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Current Trends in the Management of Prostate Cancer

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ABSTRACT

Prostate cancer has been described as the second most common cancer among men. Although it has variable incidence around the world, showing that race is a risk factor, it can be described as a global health burden. It is usually asymptomatic in its early stages and then presentation of symptoms advances with disease progression. Due to its asymptomatic nature, the cancer is usually detected incidentally or in its advance state. The use of PSA for screening has been adopted over the years to improve detection at early stages. However, the use of PSA screening has been associated with overdiagnosis and subsequently overtreatment. This has led to a decreased quality of life such as decreased bowel, urinary or sexual functions in a group of men with otherwise indolent forms of the disease. The unnecessary economic waste that comes from obtaining a treatment is another negative impact of overtreatment. This problem has posed the need of more efficient biomarkers and diagnostic markers in order to provide improved management of prostate cancer.

This article aims to explores novel biomarkers used in the detection of Prostate Cancer, their success rates while also exploring tests and models and the need for additional methods This article also aims at exploring the current treatment methods as well as their advantages and disadvantages. PubMed and Google Scholar searches were made for the following terms: prostate cancer, epidemiology of prostate cancer, current methods of diagnosing prostate cancer and current treatment methods for prostate cancer, from date up to 2000. Local studies about the incidence and progression of the disease were also included to provide a more rounded view.

Newer biomarkers such as the PCA3 antigen, the HOXC6/DLX1, microseminoprotein-beta (MSMB), macrophage inhibitory cytokine 1, Oncotype Dx, Prolaris, Decipher, Decipher PORTOS, ProMark have proven to be more efficient that an ordinary PSA test. In addition, models and tests such as the stockholm-3 model, the 4kscore test tend to incorporate more clinical, genetic and biological factors, and as a result, provide a more holistic view than an ordinary PSA screen. Treatment methods such as active surveillance and watchful waiting are preferred for more indolent forms of the disease. Other treatment methods have various advantages and disadvantages. Therefore, the decision for an efficient treatment method must include the stage of the disease, assessment by a multidisciplinary team and the choice of the patient. In addition, A combination of treatment methods is strongly recommended, in contrast to a monotherapy. The increased incidence of prostate cancer might have increased slightly over the years is strongly associated with overdiagnosis and overtreatment. The effects of overtreatment are in contrast to one of the fundamentals of medicine, which is: to do no harm. If the overdiagnosis of prostate cancer is to be abated, it is important to embrace novel biomarkers as well as models which are more efficient. In the management of prostate cancer, it is also important to prioritise the combination of treatment methods rather than monotherapy.

INTRODUCTION

Prostate cancer, a global health burden with an estimation of 1,276,000 cases as of 2018, has been described as the second most frequent cancer diagnosis among men [1]. Across different countries, the incidence rate is variable. However, its mortality rate is highest in Sub-Saharan Africa, the Caribbean and South America, while it is lowest in Asia [2]. For instance, a study reported 32·8 cases and 16·3 deaths per 100 000 men in Nigeria, a country in Sub-Saharan Africa[3].

Like many cancers, the exact cause of prostate cancer is not known. However, advanced age is an important risk factor. The risk increases after 50 years of age in White men with no family history of the cancer. In Black men or men with a family

history, the increased risk exists from age 40 [1]. Genetic traits and family history are also strong predisposing factors to the development of prostate cancer. About 20% of patients report a positive family history. Men with an immediate family member diagnosed with prostate cancer, are at a two or threefold risk of being diagnosed, relative to men without such family history [1,4]. Race is also a risk factor as the cancer seems to be more aggressive in certain races, such as in blacks[5]. Other important risk factors are environmental factors, obesity and smoking.

CLINICAL PRESENTATION

Cancer of the prostate is usually asymptomatic in the early stages. Common symptoms such as hematuria, low back pain, urinary urgency and other obstructive urinary symptoms are indicative of progression[6,7]. There could also be other symptoms due to metastasis of the cancer to other parts of the body. Examples of such include oedema of the lower extremities from the obstruction of regional lymph nodes or pain from bone involvement.

Interestingly, there have been reports of unusual symptoms associated with the disease around the world. For instance, a study from Nigeria reports presentation of symptoms such as hematochezia, tenesmus and left supraclavicular swellings in Prostate cancer patients[8]. Another Study also reported presentation with Disseminated Intravascular Cascade (DIC)[7]. Due to the unusual presentations, the disease was only suspected after an abnormal digital rectal examination or PSA (Prostate Specific Antigen) assay.

A lot of cases are detected on screening. This is partly due to the presentation of rare symptoms (as discussed above) but mostly due to its asymptomatic nature at the early stages. Still, there is evidence that early diagnosis and treatment of prostate cancer reduces mortality rate[3]. As a result, various screening procedures have been adopted over the years. The most common biomarker used over the years- PSA (Prostate Specific Antigen) has been associated with overdiagnosis [4], hence the need to develop better ones. The current biomarkers and diagnostic methods used today are discussed in the next section.

INVESTIGATIONS – SCREENING, STAGING AND DIAGNOSTIC METHODS

Serum Biomarkers

The 4Kscore Test is a blood test that is recommended for men with abnormal Prostate Specific Antigen test or Digital rectal examination results and are being evaluated for an initial or repeat prostate biopsy. The novel test incorporates a panel of four kallikrein protein biomarkers which includes total PSA (tPSA), free PSA (fPSA), intact PSA (iPSA), human kallikrein-related peptidase 2(hK2) and other clinical information in an algorithm that comes up with a percent risk for a high-grade (Gleason score ≥ 7) cancer on biopsy [9]. The Vinayak G et.al (2021) study found that combining the 4k Score with MRI in a nomogram would reduce unnecessary prostate biopsy[10].

Also, It has been documented that a non-active precursor form of PSA known as pPSA (consisting [-2]pPSA, and [-4]pPSA) is included in the free PSA present in the serum. These biomarkers are used in calculating Prostate health index (**PHI**). Researchers have demonstrated pPSA presence in 28% of transition zone samples, and 89% of corresponding cancer samples exhibited detectable pPSA suggesting that pPSA is strongly correlated with prostate cancer[11]. Ferro et al (2020) in their study assessed the PHI score, calculated using the formula [-2]proPSA/fPSA × $PSA^{1/2}$ suggested that measuring PHI could reduce unnecessary biopsies due to its superior specificity for detecting prostate cancer when compared to PSA measurement only[12].

Urinary Biomarkers

Prostate cancer antigen 3 (PCA3) is a biomarker that is found majorly in the urine after prostate massage. it is significantly associated with prostate cancer as it is a non-coding mRNA (differential display code 3 -DD3) that is highly overexpressed in this condition. A systematic review carried out by Rodríguez et.al (2019) concluded that PCA3 has acceptable diagnostic accuracy and can reduce unnecessary biopsy[13].

The development of gene expression profiling has also led to the identification of a small number of urinary biomarkers, including HOXC6 and DLX1. A urinary panel comprising three genes (HOXC6, DLX1, and TDRD1) was found to have higher accuracy than PCA3 in detecting prostate cancer with Gleason scores of 7 or higher [14]. Urinary HOXC6/DLX1 is recommended as one of the tests that may be utilized in asymptomatic men with PSA levels between 2-10 ng/mL and normal DRE to evaluate the risk of prostate cancer before performing a biopsy [15].

Radiological Imaging

In recent years, Multiparametric magnetic resonance imaging (mpMRI) scans have become increasingly popular for diagnosing prostate cancer. In 2012, the Prostate Imaging Reporting and Data System (PI-RADS) was created with the purpose of providing guidance for reporting mpMRI [16]. A pilot study exploring the use of mpMRI established that the detection rate of mpMRI for prostate cancer was superior to PSA alone [17]. The PROMIS study concluded that by triaging men with mpMRI, patients could avoid a needless primary biopsy [17]. A randomized trial called the PRECISION study also arrived at similar conclusion [18].

Another imaging modality is PET-CT scan with different radiotracers. PET, or Positron Emission Tomography, involves the utilization of a ligand-bound radioactive isotope that accumulates in specific regions of the body [19]. PET-CT aims to enhance the sensitivity of detecting small nodal and bony metastasis at low levels of PSA[20]. Recent studies have reported a sensitivity ranging from 38 to 100% and a specificity ranging from 29 to 96% in detecting primary prostate cancer and lymph node involvement.

Prostate Cancer Predictive Models/Risk Calculator

The Stockholm-3 Model (STHLM3) is one of the widely used model today. The STHLM3 model incorporates clinical factors, plasma protein biomarkers such as PSA, free PSA, intact PSA, hK2, microseminoprotein-beta (MSMB), and macrophage inhibitory cytokine 1 (MIC-1), as well as 232 single nucleotide polymorphisms (SNPs). In addition, several other clinical parameters such as age, family history, prostate examination, and prior prostate biopsy are also taken into account in this comprehensive model[21]. A study in Sweden demonstrated that the STHLM3 model performed better than PSA alone in predicting clinically significant prostate cancer with a Gleason score of 7 or higher[21].

Several other predictive models have been created over the years, however, only 6 have been externally validated with study population greater than 5[22]. These includes; Prostataclass, Finne, Karakiewez models, Prostate Cancer Prevention Trial (PCPT), Chun, European Randomized Study of Screening for Prostate Cancer Risk Calculator 3 (ERSPC RC 3). Following the systematic analysis of the six risk models, it was concluded that they exhibited superior discriminative accuracy compared to PSA testing[22].

Prostate Biopsy

According to International guidelines, performing a biopsy under TRUS guidance (transperineal ultrasound guidance) with an 18 G biopsy needle and a periprostatic block, is considered the accepted standard of care[9,23]. However, multiparametric magnetic resonance imaging (mpMRI) + MR-guided biopsy (MRGB) has been reported to decrease the detection of clinically insignificant prostate cancer (insignPCa) while increasing the detection of clinically significant prostate cancer (csPCa) when compared to TRUSGB [24,25]. Several multicenter randomized trials have confirmed that mpMRI and MR-directed biopsy are superior to TRUSGB [26, 27, 28]

CURRENT RECOMMENDATIONS/GUIDELINES – Staging and Diagnosis

Based on available studies over the years the European Association of Urology (EAU)-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy and Oncology (ESTRO)-European Society of Urogenital Radiology (ESUR)- International Society of Geriatric Oncology (SIOG) made recommendations concerning the screening, diagnosis, and treatment of clinically localised prostate cancer (PCa)[23]. The American Urological Association (AUA) and Society of Urologic Oncology (SUO) have also published similar guideline statements regarding prostate cancer screening[29].

These guidelines were based on reviews and systematic analysis of available studies.

Staging and Classification

They recommended that the 2017 TNM classification published by the American Joint Committee on Cancer (AJCC) for staging of prostate cancer should be used[30]. This version included the pT2 substage differentiation which was absent in the 2009 version.

The recommended PCa grading system remains the International Society of Urological Pathology (ISUP) 2005 modified Gleason score (GS)[31]. However, the concept of grade groups of prostate cancer to align prostate cancer grading with the grading of other carcinomas, was adopted in the 2014 ISUP Gleason Grading Conference on Gleason Grading of prostate cancer[32]. The American Society of Clinical Oncology (ASCO)-EAU-American Urological Association (AUA) also made recommendations for localised prostate cancer. They recommended the use of tissue-based biomarkers (Oncotype Dx, Prolaris, Decipher, Decipher PORTOS, and ProMark) which has been found to significantly improve the prognostic accuracy of clinical multivariable models[33].

Diagnosis

Histopathology is still the required method to diagnose prostate cancer. However, due to associated complications of

For asymptomatic men with a normal digital rectal examination and a PSA level 2-10 ng/mL before performing a prostate biopsy, use one of the following tools for further risk assessment:

- **Risk calculator**
- **Imaging**
- **An additional serum or urine-based test**

prostate biopsy, further risk assessment might be helpful in avoiding unnecessary biopsies. Here is the recommendation of the EAU-EANM-ESTRO-ESUR-SIOG regarding prostate biopsy[23]:

TREATMENT

Prostate cancer, like many similar diseases, does not have a single definitive treatment. The treatment of prostate cancer varies from person to person, depending on several factors. These factors include the age of the patient, his Gleason score, the measured amount of prostate-specific antigen, the nature of the disease's progression, the patient's preferences, etc. Considering these factors, it is safe to conclude that the optimal management of a patient with prostate cancer is not one that should be taken by a single physician and his patient. Rather, it should involve a multidisciplinary team consisting of urologists, radiation oncologists, medical oncologists, pathologists, and radiologists.

The current management strategies for prostate cancer that would be discussed in this article include active surveillance and watchful waiting, surgery, radiation therapy, brachytherapy, cryosurgery, Androgen-deprivation therapy, and chemotherapy. These management options have their side effects. Even though there is no specific acceptable optimal treatment for prostate cancer, a combination of treatment options agreed upon by the physician-in-charge and the patient is strongly recommended [34].

1. ACTIVE SURVEILLANCE (AS) AND WATCHFUL WAITING (WW)

Prostate Cancer Screening, although beneficial, has been associated with a significant amount of overdiagnosis, which often results in increased risks of overtreatment with unavoidable adverse effects. Conservative treatments such as active surveillance and watchful waiting have helped to reduce these harmful effects in favorable risks PCa.

Active surveillance (AS) is a management modality that involves the use of regular testing for disease progression to provide delayed treatments with curative intent[35]. AS has been reported to show positive results by several studies. For instance, a long-term cohort study that included 993 prostate cancer patients that opted for active surveillance reported just 2.8% with metastatic disease and 1.5% death as a result of prostate cancer in a 15-year time frame36. Another study which involved the use of active surveillance on 2,907 patients concluded that active surveillance was a safer choice in favorable-risk PCas37.

The tests and protocols in active surveillance are not standardised. However active surveillance usually involves repeated Digital Rectal Examinations (DREs), biopsies. There are variations in the criteria for Active Surveillance, but one of the most reported protocols for active surveillance involve men with low-risk disease (International Society of Urological Pathology (ISUP) grade 1 (Gleason score 3+3=6), T1c-T2a and PSA <10ng/mL), but some include intermediate-risk disease (ISUP grade 2 (Gleason score 3+4=7), T1c-T2 and PSA 10–20ng/mL 38. Patients might be required to switch to other treatment modalities in cases of increased anxiety of the patient about the current management method, disease progression, development of other comorbidities[39] etc.

On the other hand, watchful waiting involves the administration of non-curative androgen deprivation therapy on symptomatic progression. It is not curative; it is merely palliative. Although active surveillance has been reported to be more effective than watchful waiting, it is still preferred in certain conditions. Some of those conditions include old age, presence of comorbidities, increased likelihood of mortality,9 etc.

2. SURGERY

Surgery is a management modality of prostate cancer that has been used for many years now and is still relevant even in present times. However, the indication for surgery, the approach to surgery and even the methods of surgical management of prostate cancer have been slightly modified over the years. Also, surgery is mostly used now as part of a multitherapy treatment plan rather than a monotherapy[40].

Radical prostatectomy (RP) is the most applicable surgery type for prostate cancer. Although, depending on the conditions, it could be associated with pelvic lymphadenopathy40 or orchidectomy41. According to the European Urology Association, the patients more likely to benefit from RP are those with a biopsy Gleason score ≤ 8, the serum PSA level < 20 ng/ml, and the tumor ≤ cT3a42. The criteria may vary slightly from region to region, but it is widely acceptable that RP is preferred in high-risk to intermediate-risk prostate cancers. This is because it has not shown many benefits in low-risk cancers, especially when compared to active surveillance or watchful waiting.

Radical prostatectomy (RP) also has major side effects that cannot be ignored. The most common and major side effects are urinary incontinence and erectile dysfunction9. Other side-effects include changes in orgasm, loss of fertility, inguinal hernia, lymphedema[43]. The side-effects are more likely to occur in older men.

Despite these side effects, the benefits of radical prostatectomy cannot be ruled out. For instance, a SEER-based ((Surveillance, Epidemiology, and End Results) study carried out by Culp et al., reported higher five-year OS and disease-specific survival rates in patients who underwent radical prostatectomy (67.4% and 75.8%) than in those treated with brachytherapy (52.6% and 61.3%) or those without any local therapy (22.5% and 48.7%).

Currently, there are different approaches to surgery. They include perineal, retropubic, laparoscopic and robot-assisted types [44]. However, no major difference in the post-operative side effects has been noticed based on the side-effects.

3. RADIOTHERAPY

Radiotherapy or Radiation therapy simply involves the use of radiation to kill the cancer cells. Like Surgery, it is a major option to be considered in high-to-intermediate-risk prostate cancers that are localised9. Radiotherapy has also been found useful in patients that cannot undergo surgery [45]. The radiation is usually targeted at the prostate, to reduce/avoid damage to other tissues. There are various techniques used in delivering radiation specifically to the cancerous cells in the prostate. The major types are external beam radiation therapy and brachytherapy.

External Beam Radiation therapy (EBRT)

It is the most common type of radiation therapy used in treating cancers. It involves the use of a machine to deliver high-energy rays targeted directly at cancer cells [45]. There are several types of EBRT depending on the types of rays being delivered, the technique used in delivering the rays, etc. It could be used in combination with androgen deprivation therapy to reduce the effect of radiation on the normal body tissues[46].

Brachytherapy

This form of radiation therapy involves the direct implantation of radiation in the prostate gland using seeds, injections, or wires under the guidance of transrectal ultrasound. It could be done permanently (low dose) or intermittently (high dose)[46]. Brachytherapy has been shown to be preferred to EBRT, particularly in young people, because they lack side effects such as urinary/sexual dysfunctions[47].

Radiotherapy has been reported to show better urinary/sexual outcomes compared to Radical prostatectomy in patients[37]. However, in the long term, there does not seem to be any significant difference in either treatment option.[37]

4. CRYOTHERAPY

This technique involves the use of extreme cold (either in the form of supercooled liquid or gases). It could involve killing the entire prostate gland or focal therapy (whereby only the cancer cells are killed). Focal cryotherapy has been shown to have better outcomes and is currently preferred to complete cryosurgery of the prostate gland[48]. Side effects such as urinary continence and sexual dysfunction are also less common with cryotherapies. A recent study reported urinary incontinence and erectile dysfunction in just 1.8% and 3.1% of patients that received focal cryotherapy[49]. useful in patients that cannot undergo surgery [45]. The radiation

5. CHEMOTHERAPY

This treatment technique involves the use of drugs to kill the cancer. It is not a first-line treatment for prostate cancer. It is usually used in cases of metastatic castration resistant cancer or hormone refractory prostate cancer[50]. Some drugs used in chemotherapy for prostate cancers include docetaxel, mitoxantrone, doxorubicin, vinblastine, paclitaxel, and some others[40] Chemotherapy was initially only known for reducing pain and increasing the quality of life, in relation to prostate cancer. However, there is evidence now that shows that chemotherapy, especially docetaxel-based therapy can help improve the survival rates in prostate cancer patients [50].

6. ANDROGEN DEPRIVATION THERAPY (ADT)

According to Huggins and Huges, prostate cancers were androgen-dependent, and deficiency of androgens would lead to the death of the cancers[51]. Therefore, hormonal therapy/androgen-deprivation therapy simply employs techniques that suppress the availability of androgens in the body, thereby leading to the death of the cancer cells. While active monitoring, surgery and radiation therapy are standard care for localized disease, androgen-deprivation technique is a front-line treatment for metastatic disease[51].

Some of the androgen-deprivation therapy (ADT) agents used are long-acting gonadotropin-releasing hormone (GnRH) agonists (goserelin, histrelin, leuprolide, and triptorelin) or GnRH antagonists (degarelix)[52] which decrease production of luteinizing hormone (LH) or Follicle stimulating hormone (FSH). The drop in LH and/or FSH helps in reducing testosterone to castrate levels, thus eliminating the chances of survival of tumor[52].

However, ADT agents have been associated with side effects such as increased risks of cardiovascular diseases,

1. It is important to provide counselling on the potential risks and benefits before subjecting men to prostate-specific antigen (PSA) testing.

2. Individualised risk-adapted strategy for early detection should be offered to well-informed man with life expectancy of at least 10–15 years.

3. Early PSA testing should be offered to well-informed men at an elevated risk of having PCa:
- Men >50 yr. of age
- Men >45 yr. of age with a family history of PCa
- men of African descent >45 yr. of age
- Men carrying BRCA2 mutations >40 yr. of age

4. Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 yr. for those initially at risk:
- Men with a PSA level of >1 ng/mL at 40 yr. of age
- Men with a PSA level of >2 ng/mL at 60 yr. of age

Postpone follow-up to 8 yr. in those not at risk

5. Early diagnosis of PCa that is based on life expectancy and performance status should be stopped; men who have life expectancy of < 15 years are unlikely to benefit.

metabolic diseases (e.g., diabetes), skeletal abnormalities, hot flushes, etc[52].

PREVENTION- Screening and Early Detection

As mentioned previously, prostate cancer is usually asymptomatic at early stages and starts showing symptoms where the disease is becoming advanced. Therefore, leaving the detection of cancer to the presentation of symptoms is not advisable. Also, it is known that early detection and treatment improves the prognosis of most cancers. As such, screening could be seen as a technique to prevent poorer outcomes.

However, Screening for prostate cancer remains controversial, and not recommended in most countries. A reason for this is the overtreatment and overdiagnosis associated with the screening process. Following the review of available studies, the EAU-EANM-ESTRO-ESUR-SIOG developed a guideline for prostate cancer screening [9].

CONCLUSION

While the incidence of prostate cancer might have increased slightly over the years due to overtreatment and overdiagnosis, the methods of treatment and diagnosis are still largely similar. Still, there has been advancement in understanding the progression of the disease and its management.

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