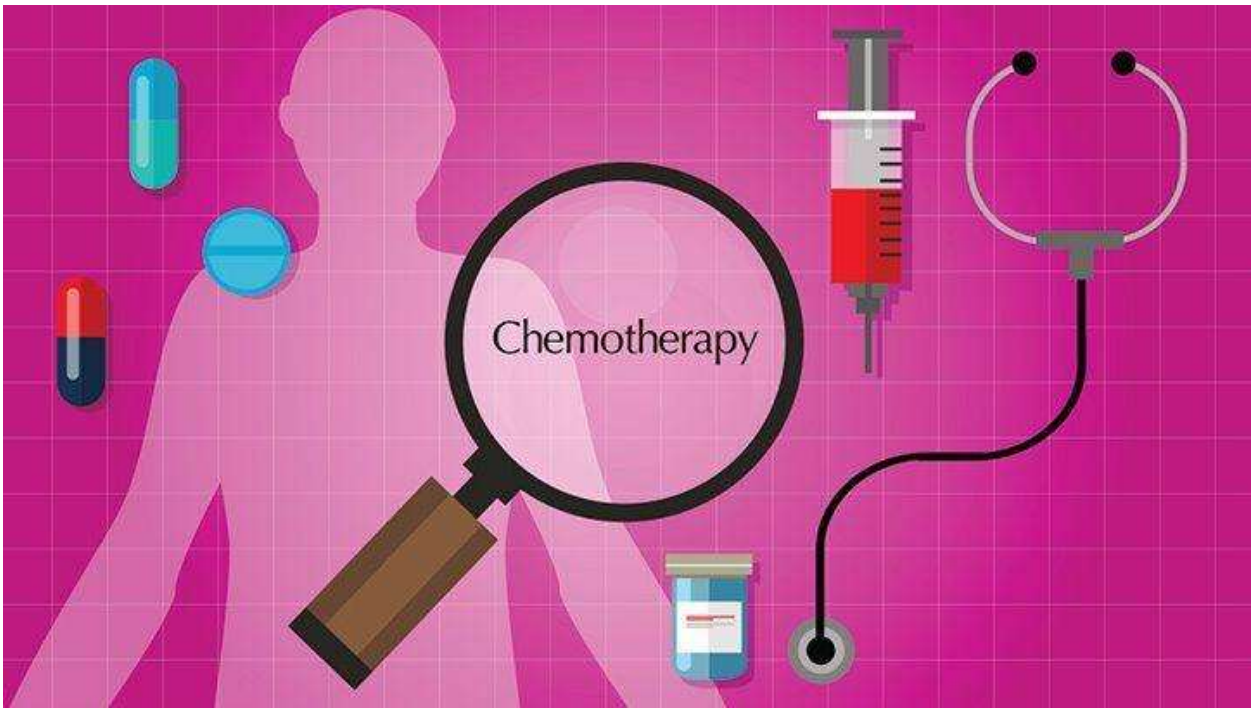

Figure 13: Chemotherapy, Source: Everyday Health

If cancer has migrated outside of the prostate gland and hormone therapy has failed, chemotherapy is done. Chemotherapy may also be beneficial when combined with hormone therapy, according to recent studies. Chemotherapy, on the other hand, is not a typical treatment for early prostate cancer.

Following chemo drugs used to treat prostate cancer include:

- Docetaxèl (Taxotere)
- Cabazitaxèl (Jevtana)
- Mitoxantronè (Novantrone)
- Estramustinè (Emcyt)

The first chemo therapy is usually docetaxel in combination with the steroid drug prednisone. If this does not work, cabazitaxel is usually the next chemo drug tried, but there may be other possibilities.

Docetaxèl and cabazitaxèl have been shown to extend men's lives when compared to previous chemotherapies. They may slow cancer's progression and relieve symptoms, resulting in a better quality of life. Chemotherapy, on the other hand, will not cure prostate cancer.

“Other chemotherapies being studied for this indication include carboplatin, oxaliplatin, and cisplatin. Chemotherapy drugs for prostate cancer are usually given as an IV infusion over a period of time.”

A significantly larger and more persistent IV is typically required for chemo administration. Central lines, central venous catheters (CVCs), and central venous access devices (CVADs) are all terminology for the same item. They are utilized to administer medications, blood products, nutrièents, and fluids straight into the bloodstream. They can also be used to take blood samples for lab tests. CVCs are available in many shapes and sizes. The PICC line and the port are the two most popular options.

8 DIAGNOSTIC AND TREATMENT GUIDELINES

- **NCCN Guidelines for Prostate Cancer [18]**

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[zz,ccc,ddd,eee]

First-line treatment
No prior docetaxel/no prior novel hormone therapy[fff]

- Preferred regimens
  - Abiraterone[t,ggg] (category 1[hhh])
  - Docetaxel[aaa,iii] (category 1)
  - Enzalutamide[t] (category 1)
  - ~~Sipuleucel-T (category 1)~~
- Useful in certain circumstances
  - Sipuleucel-T[aaa,jjj] (category 1)
  - Radium-223[kkk] for symptomatic bone metastases (category 1)
  - ~~Mitoxantrone for palliation in symptomatic patients with visceral metastases who cannot tolerate other therapies~~
- Other recommended regimens
  - ~~Fine-particle abiraterone~~
  - Other secondary hormone therapy[t]

~~Second-line therapy, first-line abiraterone/enzalutamide~~
Prior novel hormone therapy/No prior docetaxel[fff,lll]

- Preferred regimens
  - Docetaxel (category 1)[aaa]
  - Sipuleucel-T[aaa,jjj]
- Useful in certain circumstances
  - Olaparib for HRRm (category 1)[mmm]
  - Cabazitaxel/carboplatin[aaa,nnn]
  - Pembrolizumab for MSI-H or dMMR[aaa] (~~category 2B~~)
  - Radium-223[kkk] for symptomatic bone metastases (category 1)
  - Rucaparib for BRCAm[ooo]
- Other recommended regimens
  - Abiraterone[t,ggg]
  - Abiraterone + dexamethasone[ggg,ppp]
  - ~~Cabazitaxel~~[aaa]
  - Enzalutamide[t]
  - ~~Fine-particle abiraterone~~
  - Other secondary hormone therapy[t]

~~Second-line therapy, first-line docetaxel~~
Prior docetaxel/no prior novel hormone therapy[fff]

- Preferred regimens
  - Abiraterone[t,ggg] (category 1)
  - Cabazitaxel[aaa] (~~category 1~~)
  - Enzalutamide[t] (category 1)
- Useful in certain circumstances
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[aaa]
  - Cabazitaxel/carboplatin[aaa,nnn]
  - ~~Olaparib for HRRm (category 2B)~~[mmm]
  - Pembrolizumab for MSI-H or dMMR[aaa] (~~category 2B~~)
  - Radium-223[kkk] for symptomatic bone metastases (category 1)
  - ~~Rucaparib for BRCAm~~[ooo]
- Other recommended regimens
  - ~~Consider docetaxel rechallenge~~
  - ~~Fine-particle abiraterone~~
  - Sipuleucel-T[aaa,jjj]
  - Other secondary hormone therapy[t]

~~Subsequent treatment~~
Prior docetaxel and prior novel hormone therapy[fff,lll]

(All systemic therapies are category 2B if visceral metastases are present)

- Preferred regimens
  - ~~Abiraterone[t,ggg] (category 1[hhh])~~
  - Cabazitaxel[aaa] (category 1[hhh])
  - Docetaxel rechallenge[aaa,eee]
  - ~~Enzalutamide (category 1[ggg])~~
- Useful in certain circumstances
  - Olaparib for HRRm (category 1)[hhh,mmm]
  - Cabazitaxel/carboplatin[aaa,nnn]
  - Pembrolizumab for MSI-H or dMMR[aaa] (~~category 2B~~)
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[aaa]
  - Radium-223[kkk] for symptomatic bone metastases (category 1[hhh])
  - Rucaparib for BRCAm[ooo]
- Other recommended regimens
  - Abiraterone[t,ggg]
  - Enzalutamide[t]
  - ~~Fine-particle abiraterone~~
  - Other secondary hormone therapy[t]

PROS-16

FOOTNOTES

[t] See Principles of Androgen Deprivation Therapy (PROS-G).

[zz] Document castrate levels of testosterone if progression occurs on ADT. Workup for progression should include chest CT, bone imaging, and abdominal/pelvic CT with contrast or abdominal/pelvic MRI with and without contrast. Consider metastatic lesion biopsy. If small cell neuroendocrine is found, see PROS-15. See Principles of Imaging (PROS-C) and Discussion.

[aaa] See Principles of Immunotherapy and Chemotherapy (PROS-H).

[ccc] Visceral metastases refers to liver, lung, adrenal, peritoneal, and brain metastases. Soft tissue/lymph node sites are not considered visceral metastases.

[ddd] Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.

[eee] Patients with disease progression on a given therapy should not repeat that therapy, with the exception of docetaxel, which can be given as a rechallenge after progression on a novel hormone therapy in the second- or subsequent-line metastatic CRPC setting ~~if given~~ in men who have not demonstrated definitive evidence of progression on prior docetaxel therapy in the castration-naive setting.

[fff] Novel hormone therapies include abiraterone, enzalutamide, darolutamide, or apalutamide received for metastatic castration-naïve disease, M0 CRPC, or previous lines of therapy for M1 CRPC.

[ggg] The fine-particle formulation of abiraterone can be used instead of the standard form (other recommended option).

[hhh] The noted category applies only if no visceral metastases.

[iii] Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or visceral metastases despite lack of symptoms.

[jjj] Sipuleucel-T is recommended only for asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, and ECOG performance status 0–1. Benefit with sipuleucel-T has not been reported in patients with visceral metastases and is not recommended if visceral metastases are present. Sipuleucel-T also is not recommended for patients with small cell/neuroendocrine prostate cancer.

[kkk] Radium-223 is not recommended for use in combination with docetaxel or any other systemic therapy except ADT and should not be used in patients with visceral metastases. Concomitant use of denosumab or zoledronic acid is recommended. See Principles of Radiation Therapy (PROS-E).

[lll] Consider AR-V7 testing to help guide selection of therapy (See Discussion).

[mmm] Olaparib is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D* or *RAD54L*), who have been treated with androgen receptor-directed therapy. Patients with *PPP2R2A* mutations in the PROfound trial experienced an unfavorable risk-benefit profile. Therefore, olaparib is not recommended in patients with a *PPP2R2A* mutations. There may be heterogeneity of response to olaparib for non-BRCA mutations based on which gene has a mutation. (See Discussion).

[nnn] Cabazitaxel 20 mg/m2 plus carboplatin AUC 4 mg/mL per min with growth factor support can be considered for fit patients with aggressive variant prostate cancer (visceral metastases, low PSA and bulky disease, high LDH, high CEA, lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of *PTEN*, *TP53*, and *RB1*). Corn et al. Lancet Oncol 2019;20(10):1432-1443.

[ooo] Rucaparib is a treatment option for patients with mCRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. If the patient is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given.

[ppp] ~~de Wit R, de Bono J, Sternberg C, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med 2019; 381:2506-2518.~~

[ppp] Switching from prednisone to dexamethasone 1 mg/d can be considered for patients with disease progression on either formulation of abiraterone. Trials show improved PSA responses and PFS and acceptable safety using this strategy. Romero-Laorden et al. Br J Cancer 2018;119(9):1052-1059 and Fenioux et al. BJU Int 2019;123(2):300-306.

Figure 14: NCCN Guidelines for Prostate Cancer, Source: JNCCN

➢ ESMO Guidelines for Prostate Cancer [19]

1. Should PSA screening be recommended for all asymptomatic men?
   Recommendation 1a: PSA screening should not be encouraged for all asymptomatic men (and population-based screening should not be recommended).
   Level of evidence: I
   Strength of recommendation: C
   Recommendation 1b: Well-informed men suitable for screening should have access to PSA testing upon request. There is inconsistent evidence about screening men <50 years and in the age group 70–75 years. There is evidence that the harms of screening men >75 years outweigh the benefits.
   Level of evidence: I
   Strength of recommendation: A/B
2. Should an absolute level of PSA or PSA kinetics be used for selecting men for biopsy?
   Recommendation 2a: PSA with a cutoff at 3 ng/ml is the base for selecting candidates for biopsy in men suitable for curative treatment.
   Level of evidence: I
   Strength of recommendation: A
   Recommendation 2b: PSA kinetics has no role in selecting men for biopsy.
   Level of evidence: II
   Strength of recommendation: D
3. Should clinical factors including age, symptoms, family history, comorbidity, DRE and TRUS findings be considered in the decision whether to biopsy?
   Recommendation 3: Clinical factors (age, symptoms, family history, comorbidity, DRE and TRUS findings) should be used in the decision whether to biopsy
   Level of evidence: III
   Strength of recommendation: A
4. Should risk calculators (RCs) and nomograms be used in selecting men for biopsy?
   Recommendation 4: Risk calculators and nomograms can improve efficiency in selecting men for biopsy
   Level of evidence: IV
   Strength of recommendation: C
5. Which patients should have staging of pelvic lymph nodes?
   Recommendation 5a: High-risk patients having a radical prostatectomy should have an extended bilateral lymph node dissection unless prior imaging shows gross multiple lymph node involvement
   Level of evidence: III
   Strength of recommendation: B
   Recommendation 5c: Low-risk patients should not routinely have a pelvic lymph node dissection.
   Level of evidence: III
   Strength of recommendation: D
   Recommendation 5d: Intermediate and high-risk patients to be treated with radiotherapy should have pelvic imaging unless they have had surgical lymph node staging.
   Level of evidence: IV
   Strength of recommendation: B
   Recommendation 5e: Patients evaluated for salvage radiation therapy after prostatectomy should have pelvic imaging, unless low volume and low risk (PSA < 1.0, Gleason score < 7 and slow PSA progression [PSA DT > 15 months]).
   Level of evidence: IV
   Strength of recommendation: B
6. When should a rising PSA trigger treatment?
   Recommendation 6a: Patients on active surveillance should be monitored in the framework of a standardized protocol. A rising PSA or adverse PSA doubling time/PSA velocity should trigger further investigation with a view to active treatment.
   Level of evidence: III
   Strength of recommendation: B
   Recommendation 6b: In a watchful waiting policy, commencement of hormonal therapy should be led by the development of symptoms rather than PSA alone unless the patient is at high risk of complications or rapid progression (e.g. baseline PSA >50 ng/ml and/or PSA doubling time of <12 months).
   Level of evidence: II
   Strength of recommendation: B

Recommendation 6c: Routine PSA determination following radical prostatectomy is necessary to demonstrate biochemical failure early, because there are indications that early salvage radiotherapy can reduce mortality
Level of evidence: III
Strength of recommendation: B
Recommendation 6d: The optimal treatment of biochemical relapse after radical radiotherapy is not known, and radical local salvage treatments may induce considerable toxicity.
Level of evidence: IV
Strength of recommendation: C
Recommendation 6e: Early hormonal therapy is not routinely advised for PSA relapse after local treatments but is an option for those with short PSA doubling time.
Level of evidence: III
Strength of recommendation: C

7. What is the role of IAD (a) in biochemical failure after radiotherapy or (b) for locally advanced disease?
Recommendation 7a: IAD can be offered to patients who are starting salvage androgen deprivation treatment of a rising PSA >1 year following radiotherapy.
Level of evidence: I
Strength of recommendation: C
Recommendation 7b: Patients with locally advanced prostate cancer to be treated with hormonal therapy alone can be offered IAD.
Level of evidence: II
Strength of recommendation: B

8. Which patients gain from radical local treatment?
Recommendation 8a: In low-risk patients, no benefit in overall survival for PSA-detected tumors has been demonstrated. Active surveillance should be discussed and should be an option for these patients.
Level of evidence: II
Strength of recommendation: A

Recommendation 8b: Radical treatment should be discussed with intermediate and high-risk patients, if they have a minimal life expectancy of 10 and 5 years, respectively.
Level of evidence: I
Strength of recommendation: A

9. Are management options for localized prostate cancer equal in efficacy?
Recommendation 9: In patients to be treated with curative intent, options based on either surgery or on radiotherapy should be considered and their possible adverse effects discussed with the patient.
Level of evidence: I/II
Strength of recommendation: B

10. What dose of radiotherapy should be given in localized prostate cancer?
Recommendation 10a: When external beam radiotherapy is used as sole modality, dose escalation to at least 74 Gy increases biochemical control and delays time to salvage hormonal therapy.
Level of evidence: I
Strength of recommendation: A
Recommendation 10b: For salvage radiotherapy following radical prostatectomy treating only biochemical evidence of disease, a dose of at least 66 Gy is recommended.
Level of evidence: IV
Strength of recommendation: B

11. Does combined treatment with hormonal therapy improve the results of radiotherapy in localized prostate cancer?
Recommendation 11a: If moderate dose radiotherapy (<70 Gy) is used for localized intermediate risk prostate cancer, it should be accompanied by 6 months of ADT.
Level of evidence: I
Strength of recommendation: A
Recommendation 11b: In locally advanced prostate cancer (≥T2b) hormone therapy should be used with radiotherapy for at least 6 months and in high-risk patients for at least 24 months.
Level of evidence: I
Strength of recommendation: A
Recommendation 11c: Additional hormone therapy with adjuvant or with salvage radiotherapy following prostatectomy is currently being investigated in prospective trials and is not recommended as standard care
Level of evidence: V
Strength of recommendation: D

12. Is brachytherapy as effective as external beam radiotherapy in early prostate cancer?

Recommendation 12: Brachytherapy is an effective treatment option for localized prostate cancer

Level of evidence: III

Strength of recommendation: B

13. Are sophisticated radiation planning and delivery techniques required for dose-escalated external beam radiotherapy?

Recommendation 13a: To reduce the adverse effects following radiotherapy, conformal radiotherapy should be used.

Level of evidence: I

Strength of recommendation: A

Recommendation 13b: Intensity-modulated with or without image-guided treatment techniques can be used to reduce normal tissue irradiation

Level of evidence: III

Strength of recommendation: B

14. Is radical prostatectomy an option for patients with T3/T4 prostate cancer?

Recommendation 14: A decision to recommend radical prostatectomy in locally advanced T3-4 prostate cancer should be made only after careful staging and discussion in a multidisciplinary team

Level of evidence: III

Strength of recommendation: C

15. Which patients should be offered ART following radical prostatectomy?

Recommendation 15: Patients with positive surgical margins or extracapsular extension after RP should be informed about the pros and cons of ART

Level of evidence: I

Strength of recommendation: A

16. Should radical treatment be applied when positive nodes are found at lymphadenectomy?

Recommendation 16a: Radical locoregional therapy is recommended for N1 M0 patients suitable for an aggressive management approach

Level of evidence: III

Strength of recommendation: B/C

Recommendation 16b: RT added to ADT is not standard treatment in pN+ patients after radical prostatectomy but may be considered in selected cases.

Level of evidence: IV

Strength of recommendation: C

Recommendation 16c: pN1 patients after radical prostatectomy who are judged to have a high risk for progression should receive immediate ADT.

Level of evidence: II

Strength of recommendation: B/C

17. What is the management of non-metastatic castration-resistant prostate cancer?

Recommendation 17a: Patients with CRPC should continue with life-long androgen deprivation therapy

Level of evidence: V

Strength of recommendation: A

Recommendation 17b: In patients who progress on androgen deprivation, second-line hormone treatments can include the addition of an androgen receptor inhibitor (antiandrogen), antiandrogen withdrawal, estrogen, ketoconazole, or steroids.

Level of evidence: III

Strength of recommendation: B

Recommendation 17c: Patients with CRPC M0, evidence of local progression, and no possibility for local treatment shall be managed like patients with CRPC M1 disease

Level of evidence: V

Strength of recommendation: B

18. What standard treatment should be used in metastatic hormone-naive prostate cancer?

Recommendation 18a: Immediate continuous castration is the preferred treatment option for metastatic hormone-naïve prostate cancer

Level of evidence: I

Strength of recommendation: B

Recommendation 18b: An antiandrogen should be given for 3–4 weeks when starting androgen deprivation with an LHRH agonist for metastatic hormone-naïve prostate cancer, to counteract testosterone flare

Level of evidence: III

Strength of recommendation: B

Recommendation 18c: Intermittent androgen deprivation is not recommended for metastatic hormone-naïve prostate cancer outside of a trial, unless there is significant intolerance of hormone therapy

Level of evidence: I

Strength of recommendation: C

Recommendation 18d: Concomitant bone-targeting therapy with either denosumab or a bisphosphonate is not recommended for metastatic hormone-naïve prostate cancer.
Level of evidence: II
Strength of recommendation: C
Recommendation 18e: Concomitant cytotoxic chemotherapy is not recommended for metastatic hormone-naïve prostate cancer outside a clinical trial.
Level of evidence: II
Strength of recommendation: D

19. What are the treatment options in patients with metastatic CRPC?
Recommendation 19a: Docetaxel chemotherapy is appropriate for symptomatic patients with metastatic castration-resistant disease and good performance status and should also be discussed with asymptomatic patients with evidence of rapidly progressing disease
Level of evidence: I
Strength of recommendation: B
Recommendation 19b: Second, third and fourth line hormone manipulations are options to seek short-term responses
Level of evidence: III
Strength of recommendation: B

20. Are there any effective anticancer treatments for those who have failed docetaxel?
Recommendation 20a: Patients with good performance status should have discussion about further anticancer treatment if one of the following is available; cabazitaxel, abiraterone, MDV3100 (enzalutamide), radium-223
Level of evidence: I
Strength of recommendation: A
Recommendation 20b: Patients with good performance status should have discussion about retreatment with docetaxel or second-line chemotherapy with mitoxantrone if they had responded well to previous chemotherapy, unless new effective lower-toxicity agents are available
Level of evidence: III
Strength of recommendation: C

21. Should an antiosteoclastic drug be used in patients with castration-resistant prostate cancer and bone metastases?
Recommendation 21a: In patients with bone metastases from CRPC at high risk for clinically relevant skeletal-related events, denosumab or zoledronic acid can be recommended, and a large trial found that denosumab delayed skeletal-related events for longer than zoledronic acid. Neither agent has been shown to prolong survival
Level of evidence: I
Strength of recommendation: B
Recommendation 21b: In patients with bone metastases from CRPC at high risk for clinically relevant skeletal-related events, neither clodronate nor pamidronate have been shown to have palliative benefit
Level of evidence: I
Strength of recommendation: E
Recommendation 21c: Patients on antiosteoclastic drugs should have monitoring of serum calcium and oral health; patients on zoledronate additionally require monitoring of renal function
Level of evidence: II
Strength of recommendation: A

Figure 15: ESMO Guidelines for Prostate Cancer, Source: annalsofoncology

9 CONCLUSION

9.1 MARKET DRIVERS AND BARRIERS

Market Drivers

Prostate cancer is the most often diagnosed cancer in men worldwide, and it is associated with a high rate of morbidity and mortality. The prostate cancer market is poised to grow at an exponential pace, primarily due to the increasing prevalence of prostate cancer and a rapidly aging population. The factors which are expected to contribute to the market growth are as follows:

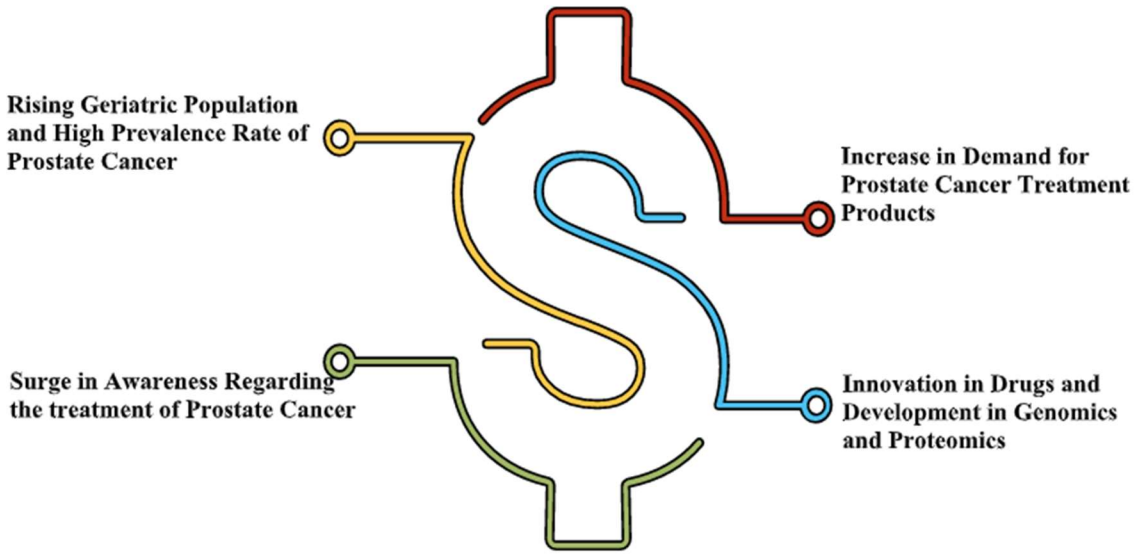

Figure 16: Market Drivers

Rising Geriatric Population and High Prevalence Rate of Prostate Cancer

It is the most common and 2nd leading cause of cancer death among men in the US. According to Surveillance, Epidemiology, and End Result, the estimated prevalence of prostate cancer in the United States was 3,170,339 men. According to a study conducted between 2015 and 2017, 12.1 percent of men will develop this disease at some point in their lives. It affects 2.1 percent of the adult male population in France, according to Colonna et al. (2015). Furthermore, health issues, obesity, family history, and food choices are all contributing to the rising prevalence of instances around the world.

Furthermore, age is the most significant risk factor for this disease. According to a white paper issued by the European Alliance for Personalized Medicine, men who reach the age of 80 or beyond have an 80% chance of having this condition, which is most common in men aged 65 and up. This disease is most commonly diagnosed in 65–74 age group males, according to the SEER; the median age at diagnosis is 66 years. People aged 65 to 74 years old had the highest number of cases, followed by 55–64 years and 75–to 84 years old.

Prostate cancer risk rises dramatically with age, and the expanding elderly population is expected to be a major driver of the worldwide prostate cancer market over the forecast period.

Increased Public Awareness About Prostate Cancer Treatment

According to the American Urological Association (AUA, 2019), in 2019, every 3 min, a new case of prostate cancer was recorded. Globally, this number increased to one new case every 41 s. Even though many men who are diagnosed with prostate cancer go on to lead long and full lives, it is still incredibly important to be aware of the risks, symptoms, and treatment of prostate cancer. As with any cancer, early detection is important, and men should be proactive in their healthcare and wellness to stay on top of their health throughout their lives.

Prostate cancer patients in major industrialized countries have been more knowledgeable in recent years as a result of cancer awareness initiatives and guidelines produced by various cancer organizations, registries, and support groups. The American Urological Association (AUA) and the Urology Care Foundation, for example, developed guidelines and suggestions to raise prostate cancer awareness. Many regional and municipal organizations, as well as healthcare organizations, have stepped forward to promote awareness of cancer-related symptoms and difficulties. Soon, this will proliferate the prostate cancer market, resulting in the adaptation of more accurate treatment.

Demand for Prostate Cancer Treatment Products Is Growing

Prostate cancer that is restricted to the prostate gland is most typically detected in its early stages, and there are numerous therapeutic options available. Treatment options and recommendations are influenced by the kind and stage of prostate cancer, as well as any side effects, the patient's preferences, and overall health.

Many unique treatment options for prostate cancer treatment are currently accessible, such as hormone therapy. Drugs that stop your body from manufacturing testosterone and medications that prevent testosterone from reaching cancer cells are included in this treatment. It is also used to shrink cancer and limit tumor growth in males with advanced prostate cancer. Hormone therapy may be used to decrease tumors before radiation therapy in early-stage prostate cancer, increasing the likelihood that radiation therapy will be successful.

As numerous licensed medicines in combination and developing therapies are in the pipeline for the evaluation of prostate cancer treatment, the market competition for prostate cancer will intensify. These new medicines, which include novel techniques and combination therapies, will drive the prostate cancer therapeutic industry forward.

Innovation in Drugs and Developments in Genomics and Proteomics

Prostate cancer has long been known to have genetic impacts, and our understanding of the disease's molecular genetics is growing. Genome-wide association studies (GWAS) have proved useful in finding genetic risk variants associated with prostate cancer, according to review research published by Malik et al. (2019). GWAS entails looking at hundreds of thousands of variants across the genome in large groups of people, frequently separated into cases and controls, to find variants linked to the trait of interest. Single nucleotide polymorphisms (SNPs) are the most prevalent types of variations in the human genome, and they are thought to play a direct role in the progression of many complex disorders, including prostate cancer. Furthermore, several genomic advances contribute to oncology patients' better outlooks. For example, advances in techniques for gene editing are assisting researchers in mapping the genetic and epigenetic aberrations that contribute to many cancers.

The discovery of cancer-specific biomarkers, improved prognosis, and therapy response biomarker identification have all been exciting areas of research for proteomics and related technology. It also helps researchers gain a better knowledge of cancer pathology and design new and effective treatments. The development of innovative therapies will be the way ahead for treating prostate cancer in the future. The findings of numerous studies conducted around the world point to the future development of precision medicine in prostate cancer.

Market Barriers

Several market barriers exist for the therapeutic market of prostate cancer like cost constraints, the complex issue of companion diagnostics, and entry barriers, among others, which are expected to impact the upcoming therapeutic market.

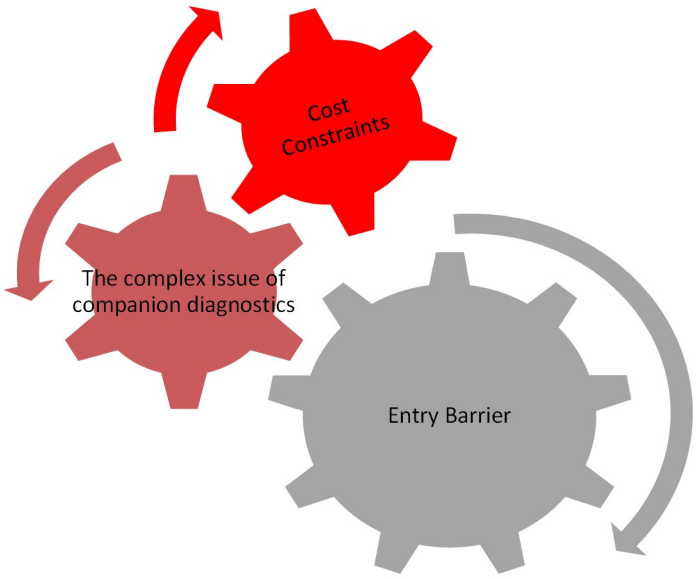

Figure 17: Market Barriers

Cost Constraints

Payers all across the world are becoming firmly confident that the cost of cancer drugs outweighs the benefits of using them. As a consequence, value-based and, increasingly, outcomes-based pricing in oncology is becoming more frequent. The main goal of this method is to match a therapy's price to its established value more closely. This value will not be confined to clinical

benefits as it has been in the past, but will also encompass the value to patients (both clinical results and broader patient-related outcome measures (PROMs)), payers, and society as a whole. Many payers still favour traditional discount and rebate strategies, thus the emphasis is on the convenience of contractual arrangements.

The complex issue of companion diagnostics

Diagnostic costs are a major worry and stumbling block for many new "tailored" treatments. Cancer drug developers are being urged by officials and insurers to develop low-cost companion tests that can indicate which patients are most likely to benefit from a drug, reducing unwanted side effects and expense for others. The US FDA issued companion diagnostics guidance to the industry in July 2011, indicating that if a diagnostic is required for the safe and effective use of a therapy, FDA will generally need approval or clearance of the diagnostic tools at the same time as the therapeutic.

Companion diagnostics development has numerous economic, scientific, and regulatory difficulties. Because diagnostics aren't always covered in many markets around the world, and if a patient can't get a diagnosis, they won't be able to get therapy. It's a huge hole that needs to be filled in order to ensure that the appropriate patient gets the proper treatment, lowering total healthcare costs for payers and national healthcare systems.

Entry Barrier

Due to a multitude of variables, the barriers to entry for biosimilar products are extremely high. Due to regulatory restrictions, production needs, patent conflicts, and demand-side issues, entry barriers hinder other competitors from joining the market. There is a tendency toward international harmonization of regulatory criteria for biosimilar pharmaceuticals, although some jurisdictions have different laws governing naming and substitution, which could create impediments to their launch and reduce competitiveness.

Furthermore, a monopolist may utilize its market power to alter rates for different customers for the same product (price discrimination). This would allow the monopolist to fully exploit it based on the price elasticity of demand of the consumers. Simply put, the monopolist would sell the product at a higher price to customers who value it more and are willing (or able) to pay more for

it at that price. Because there are barriers in place to prevent consumers in separate markets from taking advantage of price disparities and profiting from them, the monopolist would engage in price discrimination for distinct markets. Therefore, the entry barrier is also considered the major barrier in the oncology market.

9.2 CHALLENGES TO MARKET ACCESS

Prostate cancer is a complèx disease with many different clinical symptoms. Understanding the underlying genetic basis of prostate cancer has made some progress recently. This type of mechanistic information can be used to create new therapeutic targets, uncover biomarkers for early detection or discriminating between aggrèssive and indolènt disease, and predict treatment outcomes. Several tests have been developed in recent years to meet these clinical needs for prostate cancer. However, there are still certain places where improvement is needed, as well as some unmet expectations.

Figure 18: Challenges to Market Access

➢ **Need for novel Biomarkers**

Prostate cancer can be cured if detected early. While tremendous progress has been made in the development of novel therapy techniques, effective diagnostics remain a challenge. As a result, new diagnostic tools—prefèrably non-invasive—are needed for accurate prostate cancer diagnosis and assessment, particularly for stratifying risk of disease progression in men with prostate cancer confirmed by biopsy.

Diagnostic methods are now in use, although they have faults. PSA levels can be elevated by a range of conditions or activities other than prostate cancer, including as benign prostatic

hyperplasia (BPH), prostatitis, sexual activity, and exercise. When it comes to describing prostate tissue and its significance in terms of the disease, there are various grey areas. Moreover, similar developments to assess disease in patients prior to treatment are in high demand right now. As a result, patients would benefit from improved non-invasive predictive biomarkers that could detect cancer or the likelihood of developing advanced disease once cancer has been detected.

- **Lack of Therapeutic Options for nmCRPC Patients**

Although there has been significant progress in the treatment of prostate cancer, it remains the top cause of death among men. There are also a limited number of approved medicines for various clinical forms of prostate cancer, one of which is nmCRPC. On the other hand, "requirement to delay the start of castration-resistant disease in metastatic hormone-naïve prostate cancer (mHNPC) is another key unmet need for therapeutic options". For the treatment of nmCRPC, medicines like Erleada (apalutamide) and Nubeqa (darolutamide) have been licensed.

Furthermore, as evidenced by clinical trials.gov, the majority of research is focused on metastatic rather than non-metastatic prostate cancer, indicating that there is an unmet need to close this clinical gap.

- **Drug Resistance**

Drug resistance is a major unmet need in prostate cancer, as doctors have traditionally depended on hormonal drugs to treat the disease. However, these drugs are susceptible to both primary and secondary drug resistance. The majority of advanced prostate cancers will develop to CRPC.

Resistance to ADT, on the other hand, is essentially unavoidable, but only after a specific timeframe of therapy for each patient, such as biochemical recurrence or the diagnosis of advanced disease. The variety of molecular adaptations observed in this situation reflects the clinical variation in progression to metastatic CRPC.

As a result, prostate cells' seemingly simple dependency on androgens masks the complexities that occur in advanced prostate cancer, all of which precisely reflect the complexities of the mechanisms of resistance that lead to therapeutic failure in patients. The problem of resistance

must be addressed urgently, and this can be accomplished by developing non-androgen receptor (AR)-driven approaches to prostate cancer control.

- **Lack of Disease Understanding and Awareness**

Prostate cancer is a complex disease, as previously stated in the introduction of unmet needs, and according to a report by the Prostate Cancer Foundation, there is a significant lack of understanding about prostate cancer and its symptoms among Americans, with 69 percent of people either unsure or believing there are noticeable symptoms for early-stage prostate cancer. Men are more likely to dislike coming to the doctor because they assume prostate cancer screening tests will put them in excruciating pain and place them in an awkward situation with a DRE. Men are unaware that they can be checked for prostate cancer with a simple blood test. So, this gap need to be addressed to improve the problems related to the treatment and diagnosis of prostate cancer.

9.3 SWOT ANALYSIS

Strengths

- The clinical pipeline of prostate cancer is robust as there are lots of therapies that are in a late phase of development with a diverse group of drug classes such as PARPi, PD-L1i, AKTi
- The development of therapies targeting specific mutations are expected to perform better in the upcoming future (e.g. PARP inhibitors)
- Potential opportunities for label expansion within prostate cancer; for example, Xtandi was first approved in mCRPC but later got approval in nmCRPC and mCSPC as well (a similar trend in Zytiga as well)

Weaknesses

- The ADT therapies are still the treatment backbones of prostate cancer, especially in CSPC
- CRPC types are almost saturated due to already approved multiple therapies in this segment and also most of the emerging therapies are targeting this segment leading to a highly competitive landscape that might limit the uptake of emerging therapies
- Prostate cancer often grows slowly and diagnosis at an early stage is still a concern. Also, there are no definite biomarkers available for progressive or the transformative form of the disease

Opportunities

- Lucrative opportunity in CSPC due to relatively less competition compared to CRPC and broader patient pool, but have to compete against ADT
- Uptake of potential emerging therapies with better clinical profile, especially targeting the mutations like PARP inhibitors (i.e. BRCA mutation) expected to be fast
- The rising prevalence of prostate cancer due to the rapidly aging population and growing awareness among people will provide a larger window of opportunity for new treatment

Threat

- The market value of Zytiga in the US is already started declining in 2019 and sales value decline is expected to be much faster in future years due to expected multiple launches of generics; in the EU expected generic entries from 2023
- Besides Zytiga, expected generics or biosimilars of Xtandi, Keytruda, and Opdivo also expected to erode the sales value
- Healthcare authorities will seek to restrict pricing and usage of the high-cost agent with moderate efficacy or no add-on benefit compared to current treatments. For example, NICE chose not to recommend Xtandi in nmCRPC owing to no added benefit compared to the placebo.

Conclusion

Prostate Cancer is one of the most common cancers among men across the world and its epidemiology varies across countries due to multiple factors like age, diagnosis and other environmental factors. There has been a lot of advancement in terms of diagnosis and treatment and the pharmaceutical market for this disease is also experiencing growth as a result of novel therapies. The current treatment landscape of Prostate cancer includes surgery, radiation therapy, hormone therapy and systemic therapy including chemotherapy and immunotherapy. The market drivers for prostate cancer are, high prevalence rate of prostate cancer; increasing awareness; uptake in demand of products; innovation in drug development and the market barriers include, cost constraints, diagnostics, and entry barriers for new products. Overall challenges to market access include, requirement of novel biomarkers, drug resistance, lack of disease understanding and lack of therapeutic options for nmCRPC.

10 REFERENCES

1. Cuzick, J., "Prevention and early detection of prostate cancer", *The Lancet, Oncology*, 15(11), e484–e492, 2014.
2. Ankita Shukla, Ahmed Moussa, Tiratha Raj Singh, "DREMECELS: A Curated Database for Base Excision and Mismatch Repair Mechanisms Associated Human Malignancies", PLoS ONE, 11 (6), e0157031, 2016.
3. Manika Sehgal, Tiratha Raj Singh, "DR-GAS: A database of functional genetic variants and their phosphorylation states in human DNA repair systems", *DNA Repair*, 14 (April 2014), 97-103, 2014.
4. Sadhika Behl, Arushi Sharma, Prashanth Suravajhala, Tiratha Raj Singh, "Computational studies to explore the role of MSI associated DNA mismatch repair mechanisms in HNPCC through expression and interaction data", *International Journal of Bioinformatics Research and Applications*, 16 (4), 408-416, 2021.
5. Mountfort K, "ASCO 2019: Prostate cancer highlights*", touchONCOLOGY*, 2022.
6. Rawla P, "Epidemiology of Prostate Cancer", *World J Oncol*, 10(2), 63-89, 2019.
7. Siegel, RL, Miller, KD, Fuchs, HE, Jemal, A, "Cancer statistics, 2022", *ACS Journals*, 2022.
8. IARC, "Cancer Tomorrow"*,* 2022.
9. SEER, "Cancer Statistics", 2022.
10. Colonna, M., "Total and partial cancer prevalence in the adult French population in 2008", *PubMed Central,* 2015.
11. ABPI, "Prostate cancer", 2022.
12. Krebs, "Prostate cancer", 2017.
13. Lee S., "PCN52 - Prevalence and Incidence of different types of cancer in Germany: An epidemiological analysis based on claims data of more than 2.9 million insured persons*" Value in Health, 2018.*
14. Kimura, T., "Epidemiology of prostate cancer in Asian countries"*, International Journal of Urology,*25,524-531,2018.
15. Sung, H, Ferlay, J, Siegel, RL, Laversanne, M, Soerjomataram, I, Jemal, A, Bray, F. Global "cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries", *CA Cancer J Clin*, 71, 209- 249, 2021.

16. American Cancer Society, “Considering prostate Cancer Treatment Options”, 2022.
17. Ankita Shukla, Manika Sehgal, Tiratha Raj Singh, “Hydroxymethylation and its potential implication in DNA repair system: A review and future perspectives”. Gene, 2015.
18. Edward Schaeffer.,. “NCCN Guidelines Insights: Prostate Cancer, Version 1”, *JNCCN,* vol 19*,* 2021.
19. A. Horwich., “Prostate cancer: ESMO Consensus Conference Guidelines 2012”, *Annals of Oncology*, 2012.