Zodwa Dlamini *Editor*

Transforming Prostate Cancer Care

Advancing Cancer Treatment with Insights from Africa

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Preface

In the vast expanse of medical challenges, few issues demand as much attention and innovative scrutiny as prostate cancer. This book, "Transforming Prostate Cancer Care: Advancing Cancer Treatment with Insights from Africa," unfolds by recognizing prostate cancer not solely as a disease but as a complex problem that necessitates a thorough exploration. In Part 1, "Understanding Prostate Cancer," we lay the groundwork for this exploration, delving into the evolving landscape of prostate cancer care. We navigate through the intricacies of pathogenesis, risk factors, and the critical importance of early detection, acknowledging these aspects as foundational elements in addressing the complex problem at hand. Part 2, "Diagnostic Advances and Precision Medicine," scrutinizes the multifaceted nature of prostate cancer diagnosis. Here, we discuss innovative techniques and biomarkers, paving the way for transformative advancements that promise to enhance precision in addressing the diagnostic complexities of this formidable problem. Part 3, "Innovative Treatment Strategies," addresses the heart of the matter—revolutionary treatments that are reshaping the landscape of prostate cancer care. From targeted therapies to immunotherapy, surgical innovations, and breakthroughs in advanced prostate cancer management, we navigate through the dynamic solutions that stand poised to transform our approach to this complex problem. In Part 4, "Comprehensive Patient Care and Future Outlook," we acknowledge the holistic dimensions of prostate cancer care. From integrative approaches to survivorship and quality of life, we explore solutions that go beyond the traditional medical paradigm, offering a comprehensive response to the multifaceted problem of prostate cancer. This book invites you to confront the complexities of prostate cancer alongside us. As we journey through the foundational understanding to innovative solutions, our collective goal is to transform the landscape of prostate cancer care and make strides toward solving this complex problem.

Pretoria, South Africa — Zodwa Dlamini

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Editor and Contributors

About the Editor

Zodwa Dlamini In the realm of Molecular Oncology, Professor Zodwa Dlamini stands as a dedicated force, unwavering in her commitment to advancing precision oncology in Africa. At the heart of her career is the pivotal role as the Founding Director of the Pan African Cancer Research Institute (PACRI). Holding additional prestigious positions such as Director of the SAMRC Precision Oncology Research Unit (PORU) and DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Professor Dlamini demonstrates full dedication to advancing precision medicine in the ongoing battle against cancer. Beyond institutional leadership, she serves as a distinguished member of the American Association for Cancer Research (AACR) Regional Advisory Committee on Sub-Saharan Africa. In this capacity, she actively guides the AACR Pathology Resources in Africa Advisory Group, identifying strategies to address gaps in cancer pathology services across the African continent. The exceptional work in the field has earned Professor Dlamini the esteemed appointment as a distinguished Cancer Immunology Jury Member for the prestigious 2024 Innovators in Science Award. Sponsored by Takeda and administered by the New York Academy of Sciences, this accolade recognizes ground-breaking research in Cancer Immunology on a global scale. Her role on the jury affords her the privilege of providing invaluable input and guidance to the selection process, contributing a unique global perspective. Notably, Professor Dlamini is the Guest Editor and a member of the Editorial Advisory Committee (EAC) for the 2023 edition of the South African Health Review (SAHR), a special edition focusing on fortifying cancer services in South Africa. Her contributions also extend to the African Organization for Research and Training in Cancer (AORTIC), where she actively influences the organization's strategic direction and mission as a member of the Research Committee Scientific Advisory Board. The recognition of Professor Dlamini's dedication to advancing cancer research in Africa culminated in a Special Award from the Council and Executive of the African Society of Morphology, leading to her admission as an "Honorary Fellow" of the West African College of Morphologists. Moreover, she holds the esteemed titles of an Overseas Fellow of the Royal Society of Medicine (London), a Professional

Member of the New York Academy of Sciences (USA), and a member of the Academy of Science of South Africa. These affiliations underscore her significant contributions to the field of Science. Through her multifaceted efforts, Professor Zodwa Dlamini remains steadfast in her commitment to shaping the ever-evolving landscape of cancer research. Her journey is driven by an unshakable belief that cancer can be conquered, paving the way for a healthier and more equitable world.

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Part I

Understanding Prostate Cancer

The Evolving Landscape of Prostate Cancer Care

1

Zodwa Dlamini, Rodney Hull, Thifheli Luvhengo, and Kevin Gaston

Abstract

Prostate cancer is the second most commonly diagnosed cancer in men, and GLOBOCAN estimated that there were over 1.4 million newly diagnosed cases in 2020. The incidence of prostate cancer is much higher in high-income "developed" countries, but the mortality rates are comparatively higher in low- to middle-income "developing" countries. This is in part due to the cancer being diagnosed at a later stage where treatments are more difficult and less effective. In South Africa, prostate cancer overtook basal cell carcinoma as the most commonly diagnosed cancer in men. South Africa has many of the same problems as many other LMICs (low- and middle-income countries) when it comes to prostate cancer. Prostate cancer screening used to be limited to digital rectal exams and prostate biopsies with the ability to test blood samples for the presence of prostate serum antigen (PSA) only being recently available in many countries and of limited utility. However, the identification of new biomarkers, the use of AI (artificial intelligence), and the combination of imaging techniques and biop-

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sies promise to revolutionize the speed, accuracy, and availability of screening for prostate cancer. At the same time, advances in the treatment of prostate cancer have occurred in every treatment option, with new surgical procedures, new radiopharmaceuticals and radiotherapy techniques, new chemotherapeutic drugs, the increased application of immunotherapy, and better understanding of the mechanisms underlying castration resistance. At the same time, there has been an acknowledgment of the important role played by integrative medicine in ensuring that patients undergoing treatment or those that have survived treatment have a good quality of life and as such these interventions must ensure the patients' psychological well-being as well as their ability to deal with any physiological changes or alterations that have resulted from either the disease or the treatment. This chapter serves as a basic introduction to the concepts which will be covered in the chapters of this book.

Keywords

Prostate cancer incidence · Prostate cancer mortality · Digital rectal examination · Prostate-specific antigen · Biomarkers · Fusin biopsy · Castration · Integrative therapy · Quality of life

1.1 Introduction: The Etiology and Epidemiology of Prostate Cancer

Prostate cancer is a major cause of morbidity and mortality for men worldwide. In the developed world, the incidence of prostate cancer is especially higher than in the developing world. However, these developed countries have a lower mortality rate even with higher incidence levels (Fig. 1.1). For instance, in 2020, the United States had 209,512 new cases of prostate cancer with 32,438 deaths. This can be compared to the 13,152 new cases of prostate cancer with 3896 deaths in South Africa in the same year (Siegel et al., 2020). In 2020, there were 1,414,259 new cases of prostate cancer recorded globally with 376,304 recorded deaths (Rawla, 2019). Much of the increased incidence in developed countries is due to higher levels of prostate cancer awareness and more prevalent prostate cancer detection or screening using tests such as prostate-specific antigen (PSA) (Barbieri et al., 2013). The incidence of prostate cancer varies depending on geographical regions and ethnic groups, with Black men having the highest incidence rates of prostate cancer. These incidence rates are approximately 60% higher in Black Americans than in other population groups within the United States (Barbieri et al., 2013). There is less knowledge concerning prostate cancer screening and epidemiology in Africa. In many areas across the continent, the prevalence of prostate cancer screening through the use of the PSA test or digital rectal examination is unknown with the most accurate records coming from Southern and Northern Africa where there is a higher incidence and mortality rate than in Southern Africa (Bashir, 2015).

The genetic basis of prostate cancer in men of African ancestry is not well understood and requires further study (Kim et al., 2022). An analysis of prostate cancer

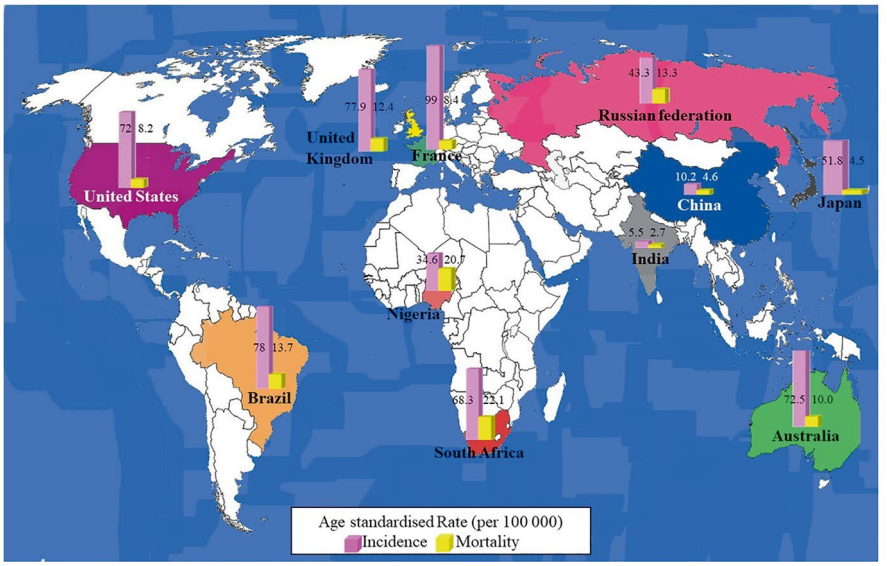

Fig. 1.1 The incidence and survival rates for prostate cancer in selected countries. The lilac bars indicate the prevalence of prostate cancer in various countries and shows that the disease is more common in high-income "developed" countries. However, the yellow bar which represents the mortality rate shows that the survival rates in these countries are much higher relative to those in low- to middle-income countries (Taitt, 2018)

patients from Ghana, Nigeria, Senegal, South Africa, and Uganda identified prostate cancer-associated genetic architectures and found variation among these different populations (Rebbeck et al., 2023). At the same time, the incidence of prostate cancer is increasing in many of these populations in sub-Saharan Africa (Seraphin et al., 2021). Figure 1.2 shows the increase in prostate cancer cases in South Africa between the years 2001 and 2020 as recorded by the South African National Cancer Registry. In South Africa, men of African ancestry tend to present late and have an aggressive disease (Le Roux et al., 2015). Screening and diagnosis of prostate cancer in South Africa also face many problems. The time taken for procedures such as biopsy to be performed in patients suspected of having prostate cancer in South Africa to confirm diagnoses is currently too long to provide effective treatment and management. A study performed in Kwa-Zulu Natal, South Africa, showed that this procedure took an average of three months (Singh et al., 2015). A study found that very few South African men of African or mixed ancestry follow up an elevated serum PSA test with further diagnostic tests (Heyns et al., 2003). Another issue surrounding prostate cancer in South Africa arises due to inadequate education concerning prostate cancer, with a study performed in 2023 in the Limpopo province of South Africa, showing that 64.1% of the men in this study lacked understanding concerning the disease. At the same time, the majority of individuals in the study had a poor attitude toward prostate cancer treatment and management (Maladze et al., 2023).

Early-stage localized prostate cancer that has not spread is generally treatable. However, as the cancer spreads through metastasis, the success of treatment decreases, and the disease is generally considered incurable. This continues to be the case, despite advances in the understanding and treatment of metastatic prostate cancer in the last few decades. These advances have led to men with metastatic castration-resistant prostate cancer (mCRPC), nonmetastatic CRPC (nmCRPC), and metastatic hormone-sensitive prostate cancer (mHSPC) living longer with a better quality of life (Rawla, 2019). By the year 2030, prostate cancer cases are expected to rise to 1.7 million new cases and 499,000 deaths globally. This is due to the exponentially growing population and the larger number of men who are 65 years and older (Taitt, 2018).

1.2 Diagnosis and Screening

A structured program known as active surveillance has been developed and is currently the main technique in the screening and treatment of prostate cancer. This program relies on both monitoring and interventions based on this monitoring and the interplay between them to increase the effectiveness of both treatment and screening of prostate cancer (Choo et al., 2002). This program recommends active surveillance as the best method to manage patients with either low-risk cancer patients or palliative care. This relies on surveillance that is centered around the characteristics of the disease, the health condition of the patient as well as the environment the patient is in, the life expectancy of the patient, any side effects caused by the monitoring or treatment process, and the patient's own wishes and desires (van den Bergh et al., 2009). Active surveillance results in decreased treatment costs, avoiding unnecessary treatments as well as an increase in the quality of the life of the patient. However it does have disadvantages such as an increased chance of tumor metastasis before treatment can be initiated resulting in the need for more complex interventions with more side effects as well as increased anxiety in patients caused by frequent medical examinations (Costello, 2020).

The mortality rate of prostate cancer is directly related to the stage at which the disease is diagnosed, with an early diagnosis resulting in better survival chances. Screening for prostate cancer is traditionally performed through the use of a digital rectal examination (DRE) (Fig. 1.1), involving the insertion of a gloved finger into the patient's rectum. The aim of this exam is to assess the size of the prostate gland and detect any abnormalities in the gland. In recent times, DRE is being replaced in favor of the prostate-specific antigen (PSA) test (Ferlay et al., 2010). This a glycoprotein is secreted by the prostate gland's epithelial cells and is found in both the semen and blood (Barbieri et al., 2013). This allows the levels of PSA to be tested through the use of blood samples obtained from the patient. The cutoff level for increased expression of PSA is 4 ng/mL. Any levels of PSA above this limit indicates the likely presence of prostate cancer, and further testing is indicated (Taitt, 2018). PSA levels between 4 ng/mL and 10 ng/mL have a 25% chance of indicating prostate cancer, while levels above 10 ng/mL indicate a 50% likelihood that the

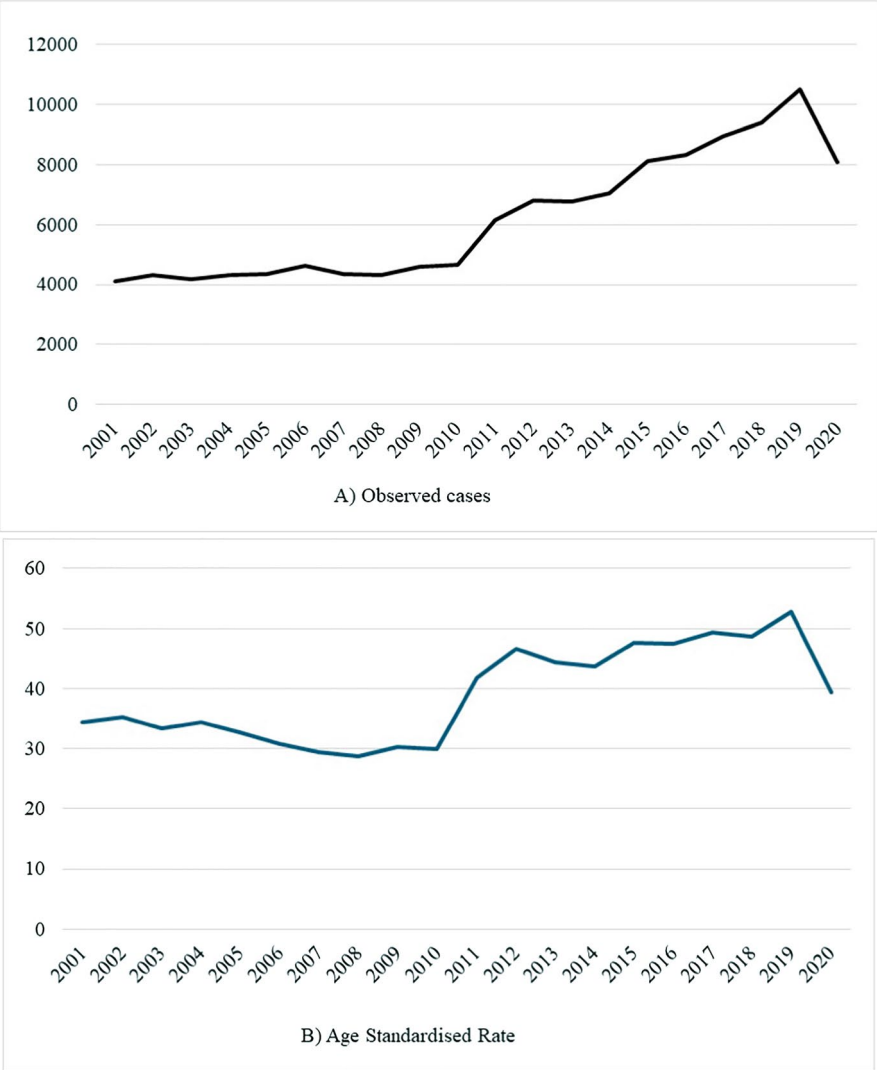

Fig. 1.2 Increasing incidence of prostate cancer in South Africa as recorded by the National Cancer Registry. (**a**) The observed number of cases shows a steady increase in the number of cancer cases until 2020 where the Covid-19 pandemic may have decreased or interfered with screening and diagnosis. (**b**) The age standardized rate shows a greater degree of fluctuation but still demonstrates the trend of increasing prostate cancer incidence (Registry, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020)

patient has prostate cancer (Bashir, 2015) (Fig. 1.3). Increased PSA levels can also indicate a benign pathology, including benign prostatic hyperplasia (BPH) and prostatitis. Additionally, many men have elevated levels of PSA without any

underlying condition, and as such elevated PSA levels must be confirmed using a prostate tissue biopsy (Ferlay et al., 2010).

Prostate biopsies are perfumed using a thin hollow needle to collect a prostate tissue sample through the rectal wall between the anus and scrotum. This tissue sample is then assessed microscopically (Matshela et al., 2014). Individual cells in the biopsy sample can also be analyzed to establish the metastatic potential of the cancer. The results of the biopsy can be negative for prostate cancer and positive for prostate cancer, or it can be classed as suspicious which means that abnormal cells are present. However, these suspicious cells do not have to be cancer cells (Adhyam & Gupta, 2012). The prostate can be located through various means including magnetic resonance imaging (MRI) and transrectal ultrasound (TRUS). MRI can also be used to identify anatomically abnormal prostate glands and identify areas where the biopsy can be taken from Babb et al. (2014) (Fig. 1.3). This has led to changes in the

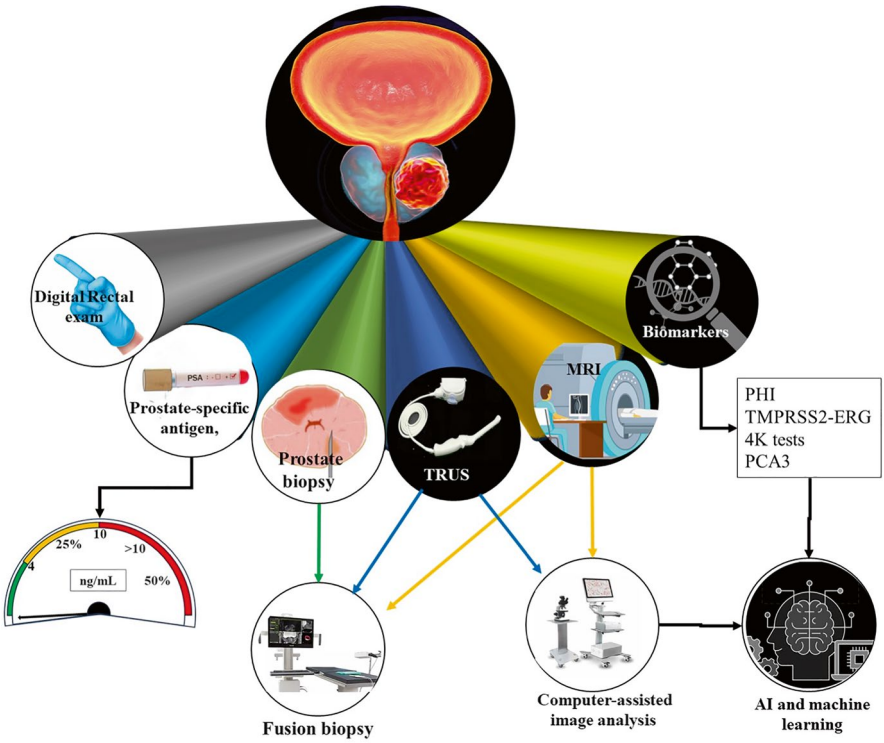

Fig. 1.3 Current and future prostate cancer screening methods. The three screening methods in the white circles on the far left represent the most commonly used or basic screening methods with the digital rectal exam and the prostate-specific antigen tests being confirmed by biopsy. The limits for the presence of PSA and what the levels indicate are reflected in the gauge. Imaging techniques such as TRUS and MRI can be used to guide cancer biopsy collection as well as being used as screening tools. The use of imaging tools can be improved through the use of AI and machine learning, while AI can be used in the search for new and +-more accurate biomarkers for prostate cancer screening

standard diagnostic procedures in many countries, which now recommend an initial MRI scan before any tissue biopsy (Albright et al., 2015). A TRUS is performed using a small ultrasound probe that is inserted into the rectum where it emits a series of sound waves that produce echoes, which the probe reads and turns into an image (Altwaijry et al., 2018).

The use of computer-assisted analysis of medical images in combination with artificial intelligence (AI) and machine learning algorithms has resulted in a more comprehensive list of conclusions that can be made using prostate tissue biopsies. The reliance on PSA is also a shortcoming of blood tests, and in this regard, there are now new novel molecular markers that are being assessed for their use as diagnostic and prognostic biomarkers (Kasivisvanathan et al., 2018). Imaging techniques are also advancing and include new techniques such as multiparametric magnetic resonance imaging (mpMRI) and prostate-specific membrane antigen positron emission tomography (PSMA-PET) (Kasivisvanathan et al., 2018).

Biomarkers can also be used to characterize the stage and aggressiveness of the cancer as well as to assess the response of the cancer to treatment. Some of these new markers include the prostate health index (PHI), the TMPRSS2-ERG fusion gene, 4K tests, and PCA3. These markers have been shown to be useful when used in combination with PSA testing where they can increase the specificity and sensitivity of the PSA test (Alford et al., 2017).

1.3 Personalized Medicine for Prostate Cancer

The risk factors for prostate cancer range from age and ethnicity to obesity. However, the most important risk factor is a family history of prostate cancer. Having a family member diagnosed with prostate cancer increases the risk of a man developing prostate cancer by 50% compared to those with no history of prostate cancer within their family (Chopra et al., 2009). Those individuals with first-degree family members who develop prostate cancer are also more likely to develop prostate cancer at an earlier age (Moran et al., 2012). This implies the presence of prostate cancer susceptibility genes, and this has been reinforced through the use of case-control, twin, and family studies. The presence of specific mutations has been identified in hereditary prostate cancer, and men who possess these mutations in these genes have an increased chance of developing prostate cancer (Wen et al., 2015). Genomic variations can occur due to single-nucleotide polymorphisms (SNPs), somatic copy number alterations (SCNAs), and copy number variations (Moran et al., 2012). Moreover, mutations that inactivate tumor suppressor genes or activate oncogenes are important underlying causes of prostate cancer (Turanli et al., 2018). In men of African ancestry, the presence of genetic variations that predispose them to prostate cancer is more prevalent, indicating the role of ethnicity and the environment as contributors to the development of prostate cancer (Wen et al., 2015).

By assessing the genomes of prostate cancer patients and men at high risk of developing prostate cancer, it has been established that approximately 5.5% of these individuals had mutations in DNA repair genes. These include mutations in the

ATM, BRCA1, and BRCA2 genes. As such, genes such as BRCA genes, HOX genes, the ATM gene, RNase L (HPC1, lq22), MSR1 (8p), and ELAC2/HPC2 (17p11) can be used as common biomarkers for prostate cancer (Wen et al., 2015).

Precision medicine involves tailor-made solutions to precisely address an individual's health needs. In prostate cancer, precision medicine would involve the use of gene-specific treatment for the disease. In addition to this, precision medicine would also take the specific environment of an individual into account and how their lifestyle and environment could influence gene expression through processes such as altered transcription and epigenetic patterns. Apart from the identification of new therapeutic targets, these altered molecular patterns can be used as diagnostic or prognostic biomarkers. These patterns could also be used to monitor treatment response allowing doctors to alter the treatment as indicated by the presence or absence of specific molecular markers or patterns.

The ultimate aim of precision medicine would be to allow healthcare professionals to make more informed and accurate decisions regarding the care and treatment of men with prostate cancer as well as to increase the sensitivity and accuracy of screening, diagnosis, and classification of prostate cancer patients (Mateo et al., 2020). Examples of treatment decisions that are currently influenced by the presence of genetic mutations include the presence of BRCA1 and BRCA2 mutations in men with mCRPCs, indicating that these patients can be successfully treated with the PARP inhibitors rucaparib or olaparib. Olaparib is also indicated in the treatment of prostate cancer patients with mutations in ATM, CDK12, CHECK2, CHECK1, PALB2, PP2R2A, and RAD54L (Giri et al., 2022). At the same time, the presence of BRCA mutations suggests that surgical- and radiotherapy-based interventions will not be successful (Liu et al., 2018).

1.4 Treatment of Prostate Cancer

The initial choice of the correct treatment for prostate cancer is based on prognostic factors such as the PSA level, the TNM stage of the tumor, and the Gleason's score (Table 1.1). In addition to these prognostic markers, the treatment choice is influenced by the health of a patient. These patient health-related factors include the presence of any comorbidities, the patient's urinary function, and finally their age (Trewartha & Carter, 2013). By classifying patients according to risk based on cancer prognosis, the most suitable treatments can be selected, with the final choice being based on the desire of the patient (Dunn & Kazer, 2011). Stage I–III prostate cancer is normally treated by prostatectomy or radiotherapy. At the early stage (I), prostate cancer can be managed through increased surveillance. Androgen-based therapies such as surgical or pharmacological castration are the recommended treatment for stage IV and some stage II patients. This is especially true in high-risk stage II patients. Many of the pharmacological strategies rely on first-generation antiandrogen drugs which act on the androgen receptor. However, it is common for stage IV prostate cancers to become resistant to these drugs due to mutations in the

Table 1.1 Prostate cancer stages

AJCC stage	Stage grouping	Stage description
Cannot be assessed	Tx, Nx	
Stage I	T1, N0, M0 Grade Group 1 (Gleason's score six or less) PSA less than 10	No evidence of tumor, nodal infiltration, or metastasis **T1a:** tumor incidental histologic finding in 5% or less of tissue resected **T1b:** tumor incidental histologic finding in more than 5% of tissue resected **T1c:** tumor identified by needle biopsy found in one or both sides, but not palpable
	T2a, N0, M0 Grade Group 1 (Gleason's score six or less) PSA less than 10	Confined to the prostate: T2a: confined to one-half or one side
Stage IIA	T2b, N0, M0 Grade Group 1 (Gleason's score six or less) PSA at least 10 but less than 20	T2b: More than one-half or one side
Stage IIB	T2, N0, M0 Grade Group 2 (Gleason's score 3 + 4 = 7) PSA less than 20	Cancer confined to the prostate can be detected by a digital rectal exam or transrectal.
Stage IIC	T2, N0, M0 Grade Group 3 or 4 (Gleason's score 4 + 3 = 7 or 8) PSA less than 20	Cancer confined to the prostate can be detected by a digital rectal exam or transrectal.
Stage IIIA	T2, N0, M0 Grade Group 1 to 4 (Gleason's score eight or less) PSA at least two	Cancer confined to the prostate can be detected by a digital rectal exam or transrectal.
Stage IIIB	T3 or T4, N0, M0 Grade Group 1 to 4 (Gleason's score eight or less) Any PSA	T3: extra prostatic extension T3a: extra prostatic extension T3b: Tumor invades seminal vesicle. T4: Tumor invades adjacent structures.
Stage IIIC	Any T, N0, M0 Grade Group 5 (Gleason's score 9 or 10). Any PSA	Any T: Cancer may or may not have spread. N0: Has not spread to nearby lymph nodes. M0: no metastasis
Stage IVA	Any T, N1, M0 Any grade group Any PSA	N1: metastases in regional node(s)
Stage IVB	Any T, any N, M1 Any grade group Any PSA	M1a: nonregional lymph node(s) M1b: bone(s) M1c: other site(s) with or without bone disease

androgen receptor gene, and patients with castration-resistant tumors have a poor prognosis (Lima et al., 2019) (Fig. 1.4).

Despite the current poor prognosis for metastatic castration-resistant prostate cancer (mCRPC), there is a hope for more effective treatments in the future. These treatments are based on the identification of cell checkpoint biomarkers in these tumors, leading to attempts to treat these tumors using checkpoint inhibitor therapy. These therapies rely on targeting genes involved in DNA repair pathways such as poly(ADP-ribose) polymerase (PARP). Another target for drug-based therapy is prostate cancer-specific antigen (PSMA) (Hofman et al., 2018). Chemotherapy is an important treatment option especially in mCRPC and metastatic hormone-sensitive prostate cancer (mHSPC) where it can prevent tumors from developing resistance to therapies that target the androgen receptor (Aggarwal et al., 2018; Halabi et al., 2014).

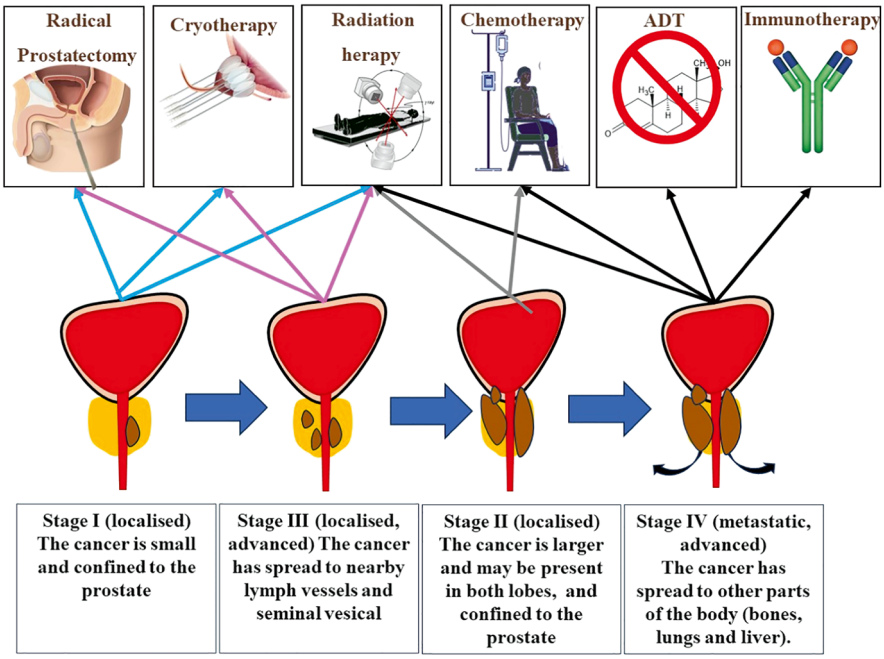

Fig. 1.4 The various treatment options for each stage of prostate cancer. The figure defines the various stages of prostate cancer and depicts the most suitable treatment options for each of the stages. The light blue arrows point to treatments suitable for early-stage cancers. The lilac arrows point to treatment options suitable for stage II prostate cancer. Treatments suitable for stage III prostate cancer are indicated by the gray arrows and those for stage IV prostate cancer are indicated by black arrows

1.4.1 Radical Prostatectomy

Radical prostatectomy is the surgical removal of the prostate gland. The procedure is performed by making a small incision at the perineum to access the prostate gland (Mellman et al., 2011). The procedure is recommended in patients with tumors showing no metastasis and is normally done in conjunction with external beam radiation therapy, brachytherapy, or cryotherapy. Patients best suited to undergo a prostatectomy are those younger than 70 years of age, have few or no comorbidities, and where the cancer is localized to the prostate (Mohan & Schellhammer, 2011). Prostatectomy does have associated complications including incontinence and erectile dysfunction as a result of damage to the urinary sphincter and erectile nerves that occur as a result of the surgery (Mohan & Schellhammer, 2011).

1.4.2 Cryotherapy

Cryotherapy involves the use of extreme cold to destroy aberrant tissue such as tumors. In prostate cancer, the cryoprobe is guided to the prostate gland using ultrasound guidance. The cryoprobe is then used to freeze the tissue of the prostate to between −100 °C and −200 °C for about 10 min (Mouraviev & Polascik, 2006). The procedure has some limitations and drawbacks including urinary incontinence and urinary retention, erectile dysfunction, fistula, and rectal pain (Mouraviev & Polascik, 2006).

1.4.3 Radiation

One of the most effective therapies to treat prostate cancer is radiation therapy, with this treatment being able to effectively kill prostate cancer cells through the use of high-energy radiation. The aim of radiation therapy is to specifically target the prostate cancer tissue and kill it using DNA damaging radioactive high-energy rays or particles, without killing the surrounding normal tissue. Radiation therapy is commonly used in patients where surgical interventions are not possible (Baskar et al., 2012). The radiation can be delivered to the prostate cancer cells through the use of brachytherapy, where radiation emitters are placed in the body or through the use of high beam radiation, where a beam of radiation is transmitted through the skin to reach the target cancer sites (Baskar et al., 2012). Brachytherapy is a type of radiation therapy where a radioactive source (emitter) is placed within the body into the prostate gland, at the site of the cancer. This is achieved using transrectal ultrasound to guide the insertion of radioactive seeds, injections, or wires. There are two different methods known as either low- or high-dose treatments. Low-dose treatments involve the placement of seeds that emit radiation into the prostate cancer tissue. These emit lower-energy radiation and lose the radioactivity slowly over a longer time (Potosky et al., 2000). High-dosage radiation emitters are called high-dosage emitters because they emit higher-energy radiation. However, while this

higher-energy emission is more damaging to cancer cells, it is also more likely that the radiation affects other organs and tissues surrounding the prostate. The speed of brachytherapy is one of its main advantages as it can be performed in a single day. It also has no effects on the risk of the patient developing incontinence or erectile dysfunction. There are side effects associated with this treatment. These include urinary retention and voiding (Wallner et al., 1997).

1.4.4 Chemotherapy

Docetaxel is the most commonly used chemotherapy drug in the treatment of prostate cancer and is marketed under the brand name Taxotere (Wallner et al., 1997). It is a type of taxoid, which are diterpenes that are composed of four isoprene units. Docetaxel is used as the first-line chemotherapy to kill CRPC tumors. It functions by inhibiting microtubule depolymerization by binding to β-tubulin. This blocks mitotic cell division, which results in the initiation of apoptosis in affected cells (Wallner et al., 1997). The needles of various species of yew trees contain a taxoid compound, which was used to derive the antineoplastic taxoid cabazitaxel. This compound is marketed under the brand name Jevtana. In prostate cancer, this second-generation therapy is used to prevent docetaxel resistance (Wallner et al., 1997). Another target for chemotherapy drugs is the androgen receptor (AR). One drug that targets this molecule is the second-generation drug, enzalutamide which was approved for use in treating prostate cancer in 2012. This drug has the ability to act as a competitive inhibitor, competing with androgen for binding sites on the androgen receptor. It also inhibits the recruitment and nuclear translocation of AR cofactors. Finally, it also acts to prevent the formation of AR heterodimers, thereby preventing the transcriptional activity of AR (Ito & Sadar, 2018).

1.4.5 Androgen Deprivation Therapy and Castration-Resistant Prostate Cancers

Due to the role played by androgen signaling in prostate cancer development and progression, androgen deprivation therapy (ADT) has been used as the cornerstone of prostate cancer treatment since the 1940s. This therapy involves decreasing the levels of testosterone by lowering its synthesis via surgical or chemical castration. Surgical castration involves performing an orchiectomy, the removal of one or both testicles. Chemical castration is performed using gonadotropin-releasing hormone (GnRH) agonists. These agonists include compounds such as goserelin, histrelin, leuprorelin, or triptorelin. It can also be achieved using GnRH antagonists, which include compounds such as degarelix and relugolix. ADT is used at all stages of the disease, from the early newly diagnosed stages where it is used as neoadjuvant and adjuvant treatment to metastatic prostate cancer. ADT is also used in combination with other therapies including radiotherapy. In cases where the cancer has spread from the prostate into surrounding lymph nodes, patients are treated using radical

prostatectomy followed by ADT as an adjuvant therapy (Shore et al., 2020). Traditional ADT was unfortunately associated with cardiovascular pathology. However, the development of the new oral AR-antagonist relugolix has helped to alleviate this problem. Studies with this agent show that its use results in fewer cardiovascular events compared to other chemical ADT agents such as leuprolide (Shore et al., 2020).

ADT has also been the treatment of choice for advanced, localized prostate cancer (stage III) and metastatic prostate cancer (stage IV) (Shore et al., 2020; Prostate Cancer Trialists' Collaborative Group, 2000). The effectiveness of this treatment can be increased when ADT is performed in conjunction with other AR targeted therapies. Although this combination of ADT and AR targeted therapy is effective in treating most patients with metastatic prostate cancer, eventual resistance to the treatment can occur. In addition to this this, treatment is not curative on its own and needs to be supplemented further with radiation or surgery (Marech et al., 2012). In most cases, resistance to ADT (known as castration resistance) occurs approximately 10–15 months after treatment is started (Sweeney et al., 2015). The effectiveness of ADT is monitored through PSA testing and medical imaging. PSA levels inversely correlate with treatment effectiveness and patient survival outcomes (Harshman et al., 2018).

1.4.6 Immunotherapy

Immunotherapy is a therapy relying on a biological process to treat cancer. Immunotherapy is not as commonly used to treat prostate cancer with many immunotherapies only recently being approved (Madan & Gulley, 2010). Immunotherapy is commonly used to treat advanced stage prostate cancer and is useful in that it shows decreased side effects compared to treatment such as chemotherapy and radiation therapy. Immunotherapy has traditionally not been shown to be as effective in the treatment of prostate cancers compared to other solid tumors (Fay & Graff, 2020). The drug pembrolizumab received FDA approval to be used to treat unresectable or metastatic solid tumors that other treatments had failed to treat. Pembrolizumab is an anti-PD1 immune checkpoint inhibitor and is also used to treat tumors with microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) (Marcus et al., 2019) and more recently tumors with tumor mutational burden (TMB) $\geq$10 mutations/megabase (Marcus et al., 2019). Despite the fact that prostate cancer was shown to respond to pembrolizumab, it has been less successful in mCRPC as responses varied wildly in different patients (Hansen et al., 2018; Abida et al., 2019). This demonstrates the importance of developing and using an assay to establish if and which immunogenic prostate cancers respond to a single-agent checkpoint inhibitor. The effectiveness of immunotherapy in mCRPC may also depend on factors such as the tumor level of mismatch repair deficiency, TMB, and tumor-infiltrating lymphocytes. Immunotherapy can also be used in combination with other therapeutic agents to increase immune infiltration (Lu et al., 2017).

1.5 Integrative Care and Maintaining the Quality of Life

The quality of life of men with prostate cancer is impacted, either by the disease itself or as a consequence of the treatments they have received. These include urinary, sexual, and bowel problems, fatigue (Watson et al., 2016; Lehto et al., 2015), and an increased risk of osteoporosis and cardiovascular problems (Resnick et al., 2013; Nguyen et al., 2011). Apart from these, the disease also affects men's psychological well-being, anxiety, and depression, as well as causing financial difficulties (Armes et al., 2009; Ream et al., 2008; Sharpley & Christie, 2007). Traditionally health services to address the needs of these patients were provided by specialist secondary care services. However, the demand for these services as a result of more prostate cancer patients surviving or living longer has meant that it is becoming more common for primary care providers to play a bigger role in providing integrated care to these patients, both during and after treatment (Tomasone et al., 2016). The field of medicine concerned with the treatment of these patients is known as integrative oncology and is different from alternative medicine since it is based on patient safety and recommends treatment based on the best available evidence. Unlike the alternative medicine's antagonistic approach to conventional medical treatment, integrative oncology is aimed at supplementing or supporting patients undergoing conventional treatment (Tomasone et al., 2016).

Interventions for these patients can be divided into lifestyle modifications, mind-body interventions, and the use of natural products. Lifestyle modifications include treatments centered around changes in diet, exercise, sleep hygiene, and stress management. They may also include behavioral changes such as changing the patient's social environment and teaching them to avoid risky behavior. These factors have all been shown to contribute to not only a decreased risk of developing prostate cancer but also play a role in reducing morbidity related to the effects of the cancer or its treatment on the patient (Tomasone et al., 2016). Mind-body-based therapeutic interventions include guided movement practices, which include the practice of tai chi or yoga. They also include contemplative and relaxation practices, which includes meditation. Other mind-body interventions include massage therapy and acupuncture (Complementary & Maryland, 2018). Natural products are defined as "a variety of products, such as herbs, vitamins and minerals, and probiotics" (Complementary & Maryland, 2018). Patients commonly use these products to alleviate symptoms of cancer or treatment. However, many patients have unrealistic expectations that the products can cure their disease. Unfortunately, the use of these natural products can be dangerous, especially in those patients who are undergoing active cancer treatment since they can interfere with the treatment. Natural products with antioxidant activities can decrease the effectiveness of radiation or chemotherapy (Lawenda et al., 2008). Natural products with anticoagulant activity can cause problems during perioperative periods (Levy et al., 2017). Some natural products may even interfere with ADT as they can be phytoestrogen compounds (Liu et al., 2005). Finally, natural compounds that stimulate the immune system may interfere with immunosuppressive therapy (Deng et al., 2009). While some natural compounds can alleviate symptoms, there is also a lack of quality control, and this

combined with the potential harm they can cause means that healthcare professionals should engage with patients concerning the use of natural products.

Improving the quality of life of patients and survivors can be achieved through the provision of good supportive care. The aim of this care is to improve the ability of the patients and their family to cope with both the cancer and its treatment (Hui et al., 2013). The needs of prostate cancer patients and survivors are once again related to psychological distress and physical issues related to sexuality-related issues and lower urinary tract symptoms (Ream et al., 2008). Much of the psychological stress in patients is due to the unknown, and this can be alleviated by providing the patient with information regarding treatments and probable outcomes (Sinfield et al., 2009). An important technique for dealing with psychological issues around prostate cancer is known as reframing. Much of the distress around prostate cancer arises due to the patient having concerns over returning to a normal life and their inability to do so. Reframing is concerned with changing the way the patients think about their life, what is normal, and their experience with the disease (Bailey et al., 2007).

1.6 Translational Research

Translating the findings of basic research into clinical applications is a challenge that must be met to ensure the rapid advancement of prostate cancer treatment and management. One of the best ways of testing the results of fundamental research especially research surrounding the use of new novel treatments is through the use of preclinical models such as patient-derived xenograft models or patient-derived organoids (Germain et al., 2023). For instance, since it has been discovered that the development of resistance to many androgen-based therapies relies on the reactivation of the androgen receptor, many research projects have attempted to identify the molecular mechanisms and pathways underlying this reactivation. In studying the effects of interventions targeting these processes with preclinical models, it has been difficult to model the situation of castration (absence or decrease in testosterone production) (Germain et al., 2023). One of the ideas that may revolutionize the translation of fundamental research and improve the data obtained from models is data-driven translational research. This is based on the accumulated multidimensional prostate cancer data available due to advances in biotechnologies and computational sciences. This allows for the integration of genomic and gene expression data, from next-generation sequencing, with clinical physiological data, and from mobile smart devices, allowing the development of translational informatics (Lin et al., 2020).

1.7 Conclusion

This book aims to be a comprehensive and authoritative exploration of the latest advancements in prostate cancer research and treatment, while providing a thorough examination of the evolving landscape of prostate cancer care. The book covers key areas such as diagnostics, genomics, targeted therapies, immunotherapy, surgical innovations, survivorship, and more. Finally, this book will focus on the treatment and research on prostate cancer in a South African context.

This first chapter of the book delves into the understanding of prostate cancer, including its pathogenesis, risk factors, and the importance of early detection. It also explores the role of genetic testing and screening methods in identifying individuals at high risk, enabling early detection. This will be followed by a chapter focusing on advancements in the diagnosis of prostate cancer. This includes innovative techniques and biomarkers used in prostate cancer diagnosis. It will also review the role of imaging modalities, such as multiparametric magnetic resonance imaging (mpMRI) and positron emission tomography (PET), in improving the accuracy of prostate cancer detection and localization. Additionally, it highlights the potential of liquid biopsies and genetic markers to revolutionize diagnosis. The next chapter explores the field of genomics and its impact on prostate cancer care. It will discuss the importance of genetic profiling and molecular characterization in guiding treatment decisions and predicting patient outcomes. It will also emphasize the emergence of precision medicine and personalized approaches in prostate cancer care and review advancements in targeted therapies. Chapter four will focus on advances in prostate cancer treatments. These include targeted treatments, novel drugs that can specifically target prostate cancer cells, and immunotherapies. The chapter will go on to discuss the modes of action of these treatments as well as the clinical evidence supporting their use. The following chapter will highlight the promise immunotherapy holds for the treatment of prostate cancer. It will discuss the role of immune checkpoint inhibitors, therapeutic vaccines, and adoptive cell therapies in activating the patient's immune system to recognize and eliminate cancer cells. It will discuss the remarkable clinical responses observed in certain subsets of patients and ongoing research efforts to further optimize immunotherapeutic approaches in prostate cancer. This will be followed by a chapter focusing on radiation-based therapies. This chapter explores the advancements in radiopharmaceuticals and radiotherapy techniques for prostate cancer. It will discuss the role of targeted radiation sources, such as radium-223 and lutetium-177, in treating metastatic disease. It will also explore the new field of precision radiation therapy, including stereotactic body radiation therapy (SBRT) and high-dose rate brachytherapy, and the role these new therapeutic approaches play in minimizing side effects. Chapter eight discusses the transformative impact of surgical innovations in prostate cancer treatment. It explores the advent of minimally invasive techniques, such as laparoscopic and robotic-assisted surgery. It will highlight the advantages these new techniques have over traditional open surgery, such as enhanced precision, reduced invasiveness, quicker recovery, and improved surgical outcomes. The chapter also discusses ongoing advancements in surgical technologies and techniques. The following