Prostate Cancer Review: Epidemiology, Risk Factors, Pathophysiology, Diagnosis and Treatment

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ABSTRACT

The principal function of the prostate is the production of ejaculate, or essential secretions for semen, which ensure the viability of sperm. Cancers of the prostate gland cells are prevalent, especially in middle age and old age. Millions of men throughout the world are affected by prostate cancer. It accounts for 7% of newly diagnosed malignancies in men globally (15% in industrialized regions) and is the second most common cancer in men, after lung cancer. Age, ethnicity, and family history are examples of modifiable risk factors for prostate cancer; dietary factors, level of physical activity, smoking, and obesity are examples of modifiable risk factors.

Prostate cancer is thought to be closely linked to the accumulation of somatic mutations in the genome of prostate epithelial cells over a patient's life. Traditional prostate specific antigen (PSA) testing has limited specificity among its many drawbacks when it comes to screening and detecting prostate cancer. Surgical excision, radiation therapy, chemotherapy, and hormonal therapies are the main methods of treating prostate cancer. The goal of PC management should be either eradicating the disease or alleviating specific symptoms.

KEYWORDS

Prostate Cancer, Prostate specific antigen, Circulating tumor cells, Androgen deprivation therapy, Gene therapy, Phototherapy

INTRODUCTION

The male reproductive organ, the prostate, is located underneath the urine bladder. Its principal function is to enhance the vital semen discharges and to preserve the viability of sperm. Core, transitional, and periphery zones are present in the adult human prostate. Located in the posterior region of the male reproductive system, next to the urethra and behind the bladder, is the prostate gland. The principal function of the prostate is the production of ejaculate, or essential secretions for semen, which ensure the viability of sperm. [1] Cancers of the prostate gland cells are prevalent, especially in middle age and old age. Core, transition, and peripheral zones comprise the adult human prostate's fibromuscular and periurethral regions. Proper prostate function is mostly the responsibility of the peripheral zone, which makes up around 70% of the prostate glandular tissue in young adult males. This area is responsible for the formation of around 80% of prostate tumors, making it the most common site for neoplasms in the aging prostate. The stroma houses the acini and ducts that make up a normal gland. One layer of simple columnar epithelium encases the ducts and acini in a basement membrane of basal epithelium. Smooth muscle myocytes and other stromal cells adhere to this extracellular matrix layer, allowing for spontaneous contractility and preventing fluid stagnation. [2] Fibroblasts, another component of the stroma, mainly serve to stabilize the adult prostate's

ducts. During prostate development, duct patterning is believed to depend on fibroblast paracrine signaling. According to laboratory findings, the stromal fibroblasts in the tumor microenvironment can promote epithelial transition and enhance survival signaling. This makes them protumorigenic inside the tumor stroma. They may help cancer cells continue to multiply even after therapy has ended. It is believed that the increased levels of AR, which encodes the androgen receptor, in both normal and cancerous epithelial cells contribute to the hormone dependence seen in prostate cancer. The cells also secrete PSA, which is particular to the prostate. In men with prostate cancer, this serine protease is elevated, and it is utilized in diagnostics and disease detection since the androgen receptor transcriptionally activates it. [3]

Epidemiology

Incidence and mortality

Millions of men throughout the world are affected by prostate cancer. It accounts for 7% of newly diagnosed malignancies in men globally (15% in industrialized regions) and is the second most common cancer in men, after lung cancer. In addition, there are more than 1.2 million new instances of prostate cancer each year, and more than 350,000 men die from this disease worldwide. [4] This makes prostate cancer one of the leading causes of cancer-related death in men. There is a strong correlation between advancing age and an increased risk of prostate cancer; in fact, more than 85 percent of newly diagnosed patients are older than 60. Consequently, countries like the United States and the United Kingdom, where life expectancy is high, have a significantly higher incidence of prostate cancer. An increase in both the HDI and GDP is associated with a lower incidence of prostate cancer worldwide. [5]

That is why developed countries tend to have more of it than developing ones. It is worth mentioning that in Asia, there are a number of countries with increased HDI, such as South Korea and Japan, but their prevalence is smaller than in Western countries with similar HDI. Nevertheless, the incidence is increasing in these regions. North America, Europe, Oceania (including Australia and New Zealand), and parts of South America (including Brazil) have the greatest incidence rates. The prostate cancer rate is currently lowest in South Asia, Central Asia, and sub-Saharan Africa, all of which include a number of low-income countries, but it is increasing at one of the fastest rates in the world. Since more frequent screening corresponds with greater incidence owing to overdiagnosis, the increase in incidence may be an indication of heightened awareness of prostate cancer as a result of improved availability to diagnostic screening in many nations. [6] Improving access to early diagnosis is expected to alleviate this issue, but these countries still have the highest age-standardized mortality rates for prostate cancer. Enhanced detection of all prostate cancers (even indolent cases) and decreased prostate cancer-specific mortality are both shown by research done in Europe with extensive follow-up data indicating that screening is beneficial. The benefits of improvements in public health and treatment are outweighed by the rise in prostate cancer risk factors associated with economic growth, which may explain why age-adjusted mortality is on the rise in developing nations. Exposure to cigarette smoking, obesity, and a predominantly Western diet are non-heritable characteristics thought to increase death from prostate cancer; however, there is a lack of data on how these factors affect the disease's incidence. [7,8]

Potential risk factors for prostate Cancer

Age, ethnicity, and family history are examples of modifiable risk factors for prostate cancer; dietary factors, level of physical activity, smoking, and obesity are examples of modifiable risk factors.

Non-modifiable risk factors

Race/ethnicity

Recent research has shown that racial and ethnic background significantly increase the likelihood of prostate cancer (PC). Black men, men of West African origin from the Caribbean, and men from South America have far higher PC incidence and mortality rates than white men, according to recent statistics (Globacan). Men from Asian, African, and Middle Eastern backgrounds tend to have the lowest rates of prostate cancer. The National Cancer Institute reports that among males of African American descent, the incidence rate of prostate cancer is 1 in 6, significantly higher than the 1 in 8 lifetime probability among non-Hispanic White men. New evidence has shown the discrepancy. [9,10]

Age

The risk of prostate cancer may increase with age. Older men are more susceptible to prostate cancer than younger men (under 40), who have a decreased likelihood of diagnosis. The incidence of prostate cancer escalates significantly post-50 years of age, with analytical research indicating that around 60% of prostate cancer cases are diagnosed in men over 65, who exhibit reduced overall survival rates. Consequently, it is strongly advised to promote regular prostate-specific antigen (PSA) test screenings for males over 60 years of age. [11]

Family history

Alongside age and ethnicity, family history is a nonmodifiable risk factor for prostate cancer in males. Zheng et al. investigated five single-nucleotide polymorphisms (SNPs) and identified a strong correlation with prostate cancer (PC) in individuals with a familial history of PC, indicating that the risk of prostate cancer escalates for males with a family history of any disease or prostate cancer in first-degree relatives. [12]

Modifiable risk factors

Overweight and obesity are complicated conditions characterised by an excessive accumulation of body fat. Recent research affirm that obesity is a significant public health concern and is linked to a minimum of thirteen distinct cancer types, including multiple myeloma, meningioma, uterine, breast, thyroid, ovarian, liver, adenocarcinoma, gallbladder, colorectal, pancreatic, and upper gastric cancers. Three recent meta-analyses have substantiated a favourable link between obesity and the risk of prostate cancer. [13]

Diet

Lipids are macromolecules that function in energy storage, signalling, and serving as structural elements of cell membranes. Lipids are categorised into two classifications: fats and steroids. A high-fat diet has been associated with an elevated incidence of prostate, breast, and colon cancers, among other malignancies. Due of their high fat and calcium content, milk and dairy products may contribute to carcinogenesis. A meta-analysis of 12 studies established a substantial association between elevated dairy consumption of milk and calcium (>2000 mg/day) and advanced-stage, high-grade prostate cancer. [14]

PATHOPHYSIOLOGY

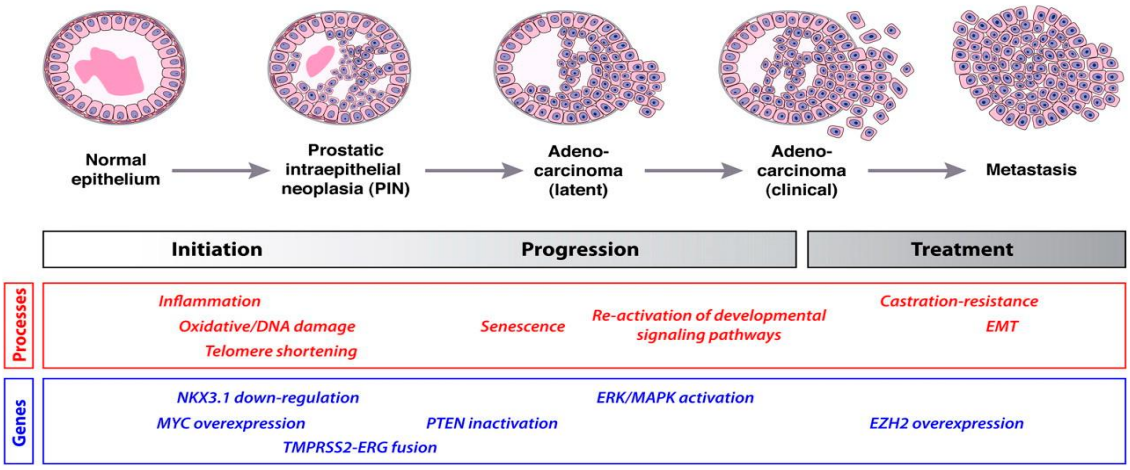
Genetics

Prostate cancer is thought to be closely linked to the accumulation of somatic mutations in the genome of prostate epithelial cells over a patient's life. These aberrations may arise in oncogenes or tumour suppressor genes, resulting in alterations in gene transcription and translation, as well as functional impairments, which culminate in disrupted cellular homeostasis. [15] Mutations mostly affect genes that govern cell proliferation. DDR, cellular proliferation, and apoptosis. Prostate cancer is classed as a C-class tumour with a restricted mutational burden (3–6% of the primary cancer genome), since the bulk of genetic alterations connected with prostate cancer are copy number alterations (CNAs) or structural rearrangements of genes. [16]

Localized disease

The most frequently observed modifications associated with the pathogenesis of localised prostate cancer are fusions of androgen receptor-regulated promoter regions with sequences encoding members of the erythroblast transformation-specific (ETS) family of transcription factors. The most prevalent fusion involves transmembrane protease serine 2 (TMPRSS2) and ETS-related gene (ERG), identified in nearly 50% of prostate cancer biopsy specimens from Caucasian men, but less commonly in Black and Asian men (27–31%), potentially contributing to racial disparities in cancer survival outcomes. [17] Whole-genome sequencing of localised, low-risk to high-risk prostate tumours has identified relatively rare gene alterations in TMPRSS2–ERG-negative tumours, including loss-of-function mutations in SPOP, fusion of TMPRSS2 with ETV1, and gain-of-function mutations in FOXA1, occurring in 11%, 8%, and 3% of primary prostate cancers, respectively. The functional validation of the transforming potential and therapeutic repercussions of these genetic occurrences is under process. Preclinical experiments have indicated that mutations in SPOP promote genomic instability in mouse models. [18] Significant genetic variations are detected between Chinese and Western prostate cancer patient cohorts: 41%, 18%, and 18% of Chinese patients have recurrent hotspot mutations in FOXA1, ZNF292, and CHD1, respectively, but Chinese patients demonstrate a considerably lower prevalence of ETS fusions. These data may suggest a significant biological differential in the development of prostate cancer among ethnically varied populations. [19] FOXA1 is necessary for prostate organogenesis and works as an oncoprotein in prostate cancer, increasing AR transcription, especially in late stages, to promote metastatic dissemination. These findings underline the requirement for systematic and thorough research of prostate cancer mutations across numerous ethnic groups to develop a global genetic map of the illness. Moreover, in an aggressive and uncommon type of prostate cancer characterized by frequently absent androgen receptor expression, known as poorly differentiated neuroendocrine prostate cancer (NEPC; often referred to as small cell carcinoma), the predominant changes are believed to be drivers of the illness. [20]

Figure 1: The developmental stages of prostate cancer [61]



Gene amplifications of AURKA and MYCN occur in up to 40% of persons with localized neuroendocrine prostate cancer (NEPC). This disease variant is most typically detected as treatment-emergent NEPC in males who have received androgen deprivation therapy (ADT). Preclinical models of these monogenic alterations recapitulate the clinical features and neuroendocrine abnormalities reported in patients. Moreover, ONECUT2 expression is enhanced in treatment-emergent NEPC and has been identified as a regulator of tumour hypoxia signaling and the cell differentiation state, diverting from hormone dependency. In contrast, these alterations in ONECUT2 are seldom detected in localized prostate cancer that continues to be hormone-dependent. [21] In patients with localised disease, identifying specific gene alterations that differentiate aggressive from indolent prostate cancer has proven challenging, likely due to the presence of various driver mutations contributing to the disease (genetic heterogeneity), and current treatment protocols are not typically guided by molecular profiling of the tumour. Genetic signatures that encompass various features, such as copy number alterations, gene methylation, and intricate mutational events like kataegis, chromothripsis, and chromoplast, may more accurately reflect disease aggressiveness, as heightened genetic instability is linked to biochemical failure and clinical progression, including the development of metastasis. For example, in non-indolent localized illness, which affects 7-10% of patients, the most common gene changed is ATM, which has druggable targets within its signaling pathways. However, none of these genes are common in prostate cancer patients. It is challenging to understand the clinical features of a prostate tumor at diagnosis and to treat it with potential targeted medicines due to the multiplicity of genes that are thought to cause the illness. [22]

Metastatic disease

Numerous advanced, incurable stages of prostate cancer are encompassed in metastatic prostate cancer. Localized inside the organ and often influencing lymph nodes and osseous domains. Tumors that progress during or after androgen deprivation treatment (ADT), also known as castration-resistant prostate cancer (mCRPC), and de novo metastatic castration-sensitive prostate cancer (mCSPC) also fall into this group. Compared to localized prostate cancer, mCSPC and mCRPC tumors, which can be seen in several places per patient, have a much higher mutational load and a higher rate of copy number changes. The majority of the biopsy samples used for whole-genome sequencing analysis so far came from mCRPC tumors that had been treated with both local and systemic active therapies. So, it's possible that some of the

mutational changes in these tumors are caused by genetic disruptions caused by the treatment. Over 70% of patients with mCRPC have mutations that inhibit AR pro-tumorigenic signaling, including amplification and gain-of-function mutations in AR, amplification of AR transcription regulators (like FOXA1), and inactivating mutations or deletions of genes like ZBTB16 and NCOR1, which are tumor suppressors. [23] Alternatively, AR changes are found in just 2-6% of cases in mCSPC, suggesting that AR amplifications and mutations have acquired relevance in mCRPC, according to follow-up targeted genetic studies in matched samples before treatment in patients who later relapsed with mCRPC. AR has been the subject of a great deal of study and is one of the oncogenes targeted by therapeutic interventions for prostate cancer. When androgens like dihydrotestosterone (DHT) bind to the luminal epithelium of a healthy prostate, it causes the androgen receptor (AR) to move from the cytoplasm to the nucleus. There, it interacts with genes that contain androgen response elements (ARE) to initiate a transcriptional response. It is possible that increased androgen receptor (AR) expression in prostate luminal cells contributes to neoplasia-induced cell proliferation. Consequently, normal prostate development control is quite stringent, but neoplasia disrupts this regulation. The main role of AR is to regulate the expression of genes that are important for maintaining cellular homeostasis and for producing proteases that are necessary for the prostate to work properly, including KLK3, which is responsible for encoding PSA. When the disease is pathological, The majority of the time, AR promotes cancer by easing a transcriptional pathway linked to growth. Over time, resistance to therapy can be conferred through multiple mechanisms when ADT causes changes in AR, AR expression, or post-translational modifications. At first, alterations to the regulatory systems controlling AR expression or amplification of the AR gene can be the cause of its overexpression. Subsequently, androgen receptor mutants that are constitutively active are the result of somatic gain-of-function mutations, most commonly found in the ligand-binding domain. [24]

There is a significant prevalence of mutations that reduce the specificity of the androgen receptor, making it easier for alternative agonists, such as glucocorticoids and oestrogen, to activate the receptor. The third point is that AR may undergo post-translational modifications that make it more activatable even at the decreased amounts of testosterone that continue after castration. The fourth point is that certain tumors undergo alternative splicing, which leads to an increase in the production of AR splice variants (SVs), which are short splice isoforms of AR. There is often no ligand-binding domain in the AR SV protein products, and play a role in transcription but are lacking in activity. [25] Clinical application of AR SVs for outcome prediction is an area of continuing research, since preclinical data suggests that AR SVs may aid the development from CSPC to CRPC. Lastly, the overexpression of AR is almost Laboratory tests confirm that higher AR levels alone are sufficient to induce treatment resistance, as only observed in CRPC. Due to its need on androgen receptor (AR) for disease progression, prostate cancer can be specifically targeted by inhibiting AR signaling. Dysregulation of key genes involved in growth regulation is thought to have a role in the progression of prostate cancer from castration-sensitive (CSPC) to castration-resistant (CRPC) and from locally to metastatic disease. [26] Around 12-17% of localized and metastatic castration-sensitive prostate cancer (mCSPC) tumors have homozygous deletions on chromosome 10q, which harbors PTEN, along with loss-of-function mutations. On the other hand, more than 40% of metastatic castration-resistant prostate cancer (mCRPC) tumors have these same mutations, suggesting that these are significant genetic changes involved in carcinogenesis and tumor development. Additionally, alterations in the phospho-inositol 3

kinase (PI3K) pathway are common; 6% of cases have gain-of-function mutations in PIK3CA and PIK3CB, while 2% of advanced tumors have mutations in AKT1. There is a lot of ongoing study on the role of PI3K pathway intermediates in the development of colorectal cancer in mouse models, and this is especially true given the abundance of small-molecule inhibitors that target these intermediates. While WNT signaling pathway activation is not typically associated with localized disease, 18% of mCRPC tumors show changes in pathway intermediates, with 9% showing loss-of-function mutations in APC and 4% showing gain-of-function mutations in CTNNB1. [27] Importantly, 20-30% of people with serious disease have chromosomal instability, which includes copy number changes (CNAs) of genes on 8q (which contains the MYC oncogene) and the deletion of 8p (which contains the NKX3-1 tumor suppressor). Since MYC is almost always expressed throughout tumor development, regardless of copy number changes, and can be upregulated by direct transcriptional targeting by different other genes to boost proliferation and resistance to treatment, it is thought to have a more extensive role in prostate carcinogenesis. One of the most important events in carcinogenesis may be the breakdown of the control of genomic stability, which occurs often in prostate cancer. Cell cycle arrest-regulating genes, such as TP53 and RB1, are often altered in metastatic castration-resistant prostate cancer (mCRPC). Metastatic disease is more common in TP53 and RB1 than in localized disease; in mCSPC, 27% and 5% of mRB1 and 50% and 21% of mCRPC, respectively, show changes; suggesting that TP53 and RB1 dysfunction may lead to metastatic development. [28] In addition, negative outcomes are strongly associated with Rb1 deletion in murine models, which is sufficient to initiate the development of CSPC to CRPC. Research in both cells and animals has shown that when Rb1 and Tp53 are lost at the same time, it can lead to lineage plasticity, the development of neuroendocrine adenocarcinoma, and metastasis when androgen deprivation therapy is continued. Metastatic castration-resistant prostate cancer is also characterized by somatic mutations in genes that respond to DNA damage. Patients with cells that have problems repairing double-strand breaks may also have problems with the homologous repair pathway, which means they have a lot of copies of damaged DNA and are more likely to be damaged by conventional treatments like ionising radiation, PARP inhibitors, and DNA strand intercalators. This could mean that some of these patients could benefit from non-standard therapies. changes in BRCA2, which is involved in homologous repair and is changed in 7% of mCSPC and 12.5% of mCRPC, and ATM, which is changed in 5% of mCSPC and 7% of mCRPC, are common in advanced illness; however, changes in both genes are rare in localized disease. Both in preclinical studies using ex vivo cancer models and in clinical trials including patients with mCRPC, medicines that specifically target the sources of genetic instability have shown promise in extending cancer-specific survival. [29]

NOVEL DIAGNOSTIC APPROACHES

Traditional prostate specific antigen (PSA) testing has limited specificity among its many drawbacks when it comes to screening and detecting prostate cancer. Because of these problems, many men who are not at high risk for developing prostate cancer are being overdiagnosed and treated. Innovative, low-cost, and non-invasive diagnostic methods have emerged as a result. help determine if prostate cancer is active or not and reduce the negative effects of repeated biopsies on treatment outcomes. [30] Biomarkers that overcome PSA's shortcomings have proliferated in the last decade, thanks to advances in our knowledge of the molecular and genetic bases of prostate cancer. More specialized biomarker-based methods have been shown to be much better. Therefore, these methods based on biomarkers can reduce the problem of prostate cancer overdiagnosis and therapy. These biomarkers are used in many

stages of decision-making, including screening, risk stratification after a positive biopsy, determining if a repeat biopsy is necessary after a negative biopsy, monitoring prognosis after treatment, and determining if further intervention is needed in cases of suspected recurrence. Because there is a lack of clinically significant data demonstrating the usefulness and benefits of biomarkers, most of them are not currently used in clinical practice, despite their potential advantages. Now we will have a look at a few biomarker-based diagnostic approaches. They have proven to be useful in clinical settings. [31]

SERUM-BASED BIOMARKERS

Prostate health index (PHI)

In collaboration with the Early Detection Research Network at the National Cancer Institute, Beckman Coulter Inc. created the PHI test, an assay that uses serum. The PHI has the following biomarkers: [-2] proPSA, total PSA (tPSA), and free PSA (fPSA). In order to reduce the occurrence of unnecessary biopsies, the individual data is processed using the formula [-2] proPSA/fPSA × √tPSA. This yields a score that differentiates between benign and malignant prostate tumors. This equation states that those at high risk for adverse events have lower fPSA levels and higher tPSA and [-2] proPSA values. [32] Therefore, men with high PHI scores should have fewer invasive biopsies since they are more likely to have aggressive prostate cancer. Commercial usage of PHI for patients older than 50 years old with PSA values ranging from 4 to 10 ng/mL and negative DRE results was authorized by the US FDA in 2012. In the early stages of prostate cancer, symptoms do not manifest in individuals. In 1979, the first prostate-specific antigen (PSA) was identified, which significantly altered the diagnostic and treatment methods for prostate cancer (PCa). PSA is a serine protease that is only expressed in benign hypertrophic and malignant prostatic tumors, and it is transcribable via androgen receptors (ARs). Overdiagnosis and overtreatment of indolent or slow-growing prostate cancer, which can be effectively managed, is a concern with the prevalent practice of PSA screening, even though PSA testing has reduced prostate cancer-related mortality and the incidence of advanced-stage disease at diagnosis. [33] Noteworthy in light of the fact that, as per a In more than 40% of cases, the prostate cancer patients had low-grade tumors, which might have at no point show any clinical signs. Enhanced blood PSA values necessitate secondary care for one million men annually in the United States and Europe. on the order of 3–4 ng/mL. Elevated PSA levels can be caused by a number of harmless medical issues.lesion types, with age and racial differences impacting its early stages A large number of men have false positive findings when their PSA levels are tested. This might result in unnecessary intrusive diagnostic procedures that are being performed on guys, which are painful and expensive so that benign lesions may be ruled out as potential malignancies. Serious consequences might also result. [34] A large number of men are undergoing prostatectomies, which are unnecessary procedures. for cases of slow-moving, locally-confined prostate cancer that poses little danger. Normally, because serum PSA levels are It is common for low-risk prostate cancer to be overdiagnosed, and this is not restricted to CSC. becomes an important issue to consider. Benign prostatic problems can also cause elevated serum PSA levels symptoms such as prostate enlargement and infection; hence, a high PSA level in the blood Each patient's baseline level should be considered while assessing the level, which might range from 3 to 10 ng/mL. At age 40, men should check their PSA level to see where they started Years to help with accurate next-generation individual prostate cancer surveillance. Therefore, well-versed Tests and screenings for prostate cancer should be based on individual decision-making. [35]

4K score

A blood-based assay developed by OPKO Health in Miami, FL, USA, known as the 4K score, is used to assess the need for an initial biopsy and for repeat biopsies in patients with elevated PSA or DRE values. Men who have a history of prostate cancer in their family are good candidates for this test, but any guy over the age of 35 who wants to know how risky he is can have it. The 4K score uses a special algorithm to calculate results as percentages between 0 and 100% based on patient data such as DRE, age, and initial biopsy findings, in addition to four kallikrein levels (fPSA, iPSA, tPSA, and human kallikrein 2; hK2). This percentage indicates the probability of significant high-grade prostate cancer before biopsy. The 4K score differentiates between men whose prostate cancer is aggressive and those whose cancer is more mild. In contrast to patients with scores below 7, individuals with scores above 7 are categorized as aggressive. Within 20 years after surgery, the evaluation might reveal the likelihood of distant metastases. [36] The clinical usefulness and importance of 4K scores were evaluated in a trial in the United States by Parekh et al. with 1021 biopsy-eligible guys. The results showed that 23% of the participants had prostate cancer with a Gleason score > 7. When pitted against the Prostate Cancer Prevention Trial Risk Calculator 2.0 (PCPT-RC), the 4K score demonstrated far higher accuracy. The overall reduction in biopsies ranged from 30 to 58% depending on the criteria used, with late diagnosis happening in just 1.3% to 4.7% of cases. A 30% reduction in biopsies, with just 1.3% of cases postponed, would be achieved by using a threshold of ≥ 6% likelihood for a Gleason score ≥ 7 to establish the necessity for a biopsy. The reduction in biopsies is 43% and 58%, with delayed cases at 2.4% and 4.7%, respectively, when the criteria are established at ≥ 9% and ≥ 15%. [37]

URINE-BASED BIOMARKERS

Prostate cancer antigen 3 (PCA3)

Long non-coding ribonucleic acid (previously known as DD3) is encoded by the PCA3 gene. Overexpression of the PCA3 gene, ranging from 60 to 100 times higher than in normal tissues, is observed in almost 90% of prostate cancer patients. Hologic, Inc. commercialized the PCA3 test. This method uses the amounts of PCA3 and PSA mRNA in urine that has been collected after DRE and is non-invasive. In order to determine the probability of prostate cancer and thereby decrease the occurrence of unnecessary biopsies, the amounts of PCA3 and PSA mRNA were measured using quantitative real-time polymerase chain reaction. The formula used to get this score was PCA3 mRNA/PSA mRNA × 1000. If the PCA3 score is greater than 25, it suggests a high probability of prostate cancer, whereas a result less than 25 indicates a low probability of prostate cancer. Different studies have shown different cutoffs for PCA3 scores. [38] The cutoff point is anywhere between 25 and 35, and the reduction in unnecessary biopsies is anywhere from 37 to 77.1%. The optimal PCA3 cutoff value is still up for debate. A clinical investigation was carried out by Merola et al. with 407 males to assess the accuracy of PCA3 in connection to total PSA and free-to-total PSA ratios. When pitted against f/t PSA, PCA3 performed better. Compared to a 20-point threshold, PCA3 showed better sensitivity (94.9% vs. 60.1% at 35 points). Based on the results of nine studies combined, PCA3 has a sensitivity of 69% and a specificity of 65%, with an area under the curve (AUC) of 0.734. A threshold score of 35 showed better clinical accuracy, according to the research the importance of this goal in comparison to others. [39]

Exo-Dx (Prostate IntelliScore) (EPI)

A urine test called Exo-Dx (Prostate IntelliScore) is available. Bilayer vesicles called exosomes encapsulate a wide variety of biological proteins that cells produce. Measurements of ERG and PCA3 mRNA, normalized to the SAM pointed domain containing ETS transcription factor (SPDEF), are used to quantify exosome expression in urine in this test. An EPI score, ranging from zero to one hundred, quantifies the results of this evaluation. [40] No prostate massage or pre-DRE is required to get samples for this test, which assesses exosome gene expression in urine. In males over the age of 50 with PSA levels ranging from 2 to 10 ng/mL, this test is useful for distinguishing between low-grade and high-grade prostate cancer, as per the guidelines of the National Comprehensive Cancer Network. There was an 89% negative predictive value (NPV), a 20% reduction in total biopsies, a 26% drop in needless biopsies, and a 7% reduction in missed biopsies in a clinical study included 503 males with an average age of 64 years and a PSA level of 5.4 ng/mL. [41]

SelectMDx

The MDx Health, Inc. SelectMDx test is a urine-based diagnostic tool. In most cases, a digital rectal examination (DRE) is followed by the collection of a urine sample. This quantifies the amounts of the biomarker genes HOXC6 and DLX1 by measuring their messenger RNA (mRNA). In addition to PSA levels and DRE findings, PSA density and a patient's history of prostate cancer were among the clinical data points that were considered for calculating the score. With a Gleason score of 7, an area under the curve (AUC) of 0.86, and a negative predictive value (NPV) of 98%, SelectMDx demonstrated its effectiveness in predicting prostate cancer in a research comprising two cohorts of 519 and 386 patients, respectively. [42] They estimated a 42% reduction in overall biopsies and a 53% reduction in needless biopsies using this test. Haese et al. examined urine samples from 1955 males in European nations whose PSA values were less than 10 ng/mg. SelectMDx had an area under the curve (AUC) value of 0.85, sensitivity of 47%, and specificity of 47%. There was a 95% Net Present Value. The area under the curve (AUC) for PCPT-RC was 0.76, while this study's AUC was 0.76. The results of the PCPT-RC were thus superseded by the test. The therapeutic usage of Select-MDx is financially feasible in European nations, according to studies. [43]

Mi-Prostate Score (MiPS)

The Michigan Labs at the University of Michigan were the ones that discovered the MiPS. Digital rectal examinations or prostate massages were used to collect urine samples. MIPS measures the amounts of TMPRSS-ERG fusion gene, PCA3, and tPSA messenger RNA expression. Patients undergoing their first prostate biopsy can use this test to gauge their risk of developing high-grade cancer. According to several studies, diagnostic effectiveness is enhanced when PCA3 and TMPRSS2-ERG are combined. [44]

TMPRSS2-ERG fusion gene test

On chromosome 21, you may find the androgen-related transmembrane protease serine 2 (TMPRSS2-ERG) and the ETS-related gene (ERG). In 2005, it was shown that 40-80% of prostate cancer patients had fused TMPRSS2-ERG. A score that can predict the chance of high-grade prostate cancer is provided by the TMPRSS2-ERG test. The figure used to calculate the score is: (TMPRSS2-ERG mRNA/PSA mRNA) ö 100,000. TMPRSS2-ERG frequently forms associations with PCA3 to improve the accuracy of its predictions. We are currently investigating this test's predictive validity. [45]

Tissue-based biomarkers

ConfirmMDx

Historically, histological evaluation of prostate biopsies had a false-negative rate of 20-30%. As a result, low-risk men were affected by the need for frequent biopsies for individuals who may have prostate cancer. So, to avoid these patients having unnecessary biopsies, ConfirmMDx was created. Tissue samples are required for the ConfirmMDx test, which is a biopsy-dependent method. The developers of this exam were MDx Health Inc. This epigenetic test evaluates APC, GSTP1, and RASSF1 DNA hypermethylation using methylation-specific polymerase chain reaction. Histologically, this test can tell healthy cells apart from cancerous ones. People whose ConfirmMDx results were negative shown a rebiopsy probability that was more than 10% lower than the initial rates, which was less than 5% lower. The ConfirmMDx test was administered within 24 months after a previous negative biopsy in a multicenter trial including 350 men from the US who had repeat biopsies. Results showed a net present value (NPV) of 88% and confirmed its predictive power in multivariate testing. As a result, unnecessary repeat biopsies might be prevented. Among 498 men whose biopsies came back negative, all of whom got the ConfirmMDx test within 30 months after their last biopsy, was the MALTOC trial. The multivariate analysis confirmed the trial's predictive significance, and its negative predictive value was 90% results. [46]

Biomarkers of liquid biopsy: new edge technology for PC patients

One non-invasive tool in the fight against prostate cancer is the liquid biopsy. When it comes to monitoring and early diagnosis of prostate cancer, this is a more advanced procedure. It uses samples of physiological fluids including blood and urine to enable tailored medications and determine the probability of resistance to these treatments. It performs real-time data analysis, identifying and counting cfDNA, ctDNA/RNA, extracellular vesicles, and circulating tumor cells. Tumor cells that have spread throughout the body and are now circulating in the circulation are called circulating tumour cells (CTCs). Epithelial cell adhesion/activating molecule (EpCAM)-expressing CTCs are a diagnostic tool for the identification and evaluation of prostate cancer (PC). EpCAM is an upregulated transmembrane glycoprotein seen in cancer cells. It controls the adherence of cancer cells, their proliferation, angiogenesis, stemness, resistance to chemotherapy, and the change from epithelial to mesenchymal architecture. Since this is the case, EpCAM is useful not just as a diagnostic biomarker but also as a potential precision medicine target. The only method approved for clinical use by the US FDA is the EpCAM-dependent CTC test. A lower progression-free interval (PFI) and overall survival (OS) are associated with circulating tumor cells (CTCs) exceeding 5/7.5 ml of blood, which is considered unfavorable. Epithelial immunospot (EPISPOT) is one of several non-EpCAM methods now in development for collecting circulating tumor cells (CTCs). One way to measure the number of healthy CTCs in the blood is to look for cells that can secrete proteins like cathepsin D, MUC1, and CK19. This method relies on antibodies.[46]

Current Imaging Tools

The detection of prostate cancer relies heavily on magnetic resonance imaging. This type of magnetic resonance imaging (mpMRI) has during the last five years has seen substantial use in the treatment of prostate cancer that has spread to specific areas. One can certainly be is defined as a method for obtaining the best possible three-dimensional (3D) Combining magnetic resonance spectroscopy (MR spectroscopy) with dynamic contrast-enhanced imaging (DCEI), diffusion-weighted imaging (DWI), and T2-weighted imaging (T2WI) to image the

prostate, if necessary and available picture depictions. mp-MRI is an advanced MRI technique that provides a more detailed picture better than what a regular MRI can. The most definitive indicators for mpMRI people with increased PSA levels, a record of negative biopsy results, and the existence with supporting evidence for its use in active surveillance (described in Section), "Treatment" with patients who did not have biopsy: mpMRI can increase the identification of CSPC, a subtype of prostate cancer that responds better to androgen deprivation treatment (ADT) in people whose first biopsies came back negative. However, low-volume prostate cancers with a lower Gleason grade cannot be detected with the resolution provided by mpMRI. Though apical lesion detection is still lacking, cancerous lesions in the prostate's mid and base areas are easier to spot. Multiple interpreters must use standardized scoring techniques, including the Prostate Imaging Reporting and Data System (PI-RADS) v2, when analyzing mpMRI data. It is recommended, worldwide, to use MRI before biopsy procedures.Using the spatial data of possible lesions obtained from The most important lesion for a targeted biopsy is the one that can be seen on an MRI this may not be the case in a therapeutic setting. Since computed tomography (CT) has poor resolution of prostate soft tissue and ambiguous gland margins, it is not advised for the detection of prostate cancer (PCa). Lymph node involvement cannot be detected by a CT scan, even though it is commonly used for prostate cancer lymph node staging, since benign reactive nodes and metastatic nodes have similar sizes. [44,47]

The detection capabilities of positron emission tomography (PET) are quite advantageous cancer that has spread beyond the prostate, with a variety of tracers that may be detected with PET scans Cancer of the prostate several examples of these include 68Ga-prostate-specific membrane antigen (PSMA), 117Lu-, 18F-fludeoxyglucose (FDG), 18F-sodium fluoride, 18F-choline, 18F-fluciclovine, 11C-choline, and several more These tracers are approved for use in clinical settings: PSMA. Metastatic lesions are characterized by increased metabolic activity, which explains why FDG is more effective in detecting them than initial lesions. Enhanced sensitivity for identifying distant metastases and positive lymph nodes is demonstrated by PSMA-PET scans, which outperform choline or acetate PET scans. Radioligand therapy 117Lu-PSMA-617 was approved by the FDA for the treatment of mCRPC (prostate cancer with PSMA positive) in 2022. [46]

Genomics

Thanks to tremendous advances in mRNA sequencing, whole-genome DNA sequencing, and proteome profiling, we have learned a lot about the genetic bases that define many subtypes of prostate cancer in the last decade. Although the vast majority of cases of prostate cancer in men do not have a history of the disease in their family, there are certain families where the disease appears to run in the blood, which might be due to genetic factors. There is a twofold increased risk of prostate cancer in men whose first-degree relatives have been diagnosed with the illness. A strong family history of cancer increases the likelihood of developing prostate cancer. There is an exceptionally high incidence of prostate cancer (PCa) among families where there is a history of cancer, as around 9% of men with PCa have a family history of cancer. [48]

Prevention

Despite several suggested methods to reduce risk, there are currently no approved treatments for primary disease prevention in the asymptomatic early stages of prostate cancer. Although there is some evidence that smoking and obesity are associated with an increased risk of

aggressive prostate cancer, it is still unclear whether or not adopting healthier habits, such as not smoking, being more physically active, and controlling one's weight, may actually lower this risk. Chemopreventive drugs have been proposed pharmacological therapies, namely 5α-reductase inhibitors (5-ARI) such as finasteride and dutasteride. Clinical trials on these drugs have had mixed results, but they seem to work by blocking testosterone's conversion to DHT and reducing androgen receptor activation; this suggests they may be able to prevent prostate cancer. In men with undetectable illness and low PSA levels, the 5-ARI chemopreventive study showed a decrease in low-grade tumor frequency but no change in the incidence of higher-grade tumors (PCPT and REDUCE trials). Therefore, 5-ARIs have not been approved for the prevention of prostate cancer because there are concerns that they do not effectively reduce the occurrence of high-grade tumors. Although there are no clinical recommendations for either condition, the REDEEM study did show that 5-ARI was beneficial when used in conjunction with active monitoring, which sparked interest in its potential use in the treatment of low-risk diseases. [49]

TREATMENT

Despite several advances in medical science, pancreatic cancer remains one of the most common cancers worldwide. Further improvement is needed in the administration of PCs. Surgical excision, radiation therapy, chemotherapy, and hormonal therapies are the main methods of treating prostate cancer. The goal of PC management should be either eradicating the disease or alleviating specific symptoms. An individual's life expectancy and risk of mortality from other causes are the two primary factors that determine the evaluation. Elevated androgen activity is noted in the early stages of disease in around 80 to 90% of prostate cancer patients. Therefore, androgen deprivation treatment primarily consists of reducing androgen levels and suppressing the androgen receptor. Since then, ADT has remained the gold standard for treating prostate cancer in men. Metastatic hormone-naive tumors can progress to mCRPC due to ADT's inconsistency; 20-30% of patients have tumor recurrence and castration resistance. Treatment options for men with localized prostate cancer include radiation, surgery, or active surveillance. Efficacious chemo-hormonal therapies, such as docetaxel, novel hormone therapy, and cell-based cancer immunotherapy, have been used to treat patients with metastatic prostate cancer. The rapid development of new therapeutic options and the approval of innovative medications means that there is no set sequential schedule for treatment in patients with PC. Now we'll take a look at a few different treatment options that doctors often use for PC. [50]

Chemotherapy

Docetaxel, cabazitaxel, mitoxantrone, and bicalutamide are therapeutic medications that have been authorized. (These treatments are first-generation antiandrogens.)

Docetaxel

One chemotherapeutic medication used to treat prostate cancer is docetaxel, which is produced from taxanes. It is thought to have some anti-androgenic properties and has anticancer effects by blocking microtubule assembly in mitosis and interphase, which causes cells to die. It wasn't until after several phase trials that this chemotherapeutic drug was found to improve overall survival in pancreatic cancer patients. Compared to 1184 patients given ADT alone, 593 patients treated with androgen deprivation therapy (ADT) in conjunction with docetaxel (75 mg/m^2) every three weeks and prednisone (10 mg/day) had a significantly better overall

survival (OS). Use of this medicine in combination with another hormonal drug and corticosteroids improves overall survival. The standard docetaxel regimen consists of 10 cycles of intravenous administration, each spaced three weeks apart. However, the decrease in medication dosage is dependent on how well the patient is able to tolerate it. Also, it has the same side effects as other chemotherapy drugs, such as cytopenia, nausea, vomiting, and neutropenic sepsis. [51]

Cabazitaxel

The US Food and Drug Administration has approved cabazitaxel, a semisynthetic molecule that is used in the second-line treatment of prostate cancer patients after docetaxel. This chemotherapeutic drug works by blocking the assembly of microtubules, just to docetaxel. Patients receiving post-docetaxel treatment or those with docetaxel-resistant cancers can benefit from its anticancer effects, and it can overcome taxane resistance. Extensive study led to the establishment of a standard fixed dosage of 25 mg/m2 for cabasitaxel, which is administered intravenously every three weeks. [52]

Mitoxantrone

When it comes to treating prostate cancer, mitoxantrone is a synthetic substance that is used as a second-line pharmaceutical. In prostate cancer cells, mitoxantrone activates eukaryotic initiation factor 2, leading to immunogenic cell death. Clinical improvement in certain patients was found in a meta-analysis of mitoxantrone phase 3 trials; nevertheless, there were no survival benefits and the drug was associated with adverse effects such as fatigue, dyspnea, and pancytopenia. [53]

Novel hormone therapies

Androgen suppression therapy is a new method of treating hormones that targets the androgen signaling pathway in an effort to reduce androgen levels. The progression of mHSPC and mCRPC are aided by the overexpression of androgens. Both abiraterone and enzalutamide have been approved by the relevant authorities.

Abiraterone

In males suffering from metastatic castration-resistant prostate cancer (mCRPC), androgen production is impeded by abiraterone acetate, an irreversible and specific inhibitor of cytochrome P450 17A1 (CYP17). Metastatic castration-resistant prostate cancer (mCRPC) is treatable with ariraterone because it targets the androgen pathway and has shown an advantage in survival rates. Overall survival (OS) was enhanced with abiraterone, androgen deprivation treatment (ADT), and prednisone, according to a randomized study including 1,917 people. A low dose of prednisone has been linked to fluid retention, hypertension, and hypokalaemia; specific side effects include raised mineralocorticoid levels as a result of CYP17 inhibition; and abiraterone is taken orally at a dosage of 1000 mg daily. [54]

Enzalutamide

One approved treatment for castration-resistant prostate cancer (CRPC) is enzalutamide, a second-generation antiandrogen medication. Men with non-metastatic CRPC benefit greatly from treatment, since it reduces the risk of death and metastasis by 71%. Enzalutamide exhibits anticancer activity and improves overall survival before and after therapy, according to many

phase 3 trials. The recommended daily dosage of enzalutamide is 160 mg taken orally. Common side effects include nausea, vomiting, lethargy, and hot flashes.

Radiotherapy

Radiation therapy is commonly used to treat early-stage prostate cancer because it can target tumors that have progressed locally and reduce the chances of metastasis. Over time, this therapy has evolved. Radiation therapy has advanced to encompass a wide range of approaches, such as brachytherapy, intensity-modulated radiation, stereotactic ablative body irradiation, and volumetric modulated arc treatment. Due to the therapy's lack of specificity, some prostate cancer patients still endure disease recurrence, even though radiation has made great strides. To get adequate anti-cancer effects, radiation dosage must be increased, which may have harmful effects on healthy tissues. Proton and carbon ion therapy are examples of cutting-edge approaches that target cancer cells specifically while sparing nearby healthy cells. Radical prostatectomy causes tumor recurrence in about 10–40% of patients; in these cases, salvage radiation therapy is quite effective, controlling the illness in 60–70% of cases. Radiation proctitis is one of the potential side effects of radiation treatment. Radiation proctitis can be reduced with careful patient positioning and verification of the setup. The mainstay treatment for localized prostate cancer, which reduces mortality, is radical prostatectomy. In patients with a primary tumor, it provides better survival rates than radiotherapy. Transurethral resection of the prostate (TURP), open prostatectomy, and laparoscopic prostatectomy are all examples of major prostatectomies. [55,56]

A radiopharmaceutical called alpha radio, which releases alpha particles targeted for bone metastases, is radium-223 dichloride. Metastatic castration-resistant prostate cancer (mCRPC) patients with bone metastases can be treated with radium-223, a radioactive isotope that induces tumor cell death by creating permanent double-strand breaks in DNA. A typical administration schedule consists of six cycles of intravenous infusion over the course of four weeks. Bone pain, fatigue, gastrointestinal issues, toxicity to the blood, low white blood cell count, and thrombocytopenia are the most commonly reported side effects that harm the nearby bone marrow. [57]

Phototherapy

The goal of phototherapy (PT) is to induce cell death in cancer patients by using materials that can absorb electromagnetic light and transform it into heat energy. This approach gets rid of the negative side effects of chemotherapy and prevents infection during the procedure. PTs usually make use of near-infrared (800-1350 nm) light. As part of the PT, photothermal agents—materials with the ability to convert near-infrared radiation into heat—have been utilized. To increase the therapeutic effect against cancers, PT has been used with other treatment plans including immunotherapy and chemotherapy. Another method for treating cancer is photodynamic therapy (PDT), which triggers apoptosis in cancer cells by encouraging the production of reactive oxygen species within cancer cells. The PDT has made use of metal nanostructures covered with polymers. It has also shown use in enhancing radiation's ability to suppress liver cancer. The experimental PC cells have used silver-gold hollow nano shells with mesoporous silica nanoparticles for the PDT. A different study created hybrid nanoparticles of gold and levonarodate for PC patients undergoing combination PDT and chemotherapy. The PDT did double duty: it reduced the dosage of chemotherapy required to treat PC while simultaneously increasing chemotherapy's effectiveness in reducing PC. [51]

Immunotherapy

In clinical settings, immunotherapy (IT) has revolutionized the treatment strategy for several tumors and malignancies. However, there has been no conclusive evidence of the effect on PC decrease. Tregs and transforming growth factor-β (TGF-β) were the main immunosuppressive components of PC, which allowed the neoplasm to survive. Regardless, PSMA and PSA are two marker antigens that have been found expressed by tumor cells. There are a plethora of immunotherapies that can improve upon the current treatment methods. Conjugates of anticancer medications with monoclonal antibodies are called antibody-drug conjugates. One example is Sacituzumab govitecan, which targets Trop2, and another is trastuzumab deruxtecan, which targets HER2. It has the ability to go straight to tumors and deliver cytotoxic chemicals. Aggressive and passive approaches are both included in the treatment of PC using immunomodulatory drugs. As part of the proactive approach, vaccines that display antigens in the hopes of stimulating an adaptive immune response are administered. Transdermal administration of monoclonal antibodies directed against tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs) constitutes the passive technology. Biomarkers such as slow tumor growth, early disease recurrence detection, and the presence of tumor-associated antigens (TAAs) like PSA, PSMA, PCA-3, mucin-1, six-transmembrane epithelial antigens of prostate (STEAP), and prostate acid phosphatase (PAP) are all ways to measure how well anticancer vaccines for prostate cancer work. Radiation and second-generation hormone therapies (docetaxel) are among the alleged medications that can be used in tandem with vaccines. Two broad types of vaccine-based treatments exist: those based on cells and those based on viral vectors. A new approach to immunotherapy treating solid tumors is chimeric antigen receptor (CAR) T-cells, which combine T cells that target tumor-specific antigens (TSAs) with fragments of antibodies. B cell haematological cancers have shown remarkable improvement with CAR T-cell treatment. Research on many new tumor-associated antigens (TAAs) is now underway. These include STEAP-1, Lewis-y antigen, CD126, immunological checkpoint B7-H3 (CD276), Mucin-1, and IL-6 receptor. The development of CAR T-cells, cytokine toxicity, and on-target off-tumor damage—the intentional targeting of normal tissues that express tumor-associated antigens—are some of the challenges that this treatment faces. A potential treatment regimen for mCRPC has emerged: IT. When used in conjunction with immune checkpoint inhibitor treatment, it can significantly improve overall response rate and progression-free survival. No matter what they do, they can't improve the OS. [58]

Cell-based vaccines

Sipuleucel-T

The autologous dendritic cell vaccination known as sipuleucel-T stimulates the immune system to attack the PAP antigen. Patients with mildly symptomatic prostate cancer have a better chance of survival when they use this autologous active immunotherapeutic medication. It boosts patients' immune systems to recognize and fight cancer, and it was the first therapeutic vaccination for cancer to be licensed by the US FDA. The recommended course of treatment consists of three complete doses given by intravenous infusion every two weeks. The most common side effects are bleeding, bruises, high body temperature, lack of energy, sick feeling, and headaches. Due to its high production costs, this drug is not widely used. [59]

G-VAX

One such vaccine is G-VAX, which involves transfecting tumor cells with the GM-CSF gene. Its dendritic cell development and proliferation can be improved by genetic engineering by expressing GM-CSF. The advantage of this approach is that it can stimulate different TAAs without requiring HLA matching. While preliminary results were promising, docetaxel's phase III tests yielded negative results.

Viral vector-based vaccines

Oncolytic virus vectors are the building blocks of viral vector-based vaccinations. The tumor cells can be infected by these vectors and killed by antigen-presenting cells (APCs). This means that APCs can produce T cell responses through the production of tumor-associated antigens (TAAs). To enhance the immunogenicity of co-stimulatory molecules, a recombinant Poxvirus vaccine was modified to include a PSA transgene with an HLA-A2 epitope. A few examples of costimulatory molecules are B7-1 (CD80), ICAM-1 (CD54), and LFA-3 (CD58), which are all related to lymphocyte activity. When it comes to treating prostate cancer, the published results of PROSTVAC-VF have failed to show any clear therapeutic benefit. [39,46]

Immune checkpoint inhibitors

There are many different components that make up the tumor microenvironment (TME). These include tumor cells, immune cells like myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), tumor-associated dendritic cells (tDCs), and regulatory T cells (Tregs). Finally, there is the extracellular matrix, stromal cells, blood vessels, soluble factors, and physical characteristics. Both insoluble and cellular components make up the immunosuppressive microenvironment, which promotes tumor growth and makes immune evasion easier. A class of monoclonal antibodies developed specifically to suppress immunological checkpoints is known as an immunocheckpoint inhibitor (ICI). Among immune checkpoint inhibitors, those with the strongest clinical backing target PD-L1, PD-1, and CTLA-4. It has been shown that the transmembrane protein PD-1 on T cells interacts with its ligand, PD-L1, on tumor cells. The PD-1 and PD-L1 proteins are located on chromosome 9p24.1 and are essential for maintaining immunological homeostasis. Cancer cells in the tumor microenvironment use the PD-1 and PD-L1 activities to avoid immune surveillance. When tumor-infiltrating lymphocytes (TILs) and cancer cells interact through overexpressed PD-L1, it phosphorylates SHP-2, interrupting the TCR-signaling cascade and preventing T-cell activation. Several transcription factors, including as MYC, STAT3, NF-κB, AP1, and HIF-1, regulate the transcriptional activation of PD-L1. The stability of the PD-L1 protein in cancer cells can be affected by modification activities such phosphorylation, glycosylation, and ubiquitination, which in turn affects its expression. Although evidence suggests that PD-1/PD-L1 expression is up in prostate cancer patients, the exact role that these molecules play when exposed to immune checkpoint inhibitors is still up for debate. [45]

Gene therapy

There are a plethora of gene therapy (GT) methods that make use of cutting-edge medication delivery systems. The use of GT to treat prostate cancer tumors has shown encouraging results. The treatment of prostate cancer (PC) makes use of a number of different gene therapies, such as immunomodulatory gene therapy (IGT), anti-oncogene therapy (AOT), tumor suppressor gene therapy (TSGT), and suicide gene therapy (SGT). The guiding idea of SGT is the delivery of a therapeutic gene into a cancer cell to eradicate it. Scientists have shown that when SGTs

infiltrate cancer cells, they cause cell death without correcting the cancerous mutations. The fact that these SGTs have no effect on healthy cells has also been proven. Enzyme-based GT in cells and other forms of SGT are the main categories. The capacity to prevent tumor development has been established by the enzyme-based SGT. The use of gemcitabine-conjugated adenovirus in the successful treatment of pancreatic cancer was explored in a different study by Lee et al. (2020). Achieving TSGT and successfully limiting tumor growth was achieved by introducing a wild-type gene into PC cells. Retinoblastoma, p53, and p21 are the genes that are commonly tested for TSGT. Transducing tumor-suppressor genes into every tumor cell is the key to a successful gene therapy. Regulating androgen receptor activation and modifying p14ARF levels in the prostate have been achieved by the use of the protein involved in tumor suppression (p14ARF). A tumor-suppressing Arv7-mediated CRPC has been engineered. This variation makes use of an active AR splice. In addition, the tumor suppressor gene PTEN has been targeted by miR-21 in an effort to inhibit PC development. [53]

Nanotherapies

Modern methods of disease diagnosis and treatment have been expanded by the use of nanotechnology. By delivering medications and genetic material to specific areas, these nanocarriers have the potential to eradicate cancer. To increase biocompatibility and enhance drug delivery, several nanocarrier technologies have been used. Oncological treatment often makes use of polymeric spheres, dendrimers, carbon nanotubes, virosomes, liposomes, extracellular vesicles, and mesoporous silica nanoparticles as drug delivery systems. Nanocarriers for tumor marker detection are also advancing rapidly, adding to the arsenal of therapeutic medicines already available. It has been shown that aptamers are easily synthesized and have low immunogenic toxicity. To decrease PC aggressiveness, polymeric nanoparticles have been functionalized with the Wy5a aptamer. These nanoparticles were synthesized by self-assembly utilizing PLGA and PEG. Additionally, in a xenograft model, these nanostructures loaded with doxorubicin considerably reduced tumor growth and eradicated prostate cancer. Nanoparticles can be made more effective in entering PC cells by adding aptamers to them. Encapsulating epigallocatechin-3-gallate in hyaluronic acid-modified nanoparticles also significantly slows the growth rate of individual computers. [34]

Recommendations and guidelines

According to the 2020 guidelines of the European Association of Urology (EUA), men whose PSA levels are below 10 ng/mL are considered to be at low risk, those whose levels are between 10 and 20 ng/mL are considered to be at intermediate risk, and those whose levels are over 20 ng/mL are considered to be at high risk. Prior to doing a biopsy, it is recommended by the European Society of Medical Oncology to perform a risk assessment and a multiparametric MRI. Instead of transrectal biopsies, they suggested transperineal biopsies. Based on the results of the EUA, there is currently insufficient evidence to recommend ConfirmMDx for rebiopsy. Therefore, it is not recommended to routinely use ConfirmMDx because there is no data to support its therapeutic benefit. [60]

Conclusions and future perspectives

The increasing number of cases and deaths caused by pancreatic cancer has made it a major health concern across the world. On a worldwide scale, it ranks as the second most common cancer. Despite the high incidence of prostate cancer, PSA screening has helped lower the mortality rate from the disease. Emerging diagnostic tools like liquid biopsy are joining modern

screening modalities including DRE, ultrasound, and mp-MRI. Overall survival in patients with metastatic castration-resistant prostate cancer (mCRPC) has been improved with the right combination of chemotherapy medicines, including cabazitaxel and docetaxel, with androgen deprivation treatment pharmaceuticals, such as enzalutamide and abiraterone. Enhanced quality of life and decreased death rates for survivors of prostate cancer have resulted from treatment choices that have been improved via the investigation of disease prognosis and patient preferences. The DNA repair route, chemotherapy based on platinum, and PARP inhibition are all potential treatments. To develop medications with fewer side effects, more studies and clinical trials are needed. Radiation and prostatectomy, when administered at the early stages of prostate cancer, impact the survivors' quality of life. Therefore, to lessen side effects, better treatment methods are needed about treatment.

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