Mini Review: Prostate Cancer Diagnosis and Therapy

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Abstract

Cancer, a non-communicable illness, is the leading cause of death worldwide. In 2030, cancer is expected to exceed 21 million cases and 13 million cancer deaths globally. One of the most prevalent and significant types is prostate cancer (PCa). It is commonly associated with adenocarcinoma, which develops from the mucous glands within the organ. This review highlights available detection systems, and therapeutic options in PCa management. One prevention of deadly PCa is early diagnoses, such as prostate-specific antigen (PSA) screening or genomic profiling. Further testing like MRI or CT scan may also be needed to detect cancers that have progressed to other body regions. There are several possible treatments for PCa, including watchful cancer waiting, surgery, radiotherapy, hormone therapy, and chemotherapy. Based on current studies, androgen deprivation therapy (ADT) combined with docetaxel therapy enhanced great results to treat advanced PCa. The latest development, called theranostics, is a single entity that can perform both diagnostic and therapeutic functions. It can detect disease borders, track therapy in real-time, and provide prognostic data. The FDA has already authorized two prostate-specific membrane antigen (PSMA) positron emission tomography (PET) devices: including Gallium 68 PSMA-11 (Ga 68 PSMA-11) and Pylarify (piflufolastat F 18).

Keywords: prostate cancer, prostate-specific antigen (PSA), docetaxel, androgen deprivation therapy (ADT), theranostics

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Introduction

Cancer is a non-communicable disease which is expected to rank as the leading cause of death worldwide. In most cases, lifestyle-related factors including tobacco and obesity remain the major contributors of attributable cancer. In addition, environmental factors (e.g., air and water pollution), bacteria, and virus infections, as well as family history can also induce human cancers. It was reported that the cancer cases worldwide in 2020 were 19.29 million incidence and 9.95 million mortality cases (Sung *et al*., 2021), and it is estimated to increase to 21.61 million new cancer cases and 11.36 million cancer deaths in 2025 (Ferlay *et al*., 2020). Furthermore, the global cancer burden is projected to reach 24.04 million cases and 12.9 million deaths from cancer in 2030 with breast, prostate, and lung cancer are remaining as the major cancer diagnoses (Rahib *et al*., 2014; Zarocostas, 2010).

Cancer development is associated with the accumulation of genetic mutations and also epigenetic changes resulting in the loss of control in cellular growth of cancer cells, which could invade normal tissues and organs, and spread throughout the body (Hanahan & Weinberg, 2011; Sharma *et al*., 2010). There are hundreds of different types of cancers, which can have distinct behaviours with various treatment approaches.

Prostate cancer (PCa) is the most common cancer diagnosed in men and a major cause of cancer-related male mortality (Siegel *et al*., 2013). In 2020, it was predicted that the PCa incidence reached 1.4 million new cases with 375,304 mortalities worldwide (Sung *et al*., 2021). The incidence rates are highest among men in developed countries, including North America, Northern and Western Europe, and Australia/New Zealand, as well as in Sub-Saharan Africa, while mortality rates are highest in developing countries. According to recent studies, the differences of incidence and mortality rates of PCa among countries are associated with genetics, environmental factors, general wellness and lifestyles, and access to

early detection and health services (Bray *et al*., 2018; Taitt, 2018). This review will focus on the recent advancements in detection and treatment modalities for PCa management.

What is Prostate Cancer?

PCa is primarily associated with adenocarcinoma, growing from the mucous glands inside the organ. Then, the cancer cells proliferate and spread to the surrounding prostate tissue, starting to form tumor nodules (Jensen *et al*., 1980). Like other solid tumor malignancies, PCa can spread to distant parts of the body, commonly into the bone. A study showed that approximately 80% of PCa deaths were related to bone metastases (Bubendorf *et al*., 2000). In clinical application, cancer staging is used to define the extent of spread of PCa. This clinical stage is generally based on physical examinations, and other detection methods (e.g blood tests, imaging tests or biopsy), commonly using TNM system with stages ranging from 0 to 4, and subclassified in every stage using the letters A, B, and C. The higher the number of a stage, describes the larger the tumor size and the further the extent of spreading from the main tumor (Figure 1) (Cheng *et al*., 2012).

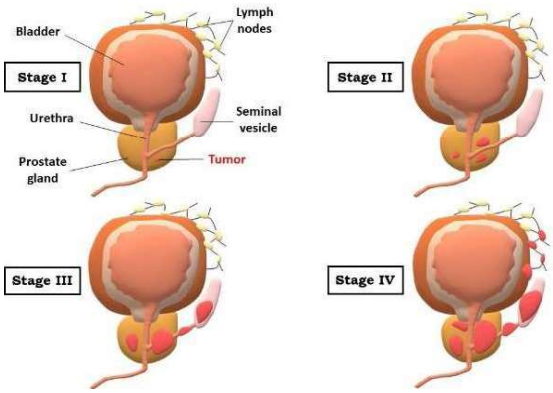

Figure 1. Stages of PCa. Stage I, tumor is only present in one side of the prostate; Stage II, tumor has progressed in one side or both sides of the prostate, but does not spread outside; Stage III, tumor has grown significantly, extends beyond the seminal vesicle; Stage IV, tumor has grown more advanced, invades adjacent tissues other than the seminal vesicle, such as bladder neck, lymph nodes, rectum, or another part of the body.

Prostate Cancer Detection

Prostate epithelial cells, both normal and cancerous, synthesize a certain glycoprotein known as prostate-specific antigen (PSA). This serine protease enzyme has main functions in ejaculation and coagulum hydrolysis. Despite being normally secreted in urine or semen, in some abnormal conditions, elevated levels of PSA also can be detected in blood. Thus, PSA is a common serum biomarker in early detection of prostate cancer (NCI, 2021; Aronson & DeKernion, 2007; David & Leslie, 2021; Gao *et al.*, 2019; Sandhu & Schlegel, 2004).

A prostate-specific antigen screening has been widely used for early detection of PCa resulting in a higher number of incidences recorded. Some studies suggest that PSA testing has resulted in improved treatment and has contributed to the modest reduction of mortality from PCa (Welch & Albertsen, 2009). However, raised PSA level in the serum is also found in benign conditions, such as benign prostatic hyperplasia (BPH) and small tumor, which means relying on PSA testing alone in prostatic cancer detection, would potentially cause overdiagnosis (David & Leslie, 2021). Overdiagnosis is defined as detection of tumors, -either benignant or malignant- through screening that are not life-threatening and unlikely to be recognised clinically or symptomatically without the screening (Loeb *et al*., 2014; NCI, 2021). Overdiagnosis could lead to unnecessary further assessments as a final screening, including prostate biopsies and radical prostatectomies (Velonas *et al*., 2013).

These non-essential confirmation tests have resulted in side effects such as urinary bleeding, rectal bleeding, hemoejaculation, and high risk of infectious complications, as well as psychological effects, including depression and anxiety (Minervini *et al*., 2014). Furthermore, the inefficiency of PSA screening also increases health care spending (Fireman *et al*., 1997).

Consequently, to improve the accuracy of PCa detection, researchers have been developing innovative diagnostic tools for effective screening methods, expecting better diagnostic capabilities, including highly sensitive and selective, reliable and accessible, non-invasive procedures resulting in low risk of harm to the patient, and low costs to reduce

the economic burden. In the past few years, the biological fluids have been used as sources of biomarkers to distinguish between healthy and PCa patients. In general, urine, blood, prostate tissue, and seminal fluid are used to identify tumor-specific compounds, which have increased significantly in PCa patients. However, urine is more favourable as a source for detection since it has several advantages, including inexpensive, non-invasive procedure for collection, easy to handle, and rich in metabolite substances.

Several potential biomarkers exist in the urine, such as DNA (single nucleotide polymorphisms, copy number variations, and methylation), RNA (mRNAs, long non-coding RNAs, and microRNAs) and protein, as well as exosomes and other metabolites which are useful for PCa detection and may improve existing clinical testing methods (Bax *et al*., 2018; Eskra *et al*., 2019). One of DNA-based markers in urine is methylated DNA. Methylated DNA is a prospective biomarker in PCa detection since it frequently occurs during the early stage of tumor development, and is able to be detected in urine. Two examples of PCa biomarkers are methylated *GSTP1* and *APC*, which are tumor suppressor genes, important in preventing DNA damage and cell overgrowth, respectively. Pyrosequencing, droplet digital polymerase chain reaction (ddPCR) and methylation-specific PCR are several methods to quantify DNA methylation, which provide accurate and sensitive assessment (Yoon *et al.*, 2012; Greene *et al.*, 2008; Richiardi *et al.*, 2013).

In term of nucleic acid-based PCa markers in urine, RNAs are the most extensively studied. Among them are PCA3 and TMPRSS2, which are prostate specific and are overexpressed in prostate cancer. Common methods to detect urinary RNA biomarkers are quantitative reverse transcription PCR (RT-qPCR) and transcription-mediated amplification (TMA) (Eskra *et al.*, 2019).

Aside from DNA and RNA, proteins also serve as potential urinary biomarkers which are specific to PCa. Protein markers in urine consist of cellular antigens from exfoliated prostate cells, proteins secreted into prostatic fluid, as well as protein in the enclosed extracellular vesicles, for instance, 5α-reductase, transferrin, and zinc α2-glycoprotein. Even though protein concentration found in urine is relatively lower than in blood, recent technologies are able to overcome the challenge of detecting the small amount of protein. There are diverse methods in PCa-specific protein detection which are high throughput and reproducible, including enzyme-linked immunosorbent assay (ELISA), immunoturbidimetric assay, radioimmunoassay, western blotting, gelatin zymography, and mass spectrometry (Eskra *et al.*, 2019).

Further examination may be performed to detect the spreading tumors in distant parts of the body using several imaging tests, including Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scans or bone scans. Study shows that MRI, using either 1.5 or 3.0 Tesla magnets, and with or without endorectal coil, can improve PCa detection and prevent overdiagnosis (Mayor, 2018; Penzkofer & Tempany-Afdhal, 2014). A bone scan, also known as a radionucleotide scan, is performed by injecting small amounts of radioactive material called tracers into the body. These tracers collect in bones and emit gamma radiation that can be detected and converted into images. The primary purpose of the bone scan is to determine whether prostate cancer has migrated to the bone, which is a very common occurrence. Therefore, a bone scan is highly recommended for patients diagnosed in the late stage of cancer to confirm bone metastases (Chong *et al*., 2014; Lin *et al*., 2017).

Another examination method to prove the spread of PCa in distant organs is by using a monoclonal antibody with radiolabeled tag. Indium-111 capromab pendetide scan (ProstaScint®; Cytogen Corporation, Princeton, NJ) approved by FDA for imaging PCa to detect metastases, particularly in the lymph nodes. This radiolabelled monoclonal antibody binds to prostate-specific membrane antigen (PSMA), the best-known PCa biomarker. The roles of ProstaScint® are basically to improve the accuracy of PCa staging and to detect the recurrent disease (Taneja, 2004). However, a study reports that this imaging agent is not sufficient for detection of bone metastases as the most common metastatic site of PCa, since the ProstaScint cannot identify most sites of abnormalities in bone uptake on bone scan (Bander *et al*., 2003).

Prostate Cancer Treatments

History of cancer treatments has been recorded since ancient Egyptian and Greek where healthy diets and surgical strategies were used for the main cancer treatments. In the late 19th century, when X-rays were discovered, radiotherapy was used for cancer treatment. Then, the revolution of pharmacological approaches resulted in the use of chemotherapeutic drugs, such as doxorubicin which had a cytotoxicity effect for numerous cancer types. Furthermore, the revolution of anti-cancer therapy discovered monoclonal antibodies with the first clinical trial was in 1992, and according to a report in 2021, there are at least 45 different monoclonal antibodies that have been approved and marketed for the treatment of various types of cancers (Arias-Pinilla & Modjtahedi, 2021). Finally, in recent years, comprehensive genomic profiling is being developed to be used in routine clinical testing, providing more accurate risk assessment methods. The genomic profiling is able to identify localized and aggressive PCa. This method is used to guide selection for targeted therapy and enables personalized medicine to optimize the management of PCa therapy (Chung *et al*., 2019; Grasso *et al*., 2015).

Several PCa treatments are available, including cancer watchful waiting, surgery, radiotherapy, hormone therapy and chemotherapy (Goldstraw, 2006). The treatments will depend on the cancer stage. For localized PCa, where the cancer growth is only in the prostate organ without spreading into nearby tissues or distant metastases, the treatment options include cancer watchful waiting and active surveillance, surgery, and radiation. Cancer watchful waiting and active surveillance involve a series of tests to monitor the progression, to prevent significant development of the disease, and to maintain the quality of life. In general, watchful waiting is appropriate for men whose cancer is unlikely to create problems during their lifespan. However, in certain circumstances, cancer may progress more rapidly than predicted and cause symptoms; in these cases, treatment can be administered to control the malignancy and manage any associated symptoms. Active surveillance, by contrast, is for men who have slow-growing cancer that has not moved outside the prostate (localized cancer). It involves more regular hospital tests than watchful waiting, such as MRI scans and prostate biopsies. Moreover, if some therapies are needed, they will usually aim to cure the cancer.

Surgery and radiation are more effective for patients who suffer a more significant PCa, with higher PSA level and palpable tumor under physical examinations. These treatments can reduce the risks of PCa progression and metastases. However, these treatments may have several disadvantages. Side effects related to urinary control and sexual functions are commonly experienced by most post-surgery patients. For patients who have radiation, several side effects are observed, including bowel dysfunction and toxicity, nocturia, and urinary problems (Litwin & Tan, 2017).

In an advanced PCa disease, initial treatment is conducted by using androgen deprivation therapy (ADT), a hormonal therapy to slow the production of testosterone to keep the PCa under control. However, this treatment has several adverse reactions, such as fatigue, sexual dysfunction, hot flashes, osteoporosis, and increase the risks of heart diseases and dementia (Nead *et al*., 2017; Nguyen *et al*., 2011, 2014). Furthermore, in general, ADT can only control the disease for 1 to 1.5 year and the majority of patients develop progressive PCa after this treatment (Seidenfeld *et al*., 2000).

In order to improve advanced PCa treatment, ADT administration along with chemotherapy drugs has been recommended by various health care organizations. Study shows that a combination of ADT and chemotherapy docetaxel have resulted in better outcomes including a decrease in PSA level, lower level of mortality, and prolong overall survival in PCa patients (Sweeney *et al*., 2015). Docetaxel belongs to the taxane class which has been used in standard management treatment of metastatic PCa for many years. Combination therapy of docetaxel with prednisone is used as a gold standard for first-line chemotherapy in men with metastatic castration-resistant prostate cancer (CRPC) (Basch *et al*., 2014; Saad & Hotte, 2010). However, clinical data shows that chemotherapy using a combination of docetaxel with estramustine and prednisolone caused PCa patients to suffer from severe toxicity (Kuramoto *et al*., 2013). In addition,

around 47% PCa patients relapse after chemotherapy treatment with combination of docetaxel and mitoxantrone followed by surgery (Garzotto *et al.*, 2010). Furthermore, a significant number of patients develop resistance to docetaxel and do not respond to this therapy. Thus, improvement of treatment for this group of patients is highly important, since limited treatment options are available (Hwang, 2012). A study shows that a novel tubulin-binding taxane, called cabazitaxel, is effective for docetaxel-resistant metastatic CRPC patients. Treatment using a combination of cabazitaxel and prednisone also improved overall survival. However, this therapy is also highly toxic with common adverse effects such as diarrhea and neutropenia (de Bono *et al.*, 2010).

In recent years, therapy management for patients with metastatic CRPC has been expanded to increase survival rates, reduce pain, and improve quality of life using several novel targeting agents as new second-line drugs, including enzalutamide, abiraterone acetate in combination with prednisone, and immunotherapy using sipuleucel T (Cornford *et al.*, 2017). Enzalutamide, a second generation of androgen receptor inhibitor, was originally designed for the treatment of patients with non-metastatic CRPC. However, it can be an option as the first-line therapy in patients with metastatic CRPC. In general, this therapy is well tolerated in both non-metastatic and metastatic CRPC with common adverse events, including hypertension, headache, and hot flashes (Scott, 2018). Abiraterone acetate, a pro-drug of abiraterone, is a CYP17 inhibitor which is able to block androgen biosynthesis preventing prostate tumor growth. A study shows that abiraterone acetate in combination with prednisone has significantly improved the efficacy and prolonged survival rates. The main adverse events are commonly related to cardiac and liver-function disorders, as well as increased mineralocorticoid level including hypertension and hypokalemia (Yang, 2011). Initially, abiraterone acetate plus prednisone was approved as the second-line therapy after docetaxel. However, after a phase III clinical study in 2013, this combination therapy has been approved as the first-line therapy for metastatic CRPC (Ryan *et al.*, 2013).

Another new therapy for metastatic CRPC is utilizing immunotherapy, redirecting patients' immune systems to diagnose and eliminate cancer cells. Sipuleucel-T, therapeutic cancer vaccine approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), effective for patients with low PSA level, with minimal symptoms or without any symptoms of metastatic CRPC. This immunotherapy prolongs overall survival and reduces the risk of death by metastatic CRPC. Low grade of adverse events were reported such as chill, fatigue, nausea, back pain and muscular weakness (Kantoff *et al.*, 2010; Pieczonka *et al.*, 2015). Denosumab, a monoclonal antibody targeting receptor activator of NF-kappaB ligand (RANK-L), is also reported as a metastatic CRPC immunotherapy approved by US FDA, which aim to prevent bone osteoclastogenesis and bone turnover (El-Amm & Aragon-Ching, 2016; Helo et al., 2012).

Radium 223 dichloride (Ra-223), an isotope of radium, is a specific radiopharmaceutical agent that uses high-energy, short-range (<100 μm; 2-10 cell diameters) alpha particles preferentially to target bone metastases. The alpha-emitter generates primarily double-stranded DNA breaks, resulting in a powerful and highly localized cytotoxic effect in the target locations while having a negligible effect on nearby healthy tissues, making it a favorable and safe treatment. Ra-223 has been approved in the US and Europe for metastatic CRPC patients who have bone metastases, acting as calcium mimetic which selectively binds to bone metastases sites. It has been reported that Ra-223 has overall survival benefits and exhibits overall improvement with less adverse events (Parker *et al.*, 2013). Other bone-targeting agents in metastatic CRPC therapy approved by US FDA, including zoledronic acid, which is a bisphosphonate therapy that potently inhibits osteoclast-mediated bone resorption and denosumab, which is a monoclonal antibody targeting Receptor activator of NF-kappaB ligand (RANK-L) (El-Amm & Aragon-Ching, 2016).

It has been reported that all emergence treatment options for metastatic CRPC have shown a significant impact on survival rates, which can improve the quality of life of PCa patients. However, metastatic CRPC is still incurable. Several new therapeutic agents are under clinical evaluation for metastatic CRPC therapy based on biomarker-selected patients, such as PD-1 and CTLA-4 based checkpoint

inhibitors, PARP inhibitor, tyrosine-kinase inhibitor and PSMA-targeted therapy. Along with the increasing therapeutic options for metastatic CRPC, it is anticipated to identify the best treatment strategy for every single patient to improve the clinical outcomes, including achieving the longest survival rate, preventing the resistance and side effects, and minimizing the cost of treatment (Nuhn *et al*., 2019).

Development of Theranostics in PCa

Theranostics is a term used to describe the combination of diagnostic and therapeutic capabilities within one single entity. This platform offers the opportunity to delineate disease boundaries, monitors therapy in real time and offers prognostic options (Fuchs *et al*., 2015; Pearce *et al*., 2014; Peng *et al*., 2015). History of theranostics in PCa is back to the use of imaging agent ProstaScint®, the radio-labelled anti-PSMA antibody targeting metastatic PCa. Currently, numerous PSMA ligands have been studied for both detection and treatment of PCa, including antibodies, aptamers and small molecule ligands. These PSMA targeting agents are labelled with radionucleotide such as Lutetium (Lu)-177 and actinium (Ac)-225.

Lutetium (Lu)-177 is a radionuclide which emits both β- and γ-radiation and could act as a theranostic isotope (Figure 2). In pharmaceutical application, Lu-177 is chelated to a peptide to effectively deliver and localise cytotoxic radiation to relatively small volume of tumors and destroy them with minimal damage to the neighboring normal tissues. Valuable characteristic of Lu-177 is that it has strong binding affinity to PSMA and highly efficient internalization into prostate cancer cells. Moderate-energy beta particles and low-energy gamma photons provide Lu-177 with a beneficial aspect in low radiation dose. Another advantage of Lu-177 in cancer therapy is its long half-life which not only minimize decay loss, but also required in purifying procedure, performing quality control and administration (Kim & Kim, 2018; Dash *et al.*, 2015; Khreish *et al.*, 2022).

Actinium (Ac)-225 is an alpha-emitting radioisotope which is administered to patients resistant to Lu-177 PSMA therapy. Similar to Lu-177, Ac-225 needs to be attached to a molecule which would selectively target cancerous tissue and deliver the radiation to the cancer area with minimum harm to the surrounding healthy cells. Actinium-225 (Ac-225) causes higher rates of double-strand DNA damage in prostate cancer cells with less tissue penetration and minimal side effects in normal cells. Thus, Ac-225 is considered to be more efficacious than Lu-177. However, its relatively short half-life (10 days), and its lack of availability limit its promising application (Muthukrishnan, 2021; Doelen *et al.*, 2018).

These radionucleotides combined with PSMA (radioligand therapies) are used as a theranostic concept for personalized medication, showing significant clinical results improvement in metastatic catastration-resistant prostatte cancer management (Kratochwil *et al*., 2016; Machulkin *et al*., 2016; Rahbar *et al*., 2018; Virgolini *et al*., 2017).

As of today, there are two PSMA positron emission tomography (PET) which have been approved by FDA; Gallium 68 (Ga 68) PSMA-11 and Pylarify (piflufolastat F 18) (FDA, 2020, 2021). Ga 68 is advantageous for routine clinical exams since commercial germanium-68 generators enable on-site generation of Ga 68 without using a cyclotron. However, Ga 68 has a physical half-life of only 68 minutes. As a result, at big centers with a high number of patients, the requirement for many generators concurrently doubles the expenditures. Due to the limitation, the F 18-labeled PSMA (half-life: 110 min) tracers can be used to increase the capacity at relatively moderate cost. Moreover, F 18 has lower positron energy than GA 68 (0.65 MeV vs. 1.90 MeV), resulting in a theoretically higher image resolution (Sanchez-Crespo, 2013; Dietlein *et al.*, 2015).

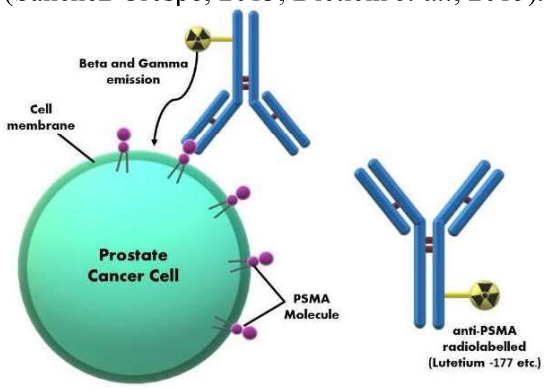

Figure 2. The targeted ligand binds PSMA on PCa cells. Once linked to the neoplastic cell, the 177Lu atom releases strong beta and gamma rays. As a result, radiation that damages DNA is generated.

Conclusion

Development of PCa testing and therapy are being researched throughout the world. Early diagnosis using PSA is not considered as a perfect method as the first screening of PCa. Therefore, several approaches are being developed and applied to get better precision in PCa diagnosis. As well as detection, the improvements in therapy are being made among standard methods for treating PCa. Finally, the combination of diagnostic and therapeutic, called theranostics are being implemented for better delineate and monitor therapy in real time and offer prognostic options.

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