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Original Article

A Brief Overview On Advanced Diagnostic Techniques And Molecular Biomarkers In Prostate Cancer

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ABSTRACT

Prostate cancer (PCa) is one of the most typically occurring malignancies and the leading cause of cancer-related morbidity and mortality in male patients worldwide. Early diagnosis and accurate risk classification are crucial to enhancing the results of therapeutic interventions and avoid overtreatment and unnecessary diagnostic tests. Though the conventional screening methods such as digital rectal examination (DRE) and prostate-specific antigen (PSA) testing are essential in the early diagnosis of prostate cancer, their low sensitivity and specificity often lead to overdiagnosis and unnecessary biopsies. The recent advancements in genomic technology and molecular biology have resulted in the development of more accurate prognostic and diagnostic biomarkers. Although blood-based tests such as Stockholm-3 (STHLM3) model and the 4Kscore provide better risk prediction, urine-based tests such as PCA3, TMPRSS2-ERG gene fusion, and SelectMDx are providing non-invasive diagnosis. The tissue based genomic assays such as Oncotype DX, Decipher and Prolaris are used to evaluate tumour aggressiveness and guide individualised plans of treatment. In order to advance the accuracy of the detection and treatment of prostate cancer, there are liquid biopsy, advanced imaging tools, and artificial intelligence.

Keywords: PCA3 and TMPRSS2-ERG, 4Kscore and STHLM3 test, Circulating tumor cells (CTCs), Exosomes, PSMA PET/CT imaging, Micro-ultrasound, MRI-fusion biopsy.

INTRODUCTION

The current estimates are 268,490 new incidences of prostate cancer and 34, 500 deaths are due to the disease, which is the second-commonest non-skin cancer in males in the US. It is interesting to mention that the men of African descent were the most prostate cancer incidence with the next there being males whose ancestry was European and Asian. It is in light of these considerations that it is important to identify a biomarker to assist in the establishment of which patient has clinically relevant prostate cancer. To predict the probability of the clinically significant prostate cancer and to prevent unnecessary prostate biopsies, several additional biomarker tests have been developed. Also, this may avoid unnecessary harm such as anxiety, blood loss, risk of infection that will lead to hospitalisation, and the psychological outcomes of a prostate cancer diagnosis. The ideal biomarker should possess high sensitivity and specificity, repeatability and be easy to use based on quantitative measures. It must also prove to be cost-effective, bring about clear results to physicians, and be easily applicable to other races. Unfortunately, comparative research between these biomarkers does not exist in large numbers and physicians are often not aware of which one contains the most informative data.[1]

Although metastatic prostate cancer remains fatal, localised prostate cancer (PCa) is the leading solid organ cancer in men in the US with 191,930 new cases and 33,330 deaths in 2020. Although the chances of developing PCa is 1 in 9 lifetimes, 2% of individuals will succumb to the disease, A digital rectal exam (DRE), prostate specific antigen (PSA) and its variants are available to screen and identify PCa at an early stage of the disease. The abnormal DRE of the individuals with elevated levels of PSA would then be subjected to a prostate biopsy which is associated with a risk of bleeding or hospitalisation due to infection in the case of about 1-3% of cases or obstructive effects. Multiparametric MRI (mpMRI) may be applied to diagnose persons at risk of clinically significant

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illness to undergo bio-psy, eliminating unnecessary bio-psy.Yet, multitiered approaches to mpMRI include wide diagnostic variability across sites, a positive predictive value (PPV) of 35% with PI-RADS 3 lesion at risk of clinically significant PCa (csPCa) and up to 35% of csPCa in men with negative mpMRI. Molecular biomarkers can be used to complement PSA and mpMRI as risk factors and early detectors of csPCa..[2]

The increased incidence of PCa with age is one of the reasons why the disease is most prevalent among the ageing populations. The chances of metastasis and disease-specific death are enhanced as the disease is often found at an advanced stage. The disease itself, as well as the side effects of its treatment, significantly decrease the quality of life and contribute a lot to the burden on the state health. PCa treatment requires a clinical suspicion, elevated tumour markers, suggestive radiographic findings, and malignancy validation through the use of prostate biopsy. PCa may result in nonspecific lower urinary tract symptoms (LUTS), haematuria, or hematospermia though it is often asymptomatic in the initial phases. These symptoms, which may hamper early diagnosis, are more prone to be caused by benign conditions, including benign prostatic hyperplasia (BPH), bladder outlet obstruction, urethral stricture, infection of the UTI, prostatitis, and chronic pelvic pain syndrome. Metastatic dissemination often occurs in bones and lymph nodes; thus, at times the pain in bones may be the initial symptom of PCa.[3]

The clinical symptoms are determined by the stage of the cancer or whether it is early or advanced. The most commonly reported symptoms are the signs and symptoms of the urinary tract such as painful and poor urine flow, frequent urine flow, erectile dysfunction, painful ejaculation, and haematuria. The vertebral PC metastases can lead to the persistent hip/back pain of patients with Pott disease. Also, urine incontinence has been reported in school-going men after having undergone radical prostatectomy as a result of the screening of the PSA biomarkers in the early detection of PC. Digital rectal examination (DRE) should be done to patients who have high levels of PSA. Transrectal ultrasound (TRUS), transperineal biopsy, multiparametric magnetic resonance imaging (mpMRI), or targeted MRI-ultrasound fusion biopsy may then be employed to conduct an overall prostate biopsy to determine the optimal treatment option to the patient. An innovative technique of diagnosis is useful to define PC in the patients not previously subjected to biopsy by means of mp-MRI before. Non-invasive diagnostic procedures such as liquid biopsy can also be used to detect PC. These diagnostic methods are mostly applied by the physicians to diagnose tumours.[4]

Early detection is necessary in a way to decrease morbidity and mortality of cancer. Authentic and reliable cancer signs are thus of dire need. Emerging biomarkers are the exosomes, microRNA and circulating tumour cells and the standard cancer biomarkers are the PSA, CEA and CA-125/MUC16. Working with biomarkers and their applications in healthcare facilities, one may face several aspects to consider and obstacles to face. The stages and elements, which lead to a possible biomarker, are analytical validity, clinical validity, and clinical utility. Analytical validity is the pre-analytical and analytical parts of the biomarker assay including sample handling, and the accuracy of the assay. Clinical validity involves independent validation and it measures the capability of the biomarker to differentiate among various groups in the target population. Clinical utility means that there is a great amount of evidence to prove the use of the biomarker in the treatment of patients as it works and the rate of potential benefits to harm.[5]

TRADITIONAL SERUM BIOMARKERS

PROSTATE-SPECIFIC ANTIGEN (PSA):

Prostate-specific antigen or PSA is a protein that is produced by both normal and cancerous cells of the prostate gland. The increase of the PSA level in the blood can be caused by prostate cancer and a variety of benign conditions, the most frequent of which are prostatitis and benign prostatic hyperplasia or BPH. The PSA test is used to ascertain the PSA level of the blood. This test can be utilized in a variety of ways: To follow up on prostate cancer among men who are already diagnosed; to monitor the signs of prostate cancer, including painful or frequent urination, the presence of blood in the urine or semen, pain in the pelvic and/or back, and/or screen men who are asymptomatic of prostate cancer. To detect patients who may require a diagnostic test, prostate-specific antigen (PSA) is one of the tests that are widely used

in diagnosing prostate cancer. There are two common reasons that make a patient do PSA testing: screening a patient who is either asymptomatic and may be at risk of having prostate cancer or evaluating a patient who has presented himself/herself to their primary care physician or general practitioner (GP) with lower urinary tract symptoms (LUTS). Patients with elevated PSA are usually referred to a urologist where they undergo diagnostic tests, which may include prostate biopsy or magnetic resonance imaging (MRI) of the prostate.[6]. PSA is considered to be one of the most popular biomarkers in the detection and treatment of PCa currently. The main predictor of PCa before PSA testing was DRE. Nonetheless, DRE as a diagnostic method has a low sensitivity and specificity, with the method also being subjective to users when it comes to doing the examination between clin icians. In 1987, PSA testing was introduced in the US to determine whether the patient was responding to curative treatment. It was an unquestionable diagnostic step. Risky patients of PCa were soon screened using PSA, thus raising disease diagnosis and reducing mortality. [7]

PSA is a member of the kallikrein family proteins; a 33 kDa enzyme protease. It consists of four carbohydrate side chains, numerous disulphide bonds and a single-chain glycoprotein with 237 amino acid residues. PSA is known as human glandular kallikrein (hK)-3 as a way of distinguishing it in relation to the hK-2 that is also a marker of prostate cancer but is 80 percent similar to it. The third kallikrein, hK-1, shares 73 and 84 percent homology with PSA and is majorly found in the pancreatic and renal tissue. The aim of the serum PSA screening of prostate cancer is to reduce the overall and disease-specific mortality in prostate cancer by detecting prostate cancer during its early stages which can be treated. In spite of the failure to reveal its survival benefit, PSA screening has decreased the incidence of metastatic prostate cancer at presentation. Instead, it is associated with an increased possibility of overdiagnosis and side effects of treatment which reduces the quality of life of the patient such as erectile dysfunction and urine incontinence. Hence, the use of screening of prostate cancer involving PSA remains to be a controversial area to some extent.[8]

Age Group (Years)	Normal PSA Level (ng/mL)	Abnormal PSA Level (ng/mL)
40–50	0 – 2.5	> 2.5
50–60	2.5 – 3.5	> 3.5
60–70	3.5 – 4.5	> 4.5
70–80	4.5 – 5.5	> 5.5

STHLM3:

Stockholm-3 (STHLM3) is a complex multimodal approach of screening that is meant to overcome these deficiencies of the conventional PSA testing in detecting prostate cancer. Unlike PSA, STHLM3 includes over 100 single nucleotide polymorphism (SNP) variants associated with prostate cancer, in addition to relevant clinical variables, human kallikrein-2 (hK2), macrophage inhibitory cytokine-1 (MIC1), total PSA (tPSA), free PSA (fPSA), intact PSA (iPSA) and beta-microseminoprotein (MSMB). This combination method enables better risk stratification and the differentiation of clinically significant (aggressive) and indolent prostate tumours. STHLM3 has a substantial reducing effect on the unnecessary prostate biopsies and enhances the diagnosis of clinically significant illness in combination with multiparametric MRI (mpMRI). Further testing in European, North American, and Asian cohorts have demonstrated uniform performance on a diverse range of ethnic groups, such as Asian, Black or African American, Hispanic or Latino and non Hispanic White populations, even though the initial method was originally tested in Swedish populations. More importantly, it has been indicated that STHLM3 has PSA-like sensitivity to detect clinically significant prostate cancer and at the same time minimizing unnecessary biopsies. Moreover, even commercial availability is largely restricted to Sweden, and additional integration with international clinical guidelines is required to make it be used in a broader manner. Nevertheless, recent studies have suggested it can be used as a risk-adjusted multi-step screening system particularly among men with an increased PSA or a more genetic predisposition to prostate cancer. [25]

FDA-APPROVED AND COMMERCIAL DIAGNOSTIC BIOMARKERS

URINE-BASED BIOMARKERS:

Biomarkers in prostate cancer urine based such as PCA3, TMPRSS2:ERG and SelectMDx give non-invasive alternatives to the usual PSA testing to improve accuracy of diagnosis, reduce unnecessary biopsies and to identify the aggressiveness of the malignancy. These tests which often come after a digital rectal examination (DRE), check on RNA or gene expressions in urine. The overexpression of PCA3, a noncoding messenger RNA (mRNA) specific to the prostate, in more than 90 percent of all prostate tumours, compared to benign prostate tissue has been discovered. The use of measuring of PCA3 RNA in the post-DRE urine has been previously reported in numerous studies. The Progensa PCA3 assay (Progensa Test Kit, Hologic, Marlborough, MA, USA) is a diagnostic test targeting males aged 50 years or more who have a positive serum PSF level and have negative prostate biopsy history. The assay provides the doctors with PCA3 score based on the ratio of the PCA3 RNA molecules to the PSA RNA molecules in a patient urine sample after a DRE.[9]

PC3:

The PCA3 (prostate cancer antigen-3) gene has four exons commonly known as DD3 (differential display 3). Exon-2 is not present in most transcripts (only 5% of them contain it), whereas exon-4 is subject to alternative polyadenylation at three possible sites. PCA3 belongs to the noncoding RNA category due to its high number of stop codons because it has the three open reading frames. PCA3 has shown the potential of a prostate-specific mRNA which can be used as a PCa diagnostic tool. PCa marker that has been proposed is urine PCA3 mRNA normalised by PSA mRNA measurement. [10]

TMPRSS2-ERG (Transmembrane Protease Serine 2- ETS-Related Gene):

One of the common gene rearrangements in PCa is that of the TMPRSS2-ERG gene forming a fusion between the TMPRSS2 and ERG genes leading to overexpression of ERG. This junction in PCa was initially reported in 2005. The process by which this involves fusion was elucidated and the fusion of TMPRSS2 and ERG was revealed. Androgens trigger ERG production with the stimulation of TMPRSS2, leading to PCa overexpressing ERG oncoprotein. A number of studies have established that aberrant ERG expression, loss of PTEN or other molecular alterations all combine to enhance the incidence and progression of PCa. According to TCGA data, the major molecular categorisation characteristic of localised PCa and an apparent prognostic marker is TMPRSS2-ERG fusion. Also, research indicates that the majority of cases of metastatic PCa contain gene TMPRSS2-ERG fusion and positive tumours are more likely to develop metastases. [11]

SELECT MDX TEST:

The National Comprehensive Cancer Network (NCCN) has approved Select MDx test commonly known as the MDx test to patients who are undergoing a screening of prostate biopsy and have an unnatural PSA and/or digital rectal examination (DRE). Following the inclusion, each of the subjects provided a first-voided DRE urine specimen which was used to obtain their SelectMDx risk score (MDxHealth B.V., Nijmegen, The Netherlands). The outcome of this SelectMDx test is a risk score in which clinical risk factors, such as age, DRE result, PSA and prostate volume (calculated by TRUS) are contrasted with the level of mRNA expression of HOXC6 and DLX1. The outcome is a risk score that is continuous ranging between -6 to 6 with larger scores having a higher probability of finding high-grade PCa. The result of this score is the percentage probability of high grade PCa in the follow up biopsy. The positive SelectMDx test is a risk score of -2.8. The result is the 13 percent chance that a subsequent biopsy would be high grade PCa. The results of the SelectMDx test were not provided to the outcomes of the biopsy. [12]

4KSCORE:

Men fearing they may have high-grade aggressive prostate cancer should obtain the 4Kscore in making the decision whether to have a biopsy of the prostate. To provide an individualised risk score, the test will examine four kallikrein biomarkers, that is, total PSA, free PSA, intact PSA, and hK2. It then incorporates these results on clinical variables. The 4Kscore is elevating the diagnosis of high-grade prostate cancer compared with PSA alone; it is also of moderate predictive accuracy and there is still the possibility

that the clinically relevant tumours would be missed. Its effectiveness may depend on risk criteria applied, biopsy procedure and demographic issues The test is not an FDA approved test and the problem of cost, access and disparate clinical integration are factors that make it an inaccessible test. These problems with generalisability are also brought up by the fact that the majority of the validation studies have been carried out on Western populations. Even in the case when the biological variability does not largely depend on the prostatic volume, the results might be influenced by it. Diagnostic accuracy is very small in comparison with other forms of assay like the Prostate Health Index. Therefore, they should conduct larger, multiethnic, and more cost-effective studies and subsequently they can be generalized into more common clinical practices. The 4Kscore unlike the traditional PSA testing differentiates those men who are at low risk of aggressive illness, and those men at high risk; the men who are at low risk score less than 1% risk of developing far metastases in ten years. The test helps physicians in making therapeutic decisions, as they can identify patients that might benefit of a biopsy and reduction of unnecessary procedure and overtreatment in case of low risk although the test does not identify prostate cancer itself.[13]

TISSUE-BASED GENOMIC ASSAYS

ONCOTYPE DX:

Twelve cancer-related genes and five housekeeping genes that are directly engaged in important biological pathways, such as proliferation, androgen receptor signalling, cellular structure, and stromal response, are measured using Oncotype DX, a reverse transcriptase-PCR-based genomic test.An expression of these gene expression resulting in a Genomic Prostate Score (GPS) between 0 and 100 is used to predict the likelihood of poor pathology, including high-grade or non-organ-confined prostate cancer at prostatectomy. GPS has been shown to predict high grade disease, unfavourable histology, and biochemical recurrence following treatment which has been confirmed in multiple cohorts. Clinical research suggests that the use of Oncotype DX in decision-making can transform the management strategies significantly as more patients would be placed on active surveillance and fewer would require immediate radiation or surgery when at low risk. Although its prognostic value is established, it is still necessary to further demonstrate its role as a definite guide of treatment decisions with respect to the prospective. As per the present National Comprehensive Cancer Network recommendations, it should be used by males with life expectancy at least ten years with very-low, low, or favourable intermediate-risk disease [14].

DECIPHER:

The Decipher genomic classifier is one of the molecular diagnostic tools that are used to find out the aggressiveness of prostate cancer. It assists doctors in tailoring the treatment regimen to the individual patient by examining the expression of genes within the tumour tissue to predict the likelihood of the disease progression, metastasis or recurrence after the treatment. The Decipher is a tissue-based genomorphologic classifier that measures 22 RNA biomarker expression to predict the risks of developing localised prostate cancer disease. It develops a genetic risk score in order to group patients into low-, intermediate-, and high-risk groups with regard to metastasis and prostate cancer-specific mortality. A number of retrospective studies demonstrate that Decipher increases the prognostic precision in comparison with the conventional clinical parameters such as PSA, Gleason score, and tumour stage and anticipates alone biochemical recovery and remote metastasis. It is particularly useful when judgements have to be made concerning adjuvant therapy following a radical prostatectomy. Although the predictive value is well established, more prospective studies need to be conducted to illustrate the impact of the same on long-term clinical outcomes.[15]

PROLARIS:

Prolaris is a genetic test which analyzes alterations in 46 genes present in samples of prostate biopsy. In men with the localised prostate cancer, it forms a risk score to help predict the risks of the disease progressing. The Prolaris molecular assay measures the expression of 31 cell cycle progression (CCP) genes that are involved in tumour growth. Prediction of 10-year biochemical recurrence (BCR) after radical prostatectomy can be done or 10-year prostate cancer-specific mortality and metastatic risk can be evaluated using biopsy specimen. The larger the score on the

scale of 0 to 10, the more aggressive disease. Clinical validation studies despite the adjustment of clinical variables and pathological variables have proved that the CCP score alone predicts prostate cancer-specific recurrence and mortality. The enormous prospect trial PROCEDURE-1000 study has proved that the CCP score significantly influenced treatment decisions, often leading to therapeutic de-escalation. The National Comprehensive Cancer Network recommends Prolaris in men with very-low, low and favourable intermediate-risk prostate cancer with a minimum ten-year life expectancy.[16]

MOLECULAR AND GENOMIC BIOMARKERS

AR-V7:

AR-V7 as an Advanced Prostate Cancer Predictive Biomarker .Androgen Receptor Splice Variant 7 AR-V7 (AR-V7) has become a therapeutically important biomarker in the metastatic castration-resistant prostate cancer (mCRPC). AR-V7, a - truncated splice variant of androgen receptor is known to lack the ligand-binding domain, but has maintained transcriptional activity, leading to constitutive activation of androgen receptor signalling independent of circulating androgens. This molecular change is responsible for resistance to androgen receptor-targeted therapies such as enzalutamide and abiraterone acetate which relies on the inhibition of ligand-dependent AR signalling. Clinical trials have indicated that patients with circulating tumour cells with AR-V7-positive respond less, respond to the tumour, and have a shorter progression free survival and the survival rate is lower when treated with these drugs. Nevertheless, AR-V7 positive does not appear to induce resistance to taxane based chemotherapy, including Cabazitaxel and Docetaxel and therefore it remains valuable in guiding treatment decisions.Minimally invasive risk classification has become less challenging with the identification of AR-V7 by molecular assays and circulating tumour cells studies. Although it has potential as a prognostic and predictive biomarker, more extensive prospective validation and standardisation of assays is required before it can be used in clinical settings in large numbers. Altogether, AR-V7 is a significant advancement towards the precision medicine in managing advanced prostate cancer.[17]

CIRCULATING TUMOR CELLS:

Circulating tumour cells (CTCs) and ctDNA/cfDNA are important liquid biopsy biomarkers of prognosis, monitoring and treatment recommendations in advanced/metastatic castrate-resistant prostate cancer (mCRPC). Circulating tumour cells (CTCs), cell-free DNA (cfDNA) and circulating tumour DNA (ctDNA) liquid biopsy has become a less invasive method of molecular characterisation of advanced prostate cancer than tissue biopsy. Research involving CTC-based detection of Androgen Receptor Splice Variant 7 (AR-V7) by RT-PCR has confirmed that AR-V7-positive patients with metastatic castration-resistant prostate cancer (mCRPC) respond worse, have a shorter progression-free survival, and an overall survival. Nonetheless, AR-V7 positivity does not make them resistant to taxane chemotherapy, including Cabazitaxel, to which better results have been reported.[18].

EXOSOMES:

An example of a non-invasive liquid biopsy indicator is exosomes and extracellular vesicles (EVs) that can be found in blood and urine and can predict prostate cancer (PCa). Exosomes, which carry molecular cargo (RNA, DNA, and proteins) inside tumour cells, have been shown to be used as a better biomarker compared to conventional methods of differentiating between high-grade, aggressive disease, and indolent disease by being able to monitor tumour growth, metastasis, and treatment response in real-time.Prostate cancer (PCa) has demonstrated the ability to be used as a non-invasive biomarker of exosomes and other extracellular vesicles (EVs), including microvesicles, apoptotic bodies These tumour-containing vesicles contain tumour biology and treatment response relying on microRNAs, tumor-derived proteins and RNA, and are released into body fluids that include urine, serum, semen and saliva. The exosomal microRNA have been identified in several studies as potential prognostic and diagnostic markers of castration-resistant prostate cancer (CRPC). Survival outcomes are associated with exosomal miR-375 and miR-1290, e.g. whereas miR-1246 can be applied in distinguishing between benign and aggressive PCa. Besides, urinary exosomal miR-21 and miR-375 are predictive. In addition, exosomal proteins have been linked to

metastatic and neuroendocrine prostate cancer in form of ITGA3, ITGB1, BRN2, and BRN4. This prognostic role of exosomes in therapy resistance is further supported by the finding of AR-V7 in exosomes. By and large, exosomes will come in handy as non-invasive biomarkers and potential therapeutic delivery systems in the treatment of prostate cancer. [19]

CIRCULATING TUMOR DNA:

The non-invasive biomarker, circulating tumor DNA (ctDNA), is an emerging biomarker that allows identifying the presence of tumor-specific mutations, methylation alterations, and DNA fragment patterns, including localized disease. GSTP1, APC, RASSF1, and RASSF2 are methylation markers that have diagnostic potential, and more sophisticated techniques like cfMeDIP-seq have been shown to be highly accurate in the localized versus metastatic disease. There is also promise in the cell-free DNA integrity index (cfDI) which is used in diagnosis and staging but the findings are yet to be confirmed. Urine and seminal plasma are considered good sources of cfDNA and it has been found that there are gene mutations and methylation markers that enhance the distinction of prostate cancer and benign conditions. Altogether, integrated molecular methods based on the usage of multiple types of biological fluids with the help of thecfDNA can be prospective in non-invasive diagnosis and risk stratification. Metastatic prostate cancer (mPC) is more severe than localized disease and has a poor prognosis, which is mainly related to resistance to treatment. The majority of the metastatic castration-resistant prostate cancers (mCRPC) are androgen receptor (AR)-mediated and the rest acquire a neuroendocrine phenotype associated with the loss of TP53 and RB1. Genomic instability that is characterized by the progression of disease including AR, BRCA1/BRCA2, PTEN, and CDK12 is increasing. The levels of circulating tumor DNA (ctDNA) become even higher between localized and metastatic tumours, proportional to the tumor burden and the response to treatment. With the NGS and ddPCR liquid biopsy techniques, actionable mutations are identified, which allows personalized treatment, such as PARP inhibitors in cases of DNA repair defects and immunotherapy in case of mismatch repair deficiency.[20].

MICRO RNAS:

MicroRNAs (miRNAs) in biofluids (blood, urine) and tissue are non-coding RNAs which may be used as non-invasive prognostic and diagnostic biomarkers of prostate cancer (PCa). Among the essential miRNAs compared with benign environments, dysregulation of miR-21, miR-145, miR-182, miR-187 and miR-940 are common. MicroRNAs (miRNAs) were observed to have a significant role in the development and progression of prostate cancer (PCa), which has great potential as a therapeutic target and a diagnostic marker. In spite of the advances to the treatment such as Docetaxel, Abiraterone, and Enzalutamide, the development of PCa to metastatic castration-resistant prostate cancer (mCRPC) remains a major clinical issue. Dysregulation in miRNA expression affects tumour growth, metastasis, epithelial-mesenchymal transition (EMT), alterations in androgen receptor signalling, and resistance to treatment. When tumour suppressor miRNAs are generally downregulated (miR-34a, miR-15/16, miR-205 and miR-200) leading to increased invasion and disease progression, oncogenic miRNAs, such as miR-21, miR-32, and miR-221/222, are generally upregulated and promote proliferation and survival pathways, including PI3K/AKT. More importantly, miRNAs are detectable in serum, plasma, and urine and they are stable in biological fluids. This renders them interesting non-invasive biomarkers that may be even more diagnostic than PSA testing. Therapeutic approaches including anti-miRNA inhibitors and miRNA mimeses, especially when paired with nanoparticle-based delivery systems, have demonstrated promising outcomes in preclinical settings.The use of miRNA-based approaches is a promising avenue of precision medicine in prostate cancer treatment although clinical translation remains scarce.[21]

CHROMOGRANIN A (CGA):

Chromogranin A (CgA) is a critical neuroendocrine biomarker that has a great clinical interest in advanced prostate cancer. The CgA identifies neuroendocrine differentiation (NED), which is a phenomenon usually seen when castration-resistant prostate cancer (CRPC) has been created, especially when treated with a long-term androgen deprivation therapy. CgA is raised in case the tumours are neuroendocrine and

androgen-independent, unlike prostate-specific antigen (PSA) which indicates the presence of the androgen receptor. High serum CgAs correlate with advanced stage disease, metastatic stage, poor prognosis and resistance to treatment. CgA is a second biomarker to follow cases that are aggressor and resistant to treatment due to the fact that the neuroendocrine prostate cancer usually leads to low levels of PSA. Although CgA has drawbacks such as inconsistency of assays and non specific increase, CgA and PSA combination in measurement enhance clinical evaluation and prognosis in treatment of advanced prostate cancer. [22] Chromogranin A (CgA) has become one of the biomarkers in progressive and metastatic prostate cancer, particularly considering neuroendocrine differentiation and castration-resistant disease. There is a possibility that some of the cancer cells can grow less dependent on androgen receptors and attain neuroendocrine traits due to the progression of prostate tumours by long-term androgen deprivation therapy. This may culminate into aggressive behaviour and resistance to treatment. In contrast to prostate-specific antigen (PSA), which is a sign of tumour activity stimulated by androgens, CgA levels rise on androgen-independent and neuroendocrine phenotypes. High serum CgA is linked to high metastatic burden, the lack of response to hormonal treatment, late stage, and reduced survival. CgA along with PSA is more effective in prognostic assessment and could assist in detecting treatment-resistant prostate cancer earlier to provide more precise treatment options, even though such adverse effects are observed as assay inconsistency and non-specific rises [23]

DNA METHYLATION:

Epigenetic changes inhibitory of tumour suppressor genes, DNA methylation markers in prostate cancer (PCa) include, primarily, hypermethylation of cytosine residues in CpG islands in promoters of genes. These consistent, tumor-specific molecular changes in tissues or fluids, which serve as diagnostic/prognostic biomarkers (as in the case of GSTP1), are used to detect cancer, distinguish it and benign hyperplasia, and assess its aggressiveness. They are epigenetic modifications, which consist of the addition of a methyl group (5-methylcytosine) to DNA. They frequently occur at CpG islands of tumour suppressor genes promoter regions, where they serve as a sort of a switch to turn these genes off. Their predictability, early appearance in cancer formation, and resistance in body fluids (urine, serum, and plasma) make them effective predictors of the disease prognosis in prostate cancer. Using conventional markers such as PSA levels, Gleason score, and tumour staging, it is difficult to separate aggressive tumours with slow-growing tumours as prostate cancer has a lot of variability in disease course. DNA methylation is one of the epigenetic modifications that regulate the expression of genes. Rapidly tumour suppressor genes have been silenced in prostate cancer, which is also abnormally methylated and contributes to tumour growth and spread. Changes in methylation are encouraging prognostic markers as they occur at an early stage of cancer and are not reversible. Many genes have been discovered such as PITX2, APC, Rarb, GSTP1 with considerable methylation signatures associated with patient survival, disease course, and lack of recurrence. The most predictive of the above is PITX2 methylation, and this can be studied by novel genome-wide methylation detection tools and may be detected non-invasively by liquid biopsy (blood or urine). Some of the weaknesses include small sample sizes, lack of standardisation and necessitating substantial clinical validation research before the application can become routine clinical practice. In all respects, DNA methylation biological markers have enormous potential in boosting risk assessment and personalised treatment of prostate cancer.[24]

DIAGNOSTIC TECHNIQUES IN PROSTATE CANCER

DIGITAL RECTAL EXAMINATION:

A digital rectal exam (DRE) can be used to detect prostate cancer. During this check, a doctor will stick a gloved, lubricated finger inside your rectum to touch your prostate gland. Evaluate the consistency of the back of the gland where most of the prostate malignancies begin. Search any hard areas or nodules (lumps) that might be a cause of cancer. The prostate-specific antigen (PSA) test has often been used together with a DRE to detect prostate cancer, especially by the physicians since its discovery in the late eighties. Screenings are conducted when one is without any signs so as to test whether he or she has a condition. Normal men may sometimes have

malignancies detected through a DRE. Thus, the Fred Hutch Cancer Center recommends men aged 55 years and above to speak to their doctor about whether DRE is acceptable to them or not. Doctors can recommend screenings to start at a younger age among some of the men who are at a greater risk like the African Americans or men with a family history of cancer. In accordance with the prostate cancer specialists at Fred Hutch, the following screening plan is recommended:

males less than 40: DRE and PSA are not recommended in the case of males who are at average risk.

Men 40-54: DRE and PSA test are not recommended in the case of moderate risk in men. Men between 55 and 69 years old: You may be a candidate of DRE, PSA, or both screening, discuss the advantages and disadvantages with your doctor.

Men at the age of 70 years and above are not usually recommended to undergo DRE and PSA screenings. Screening can however prove useful to men who are in exceptional condition. DRE can be used to examine the posterior side of the prostate that may be explored by the rectum. Approximately 70% of PCa cases are of the peripheral zone, which is readily available during DRE. The sensitivity and specificity of DRE however, cannot be regarded as effective since it has a low sensitivity and specificity of less than 60 percent when used standalone. The subjectivity of DRE is associated with a high level of interobserver variability and inconsistency in the interpretation of DRE by medical specialists due to its subjectivity. Thus, DRE is not to be regarded as a single diagnostic method, but a part of a multimodal assessment program [26].

AI in imaging-based diagnosis: Multiparametric magnetic resonance imaging (mpMRI) has become indispensable in order to diagnose and stage prostate cancer. But, there is a variation in the Prostate Imaging Reporting and Data System (PI-RADS) grading, and the interpretation of mpMRI is largely reliant on the ability of radiologists. One approach to AI-based deep learning algorithms, Convolutional neural networks (CNNs), have demonstrated excellent outcomes in automated lesion detection, segmentation and classification of clinically relevant tumours. Radiomics is a branch of artificial intelligence that processes MRI images to produce quantitative imaging features such as patterns of texture, shape and intensity. These features are correlated with the change of molecules, Gleason score, and tumour grade. Artificial intelligence-based radiomics models have shown to be more predictive when used to distinguish between non-indolent and clinically relevant diseases and this could lead to a reduction in unnecessary biopsies. Also, the AI systems are capable of offering personalised risk scores by integrating the imaging images with other clinical information, such as age and PSA levels.

AI in digital pathology: AI is finding a home in digital pathology in the application of AI in prostate cancer diagnosis. Whole-slide imaging can provide computational algorithms with a high resolution of histopathological features. Machine learning models have the potential to predict tumour volume, detect perineural invasion, detect malignant glandular architecture and automate Gleason grading. Since grading interpretation has been known to be diverse, AI-assisted Gleason scoring has demonstrated great concordance with expert pathologists, with improved reproducibility. Deep learning methods can also predict the metastases and biochemical recurrence development according to histomorphological patterns. These tools are also being evaluated as clinical decision-support systems and not pathologists substitutes in order to enhance efficiency and diagnostic confidence.[27]

PSMA BASED PET/CT IMAGING:

PSMA PET PSMA PET is a diagnostic tool to diagnose prostate cancer in any location in the body by use of positron emission tomography (PET) which is a form of medical imaging. Prostate specific membrane antigen or PSMA in short is a protein and when attached to the surface of the prostate cells it is cancerous. PET imaging has been in use to locate cancer over decades. Until recently, however, the past radiotracers of PET, radioactive molecules that adhered to the cancer cells, and which could be seen on a PET scan, did not always attach to prostate cancer, and thus it was challenging to image the disease. PET/CT imaging, which is prostate-specific membrane antigen (PSMA)-based, has emerged to be a highly specific and sensitive way to manage and identify prostate cancer. PSMA is an ideal molecular target of prostate cancer to be used in imaging because

it is significantly overexpressed in the cancer cells and particularly in high-grade and metastatic cancers. Radiotracers such as 68Ga-PSMA and 18F-PSMA offer better diagnostic capabilities than conventional CT and bone scintigraphy since they can visualise primary tumours, LN involvement and metastases on distant sites. PSMA PET/CT is especially relevant in the case of biochemical recurrence because the imaging will detect recurrent disease at low PSA levels to guide early salvage therapy. PSMA imaging plays a vital role in theranostics, in addition to diagnosis, to reveal potential candidates of PSMA-targeted radioligand therapy. Although there are disadvantages in terms of cost, accessibility, and the necessity to have comparable standards of interpretation, PSMA PET/CT is a significant advance in precision imaging and individualised treatment of prostate cancer [28].

TRANSPERINEAL BIOPSY:

Transperineal biopsy is one type of prostate biopsy, and one method of examining the prostate gland in order to determine whether it has cancer. Your doctor will use the skin to insert a biopsy needle into the prostate between the scrotum and the rectum during this ultrasound-guided prostate biopsy. A pathologist will examine the tissue sample in the lab test to determine whether prostate cancer cells are present. This form of outpatient prostate biopsy will require 30 to 45 minutes. It is much more accurate than traditional transrectal method of biopsy. In the diagnosis of prostate cancer, transrectal prostate biopsy (TRPBx) is being replaced by transperineal prostate biopsy (TPPBx) which is more advanced and secure. In patients with no prior biopsy history, the TPPBx has an equivalent cancer detection rate to that of the other technique, but in repeat biopsy, and in men undergoing active surveillance, TPPBx is an obviously superior technique to the alternative one in identifying clinically significant prostate cancer (csPCa). The transperineal approach has the significant benefit of superior access of the anterior and apical portions of the prostate which are frequently under sampled by transrectal means. Important to note, since TPPBx does not allow the passage of needles through the rectal mucosa, it significantly reduces the issues of infections. The growing concern on antibiotic resistance associated with TRPBx is that there is an estimated rate of sub 1 percent on infection and sepsis. TPPBx was again associated with urinary retention, however, this risk has been reduced by modern MRI-targeted techniques. The diagnostic accuracy of transperineal biopsy is also enhanced by the addition of multiparametric MRI which is supported by findings of the PROMIS trial particularly in anterior tumours. TPPBx is emerging as the most appropriate diagnostic tool in the new generation of prostate cancer practice because it is safer, can be used with MRI-fusion targeting, and is feasible with local anaesthesia.[29]

MRI FUSION BIOPSY:

The images of the prostate supplied by the multiparametric MRI or mpMRI are fused with real-time ultrasound images provided by the ultrasound during an MRI fusion prostate biopsy.Targeting MRI-suspicious lesions during the biopsy is intended to improve the identification of clinically significant malignancy in the right patients. MRI-ultrasound fusion biopsy is a method that involves combination of real-time ultrasound and MRI images with specific regions of interest to aid in the directing of focused sample. This helps the doctors to see the lesions that have been shown by the MRI in a live ultrasound image to ensure better targeting of collection of ten to twelve samples in the prostate (as in TRUS and TPUS biopsies). To help in documentation of the samples, some fusion platforms can be used to record and display core positions after each sample.MRI/TRUS fusion-guided biopsy can be used to pinpoint clinically significant prostate cancer (CsPCa). The drawbacks of the conventional transrectal ultrasonography (TRUS)-guided systematic biopsy are that it over-diagnoses innocent disease and under-diagnoses aggressive malignancies. The European Association of Urology has suggested that men who are suspected of having prostate cancer have multiparametric MRI (mpMRI) before biopsy. In this retrospective single-center study, transperineal MRI/TRUS fusion biopsies were carried out on 416 males that possessed at least one lesion of PI-RADS 3 or greater and the cancer detection rate was 49% overall. Fusion biopsy clinically detected malignancy of significance in 34.8% of biopsy-naive patients, and systematic biopsy alone would have missed almost half of those. It was found that tumour upgrading occurred in 43.6 percent of patients who were under active surveillance, which highlights the role of the

technique in the enhancement of risk assessment. Also, biopsy Gleason scores were found to be highly concordant (90.8) with final surgical pathology in patients who underwent radical prostatectomy. In general, the research demonstrates that MRI/TRUS fusion biopsy is an important tool in the initial diagnosis and active surveillance and enhances the identification of clinically significant prostate cancer and is moderately correlated with PI-RADS score and grading accuracy [30].

CONTRAST-ENHANCED ULTRASONOGRAPHY:

The state-of-the-art imaging method known as contrast-enhanced ultrasonography (CEUS) enhances the evaluation of the prostate in the canine body by providing real-time data about the tissue perfusion and microvascularization. CEUS has also been shown to be more effective than traditional ultrasonography, in terms of identifying small intraprostatic lesions, demarcating tumour borders and extracapsular spread of the tumour in research studies, particularly on canine models of prostate cancer. It has also been demonstrated to work very effectively in the tracking of directed therapies such as microwave thermal therapy and radiofrequency ablation in which treated regions appear as non-enhancements areas that are almost consistent with the histological observations. CEUS assists in the identification of various prostate diseases and also improves the visualisation of prostate vascular structure in veterinary clinical practice. Whereas in benign prostatic hyperplasia and prostatitis the disturbed, often disordered vascular maps are characterized by overlapping perfusion values, in normal prostates, homogenous enhancement is observed with rapid wash-in and wash-out curves. Nevertheless, prostatic adenocarcinoma is the disease that can best be determined with the help of CEUS as it is associated with irregular vascularization, reduced time to peak, as well as, much greater intensity of perfusion. Even with the advantages of CEUS in diagnosis, confirmation still needs to be done by histopathological investigation. Altogether, CEUS is a handy auxiliary tool when it comes to the diagnosis and treatment assessment of canine prostatic sickness [31]

SHEAR WAVE ELASTOGRAPHY:

Shear Wave Elastography (SWE) is an innovative ultrasound-based imaging technology that could be useful in enhancement of prostate cancer diagnosis through the evaluation of tissue stiffness. SWE provides quantitative measurements of elasticity to assist in the detection of suspicious lesions within the prostate as the malignant prostate tissues tend to be stiffer than the normal ones. According to a systematic evaluation of a number of clinical trials evaluating SWE, prostate cancer and, in particular, clinically significant prostate cancer (csPCa) can be identified with a relatively high level of sensitivity and specificity. The methodology is superior to the traditional systematic biopsy methods in that it allows better localisation of the tumour, and probably could be used to target more specific biopsies. Shear Wave Elastography (SWE) is a modern ultrasound imaging method that can be used to improve the sensitivity of diagnosing prostate cancer through measuring tissue stiffness. Given that the malignant prostate tissues are often harder than the normal tissues, SWE offers quantitative measures of elasticity that are used to raise suspicions about the existence of suspicious lesions within the prostate. The systematic review of several clinical studies that assessed SWE found out that prostate cancer, especially clinically significant prostate cancer (csPCa) can be detected with a reasonable level of sensitivity and specificity. The methodology increases diagnostic accuracy by allowing increased localisation of the tumour and possibly aiding in the direction of targeted biopsies compared to traditional systematic biopsy procedures [32].

MICRO-US:

An emerging popular method to improve the diagnosis of prostate cancer is micro-ultrasound (Micro-US). Unlike the conventional transrectal ultrasonography (TRUS), which is running 612 MHz, microUS is a higher frequency of approximately 29 MHz. This can be used to achieve a spatial resolution of nearly 70 µm and visualise microarchitecture in the prostate. This clarity in resolution facilitates easy detection of small structural abnormalities that are related to malignant transformation. MicroUS is based on the Prostate Risk Identification using Micro-UltraSound (PRI-MUS) scoring system in which

lesions are assigned a number ranging between 1 and 5 based on their likelihood of being clinically significant prostate cancer (csPCa). Lesions in the case of biopsy are focused on those with a higher PRI-MUS score and real-time lesion-directed sampling is performed, which does not require MRI-ultrasound fusion. It has been demonstrated through clinical studies that the MicroUS has the following advantages: the reduced cost, faster imaging and easier integration into the routine biopsy procedures but with diagnostic sensitivity equivalent to multiparametric MRI in detecting csPCa. Moreover, real-time visualisation aspect of MicroUS has the benefit of improving the accuracy of biopsy and the localisation of lesions. Despite the positive side of these, there exist some negative factors like the reliance on the operators and the lack of extensive validation studies. Nevertheless, there exists the promising alternative or the supplemental imaging technique, MicroUS, which may enhance the precision of the targeted biopsy techniques and the diagnosis of prostate cancer.[33]

TURP:

Transurethral resection of the prostate (TURP) remains the gold standard in the treatment of benign prostatic hyperplasia (BPH) particularly in patients with moderate to severe lower urinary tract symptoms that are not responding to pharmacological therapy. The projectile can enhance the urine flow by removing obstructive prostate tissue using the advantages of a resectoscope with the help of the urethra to remove the tissue and clear bladder outlet obstruction. Among the diseases, which require TURP, recurring urinary retention, recurring UTIs, bladder stones, chronic haematuria, and renal impairment caused by the obstruction of the prostate. Common preoperative tests include digital rectal examination, prostate-specific antigen test, imaging tests, and measurement of urine flow to eliminate the presence of cancer and estimate the size of the prostate. Removal of the enlarged prostatic tissue takes place in the process which is performed under regional or general anaesthesia. Haemostasis is achieved by applying electrocaution. Postoperative care includes bladder irrigation and temporary catheterisation to ensure that there is proper urine outflow. The two most common TURP are monopolar and bipolar TURP; the second one has better haemostasis and chance of electrolyte imbalance is reduced hence is less risky. On the whole, TURP is largely effective in terms of reduction of symptoms and enhancement of the urinary functionality in the long term with relatively minor side effects.[34].

CRYOTHERAPY:

A less invasive technique of localised prostate cancer and recurring disease following radiation therapy is cryosurgery also referred to as cryotherapy. The procedure involves exposing cancerous cells to very low temperatures with the aim of regulating its death. It involves the insertion of a number of cryoprobes into the prostate transperineally followed by a freezing agent e.g. argon gas that forms an ice ball that surrounds the tumour location. This is due to quick freezing, which leads to vascular damage, cell membrane breakdown, formation of ice crystals within the cell and eventually death of cells. In order to create maximum tissue degeneration and the least amount of damage, two freeze-thaw cycles typically are performed with a close observation of adjacent structures. Less invasive surgery, a shorter hospitalization, and appropriateness to patients who do not qualify best to undergo radical prostatectomy are only some of the benefits associated with cryosurgery. It has shown promising clinical outcomes in patients with localised prostate cancer especially and many of such cancer patients reported a significant reduction in their levels of prostate-specific antigen following treatment. Also, salvage therapy with the use of cryotherapy can be offered to patients who experience recurrence of prostate cancer after radiation therapy. Yet, rare rectourethral fistulas, urine incontinence, and erectile dysfunction are the potential adverse effects. Cryosurgery has been improved as an alternative form of treatment that can be used to treat prostate cancer because of advances in cryotechnology and imaging guidance.[35]

PDT:

Photodynamic therapy (PDT) is a treatment of prostate cancer that is less invasive. Prostate cancer is one of the most common diseases among men all over the world and extensive prostate-specific antigen (PSA) screening has enhanced the detection of the disease at an earlier stage. Though effective, the common side effects of the traditional treatments such as radical prostatectomy, radiation therapy, and the

androgen deprivation therapy often include erectile dysfunction and urine incontinence. Focal therapies whereby the tumours are targeted but leave the surrounding tissues intact are thus becoming popular. Photosensitiser (PS), light of specific wavelength, and oxygen are three constituents of photodynamic therapy, a promising focused treatment. When light hits the photosensitiser, the reactive oxygen species (ROS) produced by the photosensitiser kill cancer cells and damage the vasculature of tumours. Some advantages of PDT include minimal invasiveness, low systemic toxicity, repeatability and the ability to preserve normal tissue functioning. Clinical trials have demonstrated that PDT has the capacity to treat localised prostate cancer with the preservation of better functional outcomes as compared to major surgery. Preclinical studies have been done on how to overcome current drawbacks like low light penetration, hypoxia within the tumour, and poor selection. Moreover, PDT can be more efficient as a combination with other treatments such as chemotherapy, photothermal therapy, or photoimmunotherapy. Regardless of its potential, incomplete tumour diagnosis, post treatment recurrence, as well as limited efficacy in advanced or high-risk prostate cancer, still exists. The primary focus of future research should be on enhancing imaging, focused photosensitivity, and combined treatment systems in order to optimize PDT in the clinical practice [36].

SBRT:

Stereotactic body radiotherapy (SBRT) has been a major development in the radiotherapeutic management of localised prostate cancer. Historically, the conventional fractionation regimen of external beam radiation therapy (EBRT) of prostate cancer involved 3945 fractions over 89 weeks. Conversely, an emerging amount of radiobiological evidence suggests that prostate cancer has a low α/ β ratio which implies that it is more susceptible to increased radiation doses per fraction. This has led to the development of treatment modalities of hypofractionated and ultrahypofractionated nature. SBRT is an ultra-hypofractionated form of treatment, where high doses of radiation (typically 6 8 Gy/fraction) are delivered with a high level of precision in five or fewer treatment sessions. Radiation delivery technology, as intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and so on, has enabled the accurate targeting of the prostate with minimal radiation to the other organs, such as the bladder and rectum. Clinical trials and pooled analyses conducted on prostate cancer have demonstrated promising outcomes with SBRT with 5-year biochemical recurrence-free survival rates exceeding 90 in patients with low- and medium-risk prostate cancer. More to the point, the toxicities associated with the treatment are usually minimal; the percentage of patients exhibiting severe gastrointestinal and genitourinary side effects is negligible. Further proof that ultrahypofractionated radiation has comparable efficacy and treatment toxicity profiles to traditional fractionation regimens has come from randomised clinical trials like PACE-B and HYPO-RT-PC. Moreover, due to the reduced treatment time of SBRT, it includes significant advantages in the treatment convenience and cost-saving of healthcare expenses. In case of localised prostate cancer, the available data promotes the use of SBRT as safe, effective, and a well-known intervention among individuals.[37]

VMAT:

Lately, the level of accuracy and effectiveness of the treatment of prostate cancer has gone a long way because of the recent advancements in radiation therapy. Two of these approaches include volumetric-modulated arc therapy (VMAT) and intensity-modulated radiotherapy (IMRT); these techniques are commonly used to deliver highly conformal radiation doses to the prostate and minimal exposure to adjacent normal tissues. An analytical dosimetric analysis was used to evaluate the efficacy of multiple radiation planning approaches to prostate cancer which included 7-field IMRT, 9-field IMRT, single-arc VMAT and double-arc VMAT. All of them were planning target volume (PTV) coverage, dose conformity, homogeneity index, radiation exposure to organ at risk (OARs), monitor units and time in which the treatment was delivered. The results indicated that, compared to IMRT designs, VMAT, namely, the double-arc method, had better targets coverage and dose distribution. Moreover, VMAT reduced the radiation dose to neighboring organs such as bladder and rectum which are very susceptible to radiation toxicity by a large margin. Another outstanding

advantage of VMAT was better treatment efficiency as it only took a smaller number of monitor units and much less time to deliver treatment as compared to IMRT. Workflows of radiations in clinical settings are made more efficient, and they enhance the comfort of patients. In general, the findings indicate that VMAT is a more effective and successful way of planning radiations when it comes to treating prostate cancer. Due to the ability of VMAT to reduce the side effects associated with treatment and the ability to deliver maximum tumour control, VMAT is gaining increasing use in the modern radiation [38].

BRACHYTHERAPY:

Prostate brachytherapy is one of the most popular forms of radium therapy that is minimally invasive and used to treat localised prostate cancer. To ensure minimal exposure to the neighbouring organs and consequently deliver a high dose of radiation to the tumour tissues, radioactive sources are inserted directly into the prostate gland. the wide range of methods and technical advances that increase the precision and effectiveness of prostate brachytherapy. The two common ways through which the operation is normally performed are low-dose-rate (LDR) brachytherapy that permanently implants radioactive seeds into the prostate, and high-dose-rate (HDR) brachytherapy that delivers transient radioactive sources using catheters. To achieve maximum treatment outcomes, accurate needle placement is required. Nevertheless, several complications, such as needle deflection, tissue deformation, and multiple needle-to-tissue interactions may hinder accuracy, so imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), and transrectal ultrasonography (TRUS) are commonly used as a way to counter these problems. Moreover, the novel technologies such as robotic-assisted insertion systems of the needles, and MRI-ultrasound fusion imaging, have been created to enhance the uniformity of the procedure and the precision of the targeting. It is also in the paper that advances in force-feedback, needle steering strategies, and computational model predicting and correcting needle deviation during insertion are pointed out. The purpose of these developments is to enhance the effectiveness of treatments overall as well as the accuracy of seed placement. It is expected that the combination of advanced imaging, robotic assistance, and improved needle control methods will significantly improve the accuracy, safety and clinical outcomes of prostate brachytherapy during the management of prostate cancer.[39]

CONCLUSION

Another more precise-based, biomarker-oriented approach to prostate cancer diagnosis is rapidly supplanting the older screening methods; their limitations in sensitivity and specificity implies that more sophisticated diagnostic tools are necessary. Although PSA and DRE will continue to be significant components of the clinical tool, their inability to be sensitive and specific implies that a more sophisticated diagnostic tool is needed. Much has been advanced in modern molecular biomarker of clinically significant prostate cancer, including urine-based, blood-based, tissue-based or liquid biopsy technologies, which have significantly enhanced the ability to identify clinically significant prostate cancer, increase the accuracy of prognosis and provide customised treatment options. At the same time, the clinical procedure and diagnostic accuracy of treatment targeting prostate cancer are undergoing revolution with the development of imaging techniques like mpMRI, PSMA PET/CT, MRI-fusion biopsy, and micro-ultrasound, along with the adoption of the artificial intelligence to interpret the data. Nevertheless, assay harmonisation, large-scale validation, cost and practical use are still problematic. Further innovations will require the effective combination of multimodal biomarkers, imaging, and computational analytics into standardised clinical practice in order to make the prompt detection of prostate cancer, reduce overtreatment, and offer more personalised care possible.

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