Chapter 1
Brief Overview of Prostate Cancer Statistics, Grading, Diagnosis and Treatment Strategies

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Abstract This chapter provides a brief overview of prostate cancer statistics, grading, diagnosis and treatment strategies that are discussed in more detail in the subsequent chapters of this book and the companion book titled "Clinical Molecular and Diagnostic Imaging of Prostate Cancer and Treatment Strategies". It also points to websites that provide additional useful information for patients affected by prostate cancer and for students and teachers to obtain practical and updated information on research, new diagnostic modalities and new therapies including new updated clinical trials. Three sections are focused on overview of prostate cancer statistics; overview of detection, diagnosis, stages and grading of prostate cancer; and treatment possibilities and options.

Keywords Prostate cancer · Grading · Diagnosis · Treatment · Cytoskeleton · Microtubules · Microfilaments · Metastasis · Chemotherapy

1.1 Introduction

This chapter introduces various aspects of prostate cancer that are discussed in more detail in the subsequent chapters of this book and the companion book titled "Clinical Molecular and Diagnostic Imaging of Prostate Cancer and Treatment Strategies". It also points to websites that provide additional useful information for patients affected by prostate cancer and for students and teachers to obtain practical and updated information on research, new diagnostic modalities and new therapies including new updated clinical trials.

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1.2 Overview of Prostate Cancer Statistics

Along with skin cancer prostate cancer is the most common cancer in American men. Prostate cancer ranks third in the leading cause of cancer-related deaths in American men behind the first and second leading cancer-causing deaths resulting from lung cancer and colorectal cancer, respectively. It is a disease mostly occurring in older men with 6 cases out of 10 being diagnosed in men aged 65 or older with an average age of about 66 at the time of cancer diagnosis. According to the American Cancer Society (https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html); (https://cancerstatisticscenter.cancer.org/); (/cancer/prostate-cancer/detection-diagnosis-staging/survival-rates.html) so far for 2017 it is estimated that about 161,360 new cases of prostate cancer will occur with about 26,730 deaths resulting from the disease. Confirmed numbers are available for previous years up to 2014. In 2013, 241,740 new cases of prostate cancer were diagnosed and approximately 28,170 men died from the disease. In 2014, 233,000 new cases with 29,480 deaths resulting from the disease have been reported in the US with similar statistics in other countries.

Based on data obtained for 2010–2014, the number of new cases of prostate cancer was 119.8 per 100,000 men per year and the number of deaths was 20.1 per 100,000 men per year. Based on statistical models for analysis, the rates for new prostate cancer cases have been falling for the past 10 years with death rates falling an average of 3.4% each year which has been attributed to early diagnosis and improved treatment options. Current statistics show that 1 out of 7 men will be diagnosed with prostate cancer during his lifespan and that 1 in 39 men will die of the disease.

Prostate cancer is characterized by abnormally dividing cells in the prostate gland resulting in abnormal prostate gland growth. Most men do not die from prostate cancer but will either be affected by a slow growing tumor or live because of steadily improving and effective treatment. Death from prostate cancer mainly occurs due to metastasis when cancer cells spread to other areas of the body including the pelvic and retroperitoneal lymph nodes, the spinal cord, bladder, rectum, bone and brain.

As our life expectancy has increased significantly over the past few decades it can be expected that the male population with prostate cancer will increase accordingly and it will be important to find new approaches to manage or cure the disease. Currently, there are no sure ways to prevent prostate cancer although some dietary suggestions have been advocated which includes nutrition and lifestyle changes. Most of the research on dietary compounds is still ongoing and clear results and recommendations are not yet available. Some compounds have been proposed to prevent or delay prostate cancer and include extracts from pomegranate, green tea, broccoli, turmeric, crocetin, curcumin, flaxseed and soy among others. Vegan diet (no meat, fish, eggs, or dairy products) and exercise have also been proposed to lower the risks of developing prostate cancer but many of these studies are still not conclusive and the dietary approach and effect may be different for different individuals. Most of these studies including studies of botanical compounds have been

tested in animal models to examine the effects on preventing, delaying, or inhibiting prostate cancer but it is not clear how far these results can be extrapolated and applied to human prostate cancer.

The awareness and benefits of early detection and treatment possibilities for prostate cancer has increased success rates to manage or control the disease and new clinical trials are now available to combat the disease in different stages of disease progression. Good progress has been made in developing efficient chemotherapies that will be discussed below in Sect. 1.3.

1.3 Overview of Detection, Diagnosis, Stages and Grading of Prostate Cancer

The various diagnostic methods are only briefly mentioned in this chapter and will be discussed more fully in the individual chapters of this book and the companion book titled "Clinical Molecular and Diagnostic Imaging of Prostate Cancer and Treatment Strategies".

Early Detection Tests Early detection of prostate cancer is important for efficient cures but perfect tests for early detection are not yet reliably available. The prostate-specific antigen (**PSA**) blood test had been used for most previous tests but this test has been critiqued because it may miss some cases of cancer while it may indicate the presence of cancer when prostate cancer could not be found. Aside from the PSA test other tumor markers have been determined (reviewed in detail by [6]) which includes the **phi** test that combines the results of total PSA, free PSA, and proPSA. The **4Kscore** test combines the results of total PSA, free PSA, intact PSA, and human kallikrein 2 (hK2) in addition to other factors that may indicate prostate tumor. The prostate cancer antigen3 (**PCA3**) in the urine is also being assessed after digital rectal exam (DRE), as DRE frees some prostate cells that can be assessed in the urine. More freed prostate cells may indicate a likelihood that prostate cancer is present. Other tests examine abnormal gene changes (**TMPRSS2:ERG**) in cells collected from urine after DRE. This gene is typically not found in men without prostate cancer. **ConfirmMDx** is a test for certain genes in cells obtained from prostate cancer biopsies. These tests may be used to better indicate prostate cancer but more research is needed for more reliable non-invasive tests.

Diagnosis Several methods and technologies are available for diagnosis of prostate cancer. It includes transrectal ultrasound (**TRUS**) to obtain images from areas to be selected for biopsies although TRUS may not reliably detect all areas affected by prostate cancer. Color Doppler ultrasound is an improved technology to detect prostate cancer by measuring blood flow within the gland which may more accurately indicate the areas to be selected for biopsies. This technology has been further improved by employing a contrast agent that can be used to enhance the ultrasound images. Combinations of these technologies can be used for improved detection which includes a combination of MRI with TRUS-guided biopsies.

Stages and Grading of Prostate Cancer Knowing the extent (stage) of prostate cancer is an important factor for determining the treatment options. As new technologies have become available to determine the extent of prostate cancer and new treatment options are also available it has been possible to more accurately diagnose and treat prostate cancer in individuals to determine individualized (personalized) medicine options. Newer methods include multiparametric MRI (reviewed in Sarkar [20]; Schütz et al [31]) to determine the extent and the aggressiveness of prostate cancer and treatment options. This involves a standard MRI and one other type of more detailed MRI such as diffusion weighted imaging (DWI), dynamic contrast enhanced (DCE) MRI or MR spectroscopy.

Another newer method to determine the extent and stage of prostate cancer is enhanced MRI to check lymph nodes for the possibility of containing cancer cells. This method involves a standard MRI followed by an MRI detecting injected magnetic particles.

A newer positron-emission tomography (PET) application involves using radioactive carbon acetate instead of labeled glucose to detect prostate cancer in different parts of the body and to evaluate treatment.

The above mentioned methods are used to determine the stage and possible spreading of cancer. The stages and grades of prostate cancer are described in excellent detail at https://www.cancer.net/cancer-types/prostate-cancer/stages-and-grades which also provides excellent illustrations of the different prostate cancer stages which are briefly described in the following.

Staging and grading of prostate cancer refers to the cancer's growth and spread as well as the particular histology and cellular changes within the tumor. The diagnostic tests described above are used to determine the stages and spread of the cancer. Different grading systems are used for different types of cancer. For prostate cancer, 2 types of staging are used, referred to as the clinical stage and the pathologic stage. The clinical stage is determined by using DRE, biopsy, x-rays, CT and/or MRI scans and bone scans. The pathologic stage refers to information obtained during surgery and test results from the pathology laboratory.

In recent years, the grading system has been redefined based on newly gained results from imaging analysis and newly gained knowledge on prostate cancer. The TNM staging system refers to Tumor (T), Node (N), and Metastasis (M) to address the seizes and location of the tumor (T), spreading of the tumor to lymph nodes (N), and metastasis to other parts of the body (M). The results are then combined to determine the stage of cancer for each individual. Five stages are used to assess the extent of cancer in which 0 refers to no cancer while stages I to IV describe the extent of cancer progression. The details of this grading system are available at the above mentioned website (https://www.cancer.net/cancer-types/prostate-cancer/stages-and-grades) and are not described in this brief overview. Cancer stage grouping is then determined. Stage I describes cancer being confined to the prostate; Stage II describes a tumor in the prostate which is still small and has not spread outside the prostate gland but cells are more abnormal than those found in stage I and cancer has not spread to lymph nodes or distant organs; Stage III refers to the cancer having spread beyond the outer layer of the prostate and can be detected in

nearby tissue and also in the seminal vesicles; Stage IV describes a tumor that has spread to other parts of the body, particularly to the bladder, rectum, bone, liver, lungs, or lymph nodes.

Up to recently the Gleason score for grading prostate cancer has mainly been used (reviewed by Giannico and Hameed [9]) and is described as follows. This score is mainly based on morphology/histology/pathology and compares the extent of cancer progression to normal tissue. The Gleason scoring system is the most frequently used grading system and uses a scale of 1 to 5 which determines the pattern of cell growth of the tumor. The specific assessment of cancer cell growth areas are assessed on a scale between 2 and 10 which is then adjusted to the scale of 1–5. Based on the scale between 2 and 10 in recent years physicians are no longer using Gleason scores of 5 or lower for cancers found in biopsies but use 6 as the lowest score to refer to low-grade cancer (reviewed in Giannico and Hameed [9]). A Gleason score of 7 refers to a medium-grade cancer, and a score of 8–10 refers to a high-grade cancer.

On a cellular basis, a Gleason score of x indicates that a Gleason score cannot be determined; a Gleason score of 6 or lower indicates that cells are well differentiated and do not look significantly different than healthy cells; a Gleason score of 7 indicates that cells are moderately differentiated and do not have a pathologic appearance compared to healthy cells; a Gleason score of 8, 9, or 10 indicates that cells are poorly differentiated or undifferentiated and have an abnormal appearance compared to healthy cells. Pathologists have now adopted a Gleason grouping system which simplifies the groups as follows.

Gleason Group I = Former Gleason 6; Gleason Group II = Former Gleason 3 + 4 = 7; Gleason Group III = Former Gleason 4 + 3 = 7; Gleason Group IV = Former Gleason 8; Gleason Group V = Former Gleason 9 or 10.

There are other criteria for staging that have been used by different organizations and are only briefly mentioned here. These relate to risk assessment methods used by the National Comprehensive Cancer Network (NCCN) and the University of San Francisco (UCSF).

The NCCN uses 4 risk-group categories based on PSA level, prostate size, needle biopsy results, and the stage of cancer. The UCSF Cancer of the Prostate Risk Assessment (UCSF-CAPRA) uses a person's age at diagnosis, PSA at diagnosis, Gleason score of the biopsy, T classification from the TNM system, and the percentage of biopsy cores involved with cancer. These criteria are then used in combination to assign a score between 0 and 10 in which a CAPRA score between 0 to 2 indicating low risk, a CAPRA score between 3 to 5 indicating intermediate risk, and a CAPRA score between 6 to 10 indicating high risk.

1.4 Treatment Possibilities and Options

The treatment options are based on the diagnosis that has previously been established by various methods and may include the following. Computerized Tomography (**CT scan)** that uses x-rays to monitor the potential spread of cancer in the body. CT scans will detect cancer that may have spread to lymph nodes or other

organs; Magnetic Resonance Imaging (**MRI scan**) is used to image the soft tissue in the body. MRI uses magnets and radio waves instead of x-rays to obtain more detailed images compared to CT scans. It allows imaging of prostate cancer and prostate cancer spread to the prostate-surrounding tissues; Positron Emission Tomography (**PET scan**) uses a tracer liquid to visualize cancer cells. It is oftentimes employed to find potential cancer remission after treatment; **Lymph node biopsy** is used to determine cancer spread to lymph nodes including lymph nodes in the groin area; **Bone scan** is employed to assess whether or not the cancer has metastasized to bones. For bone scans a low-level radioactive substance is injected to label the bone areas that may be affected by cancer; **Bone biopsy** is performed to assess and confirm results obtained with bone scan. Bone metastasis is among the most frequently observed spreads when prostate cancer metastasizes to different areas in the body. It accounts for about 80 percent of the time when prostate cancer cells metastasize, affecting mostly hip, spine, and pelvis bones. Spreading of prostate cancer cells can occur by direct invasion into bones or through the blood or lymphatic system.

Several treatment possibilities are available to control prostate cancer which are discussed in detail in the companion book titled "Clinical Molecular and Diagnostic Imaging of Prostate Cancer and Treatment Strategies". Specific treatments depend on the stages and individual cancer progression. These treatment possibilities are listed in more detail at the American Cancer Society's website (https://www.cancer.org/cancer/prostate-cancer/treating.html) and include the following.

Active Surveillance but no actions are needed (/cancer/prostate-cancer/treating/watchful-waiting.html).

Surgery (/cancer/prostate-cancer/treating/surgery.html). Surgical techniques are constantly improving with the goal to remove all cancer tissue while lowering the risk of complications and side effects resulting from surgery.

Radiation Therapy (/cancer/prostate-cancer/treating/radiation-therapy.html). Radiation therapy has improved significantly in recent years and new technologies are aimed at applying radiation precisely only to the tumor tissue. New technologies include conformal radiation therapy (CRT), intensity modulated radiation therapy (IMRT), and proton beam radiation. As with surgery, the goal is to reduce side effects resulting from radiation therapy. Details for radiation therapy are available in the chapter by Schütz et al. [31].

High-Intensity Focused Ultrasound (HIFU) is a newer treatment procedure used for early stage cancers. It can be used as a first line of therapy or after radiation therapy to treat tissue that has not responded to radiation therapy. HIFU destroys cancer cells by heat using highly focused ultrasonic beams.

Cryotherapy (cryosurgery) (/cancer/prostate-cancer/treating/cryosurgery.html) is also a treatment option.

Hormone Therapy (/cancer/prostate-cancer/treating/hormone-therapy.html). Several new improvements have been made to hormone therapy and include never drugs such as abiraterone and enzalutamine as well as drugs that block the conversion of testosterone to the more active dihydrotestosterone (DHT), 5-alpha reductase inhibitors, such as finasterine and dutasteride. Hormone therapy is further addressed in the text below.

Chemotherapy (/cancer/prostate-cancer/treating/chemotherapy.html) includes taxol in form of paclitaxel or docetaxel and cabazitaxel that are discussed in the text below and target the microtubule system of fast proliferating cancer cells.

Immunotherapy has seen significant progress in recent years and is aimed at boosting the patient's immune system to destroy cancer cells (reviewed in Yadav et al. [32]).

Vaccine Treatment (/cancer/prostate-cancer/treating/vaccine-treatment.html). This prostate cancer treatment (not a prevention treatment) is still limited and currently employs treatment with sipuleucel-T. Several other treatment possibilities in this line of treatments are still in the research phase or in early clinical trials.

Immune Checkpoint Inhibitors are used to prevent cancer cells from disabling the immune system and include drugs such as pembrolizumab and nivolumab that target the immune checkpoint protein PD-1 and lipilimumab that targets the checkpoint protein *CTLA-4* on certain immune cells.

Targeted Therapy Drugs include angiogenesis inhibitors that prevent the growth of new blood vessels to prevent tumor growth. Some angiogenesis inhibitors are currently being tested in clinical trials.

Bone-directed Treatment (/cancer/prostate-cancer/treating/treating-pain.html) uses radiofrequency ablation (RFA) to control metastatic cancer to bones. RFA uses a CT scan or ultrasound to guide a small metal probe into the tumor-affected area, passing a high frequency current through the probe to heat and destroy the tumor.

These treatments can either be applied individually or in combination with other treatments.

Clinical Trials are also available and these are constantly updated as new possibilities become available (/treatment/treatments-and-side-effects/clinical-trials.html).

Basic research has been important for understanding how prostate cancer develops and how abnormalities can be managed. This research has as a goal to understand and increase the treatment options and find new treatment possibilities. Basic research has opened up new directions and new avenues for new treatment possibilities as had been most apparent by the development of taxanes for biomedical research leading to potent treatment of prostate cancer and other cancers. Some of

the new basic research has yielded promising translational potential and is advancing into testing in animals and in human clinical trials.

In the early stages of advanced prostate cancer androgen deprivation therapy (ADT) can be successful but most often resistance to androgen deprivation occurs and different treatments are needed which includes taxane-based chemotherapy. We do not yet completely understand the mechanisms leading to resistance to androgen deprivation but it likely involves changes in signal transduction pathways that become aberrant in prostate cancer including the Wnt, PDGF and MAPK pathways. Extensive research on signal transduction pathways has provided some indications for targeted therapies to control prostate cancer cell proliferation (reviewed in Yadav et al. [32]).

The history of prostate cancer treatment has been described by Denmeade and Isaacs [4] and has emphasized the achievements of Huggins and Hodges, who first established the role of male steroid hormones in prostate cancer cell proliferation and the beneficial effects of withdrawal to control prostate tumor growth (reviewed in Martin et al. [16]). Much research has been devoted to the AR which resulted in new cell and molecular data that have led to a better understanding of the effects of androgen withdrawal although we still do not yet clearly understand the pathways involved in AR signaling. It is now known that in the absence of androgen, AR is sequestered in the cytoplasm associated with the Heat Shock Protein 90 (Hsp90) super complex and Filamin A before associating with its ligand, DHT [5, 15]. The structural conformation of the nuclear localization signal (NLS) of the AR does not allow its translocation before binding to DHT [15] but after binding to DHT, AR proteins undergo phosphorylation by Protein Kinase A (PKA) that enables translocation to the nucleus. This process is dependent on the microtubule motor protein dynein that facilitates translocation along microtubules in an ATP- dependent mechanism. This translocation allows binding of the AR to androgen responsive elements (ARE) of the DNA, resulting in proliferation, apoptosis resistance, and epithelial to mesenchymal transition (EMT) (Martin et al. [15]; reviewed in Martin et al. [16]).

The AR is involved in a number of different pathways associated with EMT and metastasis. The pathways involve cadherin switches, Wnt signaling, TGFβ signaling, and Notch signaling (Martin et al. [15]; reviewed in Yadav et al. [32]). During EMT, E-cadherin expression is lost which affects interactions with neighboring cells, as proteins associated with tight junctions are downregulated and cell communication is lost. Loss of cellular communication and subsequent aberrant signal transduction cascades will lead to further metastasis.

When resistance to ADT develops many of the subsequent treatment possibilities involve inhibiting abnormal cytoskeletal dynamics and aberrant cytoskeletal functions to mainly target the microtubule and microfilament activities that are implicated in abnormal cell division and in metastasis to pelvic and retroperitoneal lymph nodes, and to bone [11].

Specific cell and molecular mechanisms that are affected in prostate cancer and specific treatment possibilities are addressed in specific chapters of this book and in the companion book titled “Clinical Molecular and Diagnostic Imaging of Prostate Cancer and Treatment Strategies”.

1.4.1 Treatment Possibilities Aimed at Cytoskeletal Abnormalities

The role of the actin and microtubule cytoskeleton in prostate cancer development has been well recognized and drugs targeting their dysfunctions in prostate cancer have been employed successfully with new drugs being developed and tested in laboratory and clinical settings. The cytoskeleton with two of its main components (microtubules and microfilaments) plays a major role in the early stages of prostate cancer initiation leading to abnormal cell proliferation and in cellular mechanisms that allow cancer cells to dissociate from their cellular and tissue organizations to become metastatic. These dissociated cancer cells form seeds to metastasize to different organs, thereby facilitating the epithelial to mesenchymal transition (EMT) (reviewed in detail by [12]). This process includes cells losing their fibroblastic appearance to change their cell shape and become motile. Cell surface changes are significantly associated with changes in the actin cytoskeleton resulting in decreased focal adhesions and downregulation of E-cadherin. Loss of E-cadherin is a critical step in the loss of epidermal adherent junctions that are essential for cells to adhere to each other, allowing cellular communication with neighboring cells and providing cell-cell interactions in normal tissue organizations. Knowing the cell and molecular aspects that are aberrant in cancer development and progression allows the targeted development of therapeutic strategies to eliminate or correct the aberrant processes associated with cancer [23].

As mentioned above, in prostate cancer, the first choice of treatment so far has been the endocrine-targeting approach through androgen deprivation [4] which is highly successful until in many cases tumors become androgen independent and reactivate AR signaling pathways following androgen ablation. The next therapy approach typically employs administration of cytotoxic agents that target the cytoskeleton with the most frequently used microtubule drug taxol [25, 26, 28–30]. While previous studies had used microtubule drugs such as nocodazole or colcemid taxol is unique in that it targets multiple cellular processes to inhibit cell division as well as causing cell destruction. Taxol was isolated from the Pacific Yew tree and modified for the purpose to be used as drug in the 1970's. Taxol binds to microtubules with very high affinity [30], thereby stabilizing microtubules and preventing their dynamic instability that is essential for multiple cellular processes including mitosis and cell division. Paralyzing microtubule functions with taxol results in mitotic block, mitotic cell death and apoptosis [14, 25, 26, 28–30]. Taxol therefore is especially effective in rapidly dividing cancer cells. The specific mechanisms of paclitaxel binding to microtubules have been well studied and discussed above.

Microtubules are highly dynamic cytoskeletal fibers composed of α/β subunit heterodimers that typically are assembled into laterally associated 13 protofilaments to compose one single cylindrical complete microtubule of ca 25 nm diameter. Microtubules display structural polarity characterized by slow growing minus ends and fast growing plus ends. The minus ends can be stabilized by attachment to cellular components such as microtubule organizing centers (MTOCs; centrosomes),

the Golgi apparatus, or cell membranes (reviewed in more detail in Schatten and Sun [22, 26]). Individual microtubules undergo phases of growth (polymerization) and shrinkage (depolymerization) in a process termed 'dynamic instability' which allows varied and a great diversity of functions such as forming the mitotic apparatus that separates chromosomes during mitosis and cell division, and a variety of different functions during interphase including maintenance of cell shape, cell motility, cellular transport of membrane vesicles, macromolecules and organelles such as mitochondria.

The role of centrosomes in microtubule organization and functions has been reviewed in several recent papers [21, 22, 24–27] and will be addressed in Chap. 4 of this book.

As mentioned above, several microtubule drugs are known to either inhibit microtubule polymerization (colcemid, colchicine, nocodazole, podophyllotoxin, and griseofulvin) or prevent depolymerization (taxol, paclitaxel). These drugs have different binding properties to microtubules and had been proposed as anticancer drugs to inhibit abnormal cell divisions but taxol has proven the most potent drug that had been identified through basic research [30] and was further developed for clinical applications by investigators at the National Cancer Institute (NCI). Paclitaxel binds to the β subunit of the microtubule (+) end which dimerizes with the α-tubulin subunit [19]. The binding of paclitaxel to the (+) end of microtubules prevents microtubule elongation and prevents microtubule functions. Taxol also blocks cells in the G1 stage of the cell cycle, causing an additional block in interphase added to the block in mitosis.

Microtubule dysfunctions are frequently observed in aging cells and in mitotic cells in which the highly labile microtubules become dysfunctional resulting in spindle abnormalities and aneuploidy. Destabilization of microtubules in aging cells may play a role in the development of age-related cancers and may provide future targets for the prevention of cancer development due to cellular aging.

The actin and microtubule cytoskeletons play a major role in cancer progression with specific roles of the actin cytoskeleton in cellular migration, invasion and metastasis to secondary sites. The actin cytoskeleton consists of its major fiber, the microfilament (F-actin or filamentous actin) composed of its subunits (G-actin or globular actin). Microfilaments consist of a double-helical structure of actin filaments with an intrinsic polarity. One end can rapidly polymerize, termed the plus-end or barbed-end while the other end is the slow growing end called the minus-end or pointed-end.

F- and G-actin interact with a large group of proteins called actin binding proteins (ABPs) [2]. Over 150 ABPs are known to interact with F- and G-actin making up different microfilament organizations to carry out widely different functions. Components of the highly dynamic actin filament system are constantly rearranged and some moving cells form filopodia containing parallel actin filaments that display motility towards an attachment site. Aberrations of regular organizations and functions can lead to various diseases including cancer. In addition, numerous actin-associated proteins are known to play a critical role in regulating actin dynamics and functions. Cellular regulation of the actin cytoskeleton is essential for normal cell function such as cell division, cell locomotion and a great variety of other functions.

Cofilin is an actin binding protein that severs and disassembles actin filaments. Cofilin plays a role in cancer cells and is involved in forming metastatic lesions in patients [33] which is the result of mis-regulation of cofilin. Another prostate cancer promoting factor is TGF-β that functions as tumor growth suppressor in the early stages of cancer, but it becomes activated and enhances cell invasion leading to EMT and metastasis during the late stages of tumor progression (reviewed in Yadav et al. [32]). TGF-β plays a major role in prostate tumor metastasis and invasion; TGF-β and epidermal growth factor (EGF) both stimulate aberrant cofilin expression [34]. In the early stages TGF-β signaling is required to initiate the invasive characteristics towards metastasis [17]. Together with cofilin TGF-β plays a critical role in remodeling of the actin cytoskeleton [2] towards progression to metastasis. The focal adhesion regulator and effector, talin, that acts as an intermediate between integrins and actin is involved in activation of survival pathways towards metastasis.

Although actin and actin-binding proteins can be targeted to arrest cancer cell growth and metastasis based on the significant role in cellular functions and dysfunctions in cancer, so far potent actin-inhibiting chemotherapies aimed at arresting cancer cell proliferation and metastasis have not yet been developed successfully for the clinic to combat prostate cancer although several excellent possibilities have been advanced for translational potential and clinical trials (reviewed in Brayford et al. [1]). So far, the most successful chemotherapeutic drug against cancer cell proliferation and cancer cell destruction remains the microtubule-targeting drug taxol and its new improved derivatives. This is especially true for patients with castration-resistant prostate cancer (CRPC) for which combination therapies are used such as taxanes combined with antiandrogen strategies to increase the survival rate.

Taxane and taxane derivatives inhibit essential microtubule functions and either arrest cells in their cell cycle or cause apoptosis. As mentioned above, microtubules are major components of the mitotic spindle and microtubule dynamics are essential for chromosome separation into the two daughter cells after cell division. Paclitaxel stabilizes microtubules, thereby preventing microtubule dynamics that are essential for spindle functions and chromosome separation, leaving the cell arrested in mitosis and unable to undergo chromosome separation and cell division. Cells in this arrested stage can either undergo mitotic cell death or apoptosis (reviewed in Schatten [21, 25, 26]). Taxol also blocks interphase functions of microtubules that are important for carrying cargo to their functional destinations. This is important for AR translocation, as the N terminal domain of the AR is associated with the α-tubulin subunit of the microtubule. In prostate cancer cells, interphase microtubules play a role in translocation of the androgen receptor (AR) from the cytoplasm to the nucleus. Taxane-induced blockade of microtubule functions can impair androgen receptor activity in prostate cancer by preventing the translocation of the AR into the nucleus, thereby preventing the associated downstream transcriptional activation of AR target genes [3, 35].

Despite the success of employing paclitaxel (taxanes) in prostate cancer chemotherapy cells eventually develop resistance which is mainly due to an affinity of paclitaxel for the overexpressed P-gp (P-glycoprotein) efflux pump that results in loss of effective treatment. For this reason new taxanes have been developed and a

second generation taxane, cabazitaxel, is now used, which had been developed based on the rational design of the α-tubulin crystal structure [18]. This new taxane drug carries additional methyl groups that are indirectly attached to ring structures, which allows it to pass the blood brain barrier, thereby affecting tumors metastasizing to the brain which is common for late stage prostate cancer [18].

Other newer microtubule-targeting drugs have been developed which includes the epothilones that also cause microtubule stabilization in similar ways as the taxanes [10]. Unlike taxanes, epothilones and its derivatives similar to cabazitaxel are not affected by the P-glycoprotein efflux pumps, therefore not developing resistance but retaining their cytotoxicity [10, 14] although other types of resistance to epothilones can develop [10].

Other prostate cancer drugs are being developed that target different cellular processes. Novel quinazoline-based compounds, with the lead agent, DZ-50, have been developed as antagonist to the α1-adrenoreceptor [7, 8]. DZ-50 affects metastatic potential in vivo by inhibiting angiogenesis, migration and invasion through targeting focal adhesions [13]. It targets talin and fibronectin in focal adhesion complexes [13]. DZ-50 has now moved into Phase I clinical trials for patients with metastatic CRPC.

1.5 Conclusions and Future Perspective

Prostate cancer is the most common non-cutaneous malignancy for men with new cases resulting in deaths each year. In 2014, 233,000 new cases with 29,480 deaths resulting from the disease have been reported in the US with similar statistics in other countries. Multi-modal approaches are oftentimes required to manage prostate cancer and achieve positive outcomes which requires patient-specific evaluation and analysis for specific management.

New advances in prostate cancer biology have led to significant progress in prostate cancer diagnosis and treatment in which individualized medicine plays an increasingly important role. Basic research, improved imaging modalities as well as new clinical trials has opened up new avenues to treat this heterogeneous disease with new possibilities of patient-specific approaches. While progress has been made in early detection of the disease due to improved diagnostic imaging, treatment of advanced stages of prostate cancer is still in the early stages of research but progress can be foreseen due to intense efforts to understand cell migration, epithelial-mesenchymal transition points, and metastasis on genetic, cell, and molecular levels that has become possible with newly developed research methods.

The advent of molecular technologies has significantly improved our understanding of the biological processes underlying prostate cancer. Targeted therapies are now available to inhibit specific signaling pathways that are aberrant in prostate cancer cell populations and we are now able to image signaling molecules with specific markers in live cells. Progress has also been made in designing nanoparticles that may be utilized for imaging and targeted prostate cancer treatment. The joint initiatives and efforts of advocate patients, prostate cancer survivors, basic

researchers, statisticians, epidemiologists, and clinicians with various and specific expertise have allowed close communication for more specific and targeted treatment. Major forces supporting these efforts are the Department of Defense, the American Cancer Society, and several other Foundations that effectively recognized the need for intensified advocacy to find treatments for the disease which has led to falling rates for new prostate cancer death cases to an average of 3.4% for the past 10 years. These efforts are likely to continue due to highly talented and dedicated individuals who are devoted to help combat the disease.

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