Prostate Cancer: Etiology, Diagnosis, and Treatment

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ABSTRACT

Based on cancer statistics in 2025, 313,780 American men were diagnosed with prostate cancer, and 35,770 of them died from the disease; thus, prostate cancer remains a serious health issue for American men. In this article, we review multiple aspects of the disease, including etiology, diagnosis, and treatment. Regarding disease etiology, we summarize current knowledge of prostate cancer initiation and progression, with a focus on androgen receptor signaling. We discuss the genetic landscape of prostate cancer, including alterations in the DNA damage response pathway, FOXA1, SPOP, the PI3K pathway, WNT signaling, AURKA, and MYCN. We also address the potential contribution of inflammation to prostate cancer development. In the diagnosis of prostate cancer, the Gleason score is discussed. Measurement of prostate-specific antigen (PSA) levels has been the gold standard for diagnosing prostate cancer and monitoring disease progression. We also review additional diagnostic methods, including magnetic resonance imaging, the 4Kscore, the Prostate Health Index, and bone scintigraphy. Various treatments have been used clinically. For localized prostate cancer, active surveillance, radical prostatectomy, radiotherapy, and androgen deprivation therapy are available options. For metastatic prostate cancer, androgen deprivation therapy remains the standard of care. For castration-resistant prostate cancer, cabazitaxel and second-generation androgen receptor inhibitors are the major therapeutic approaches. We also review several non-canonical treatment strategies.

1. Introduction

According to the cancer statistics of 2024, prostate cancer (PCa) continues to rank as the third most diagnosed type of cancer and the sixth leading cause of death [1]. As a disease that is closely related to aging, PCa tends to happen in older men [2]. In addition, other determinants such as ethnicity, family history, and hereditary changes of the genome are also implicated in PCa [3]. Androgen receptor (AR) signaling, which is the well-established pathway to sustain PCa's survival and proliferation [4, 5], is essential for disease progression. Accordingly, medical interventions that deplete endogenous androgen, named androgen-deprivation therapy (ADT), remain the major treatment against PCa [6, 7]. Despite the slow progression of this disease, nearly all patients eventually progress to the deadly metastatic castration-resistant prostate cancer (CRPC) that is resistant to ADT. Significant efforts have been put into dealing with this situation, and that leads to the modification

of current therapy regimens and the discovery of novel therapeutic agents.

In the past decades, significant breakthroughs have been made in this field, especially the discoveries of highly selective therapeutic agents targeting PCa vulnerabilities. These unparalleled advances were achieved through the large-scale screening of genomic data using whole-genome DNA sequencing, mRNA sequencing, and proteome profiling, which have delivered unique insights into the molecular contents underpinning different subtypes and the nature of PCa [8, 9]. However, we are still facing new challenges to be solved. Recently, as the immune checkpoint inhibitors have been successful in multiple cancers, immunotherapy in PCa is being intensively investigated [10]. Unfortunately, as one of the "cold tumors", PCa is notorious for its weak induction of immune response and a profound immunosuppressive microenvironment [11]. Further study will need to unravel the molecular mechanism of the
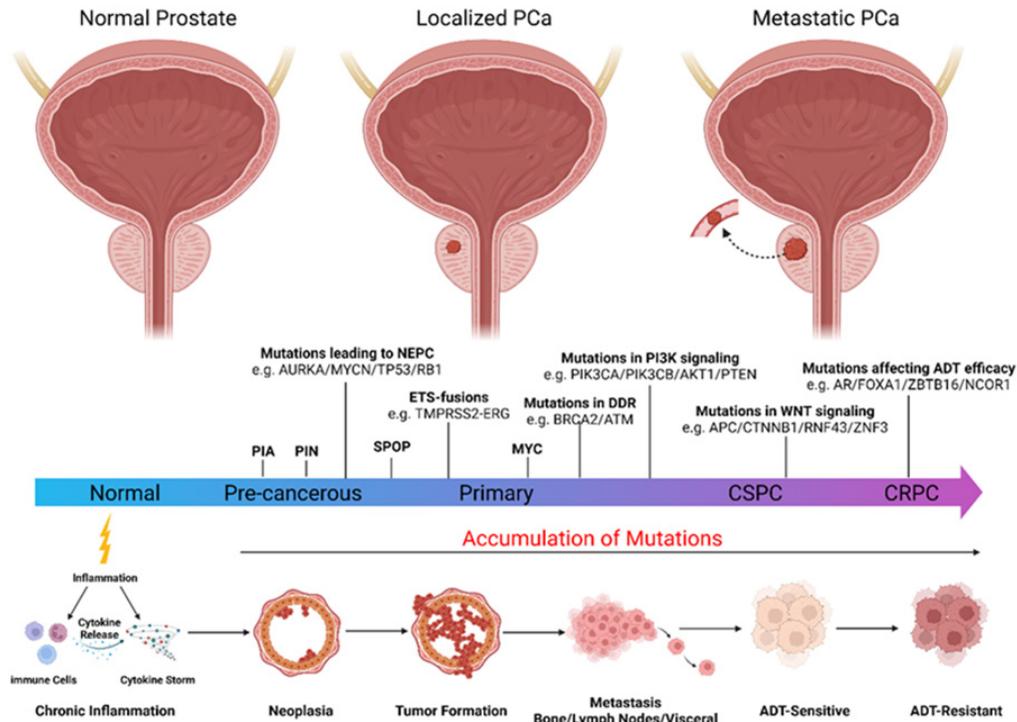
Figure 1. Prostate carcinogenesis. PCa is thought to be driven by the accumulation of harmful mutations. Inflammatory events triggered by either external or internal stimuli are the early sin of carcinogenesis. Marked by the infiltration of multiple types of immune cells, these cells will release cytokines, leading to cytokine storm and genetic instability. Certain pioneer mutations will cause abnormal proliferation of prostate tissue, termed PIA or PIN. Those pre-cancerous stages will eventually develop to primary tumor. Further mutations promote the progression and formation of metastatic PCa. Initially, metastatic PCa is sensitive to ADT, termed castration-sensitive PCa (CSPC). After a period, PCa is resistant to ADT, termed CRPC. It is believed that mutations affecting AR pathways are the key determinant of this transition. Created with BioRender.com.

immunosuppressive milieu of PCa, such as the infiltration of immunosuppressive cells and the release of cytokines that lead to this unfavorable outcome.

Indeed, research about PCa is a multidisciplinary area that incorporates computational biology, laboratory, and clinical testing. Before the final application of a certain practice, a series of steps that validate preclinical hypotheses and scientific findings must be done to successfully translate them into clinical scenarios. These rigorous procedures are critical to improve disease management. As our knowledge about this disease continues to grow, improvement in early detection and treatment of the disease will finally transform the pattern of clinical care and benefit patients' survival. This review will briefly summarize the current understanding of PCa, with a focus on the carcinogenesis, diagnosis, and treatment of this disease. Finally, the future direction of PCa research will be discussed.

2. Disease Etiology

The carcinogenesis of PCa is complicated and has not been completely understood yet. However, it is generally accepted that multiple pathological events are involved in this malignant change (Fig. 1). Accumulation of mutations is the ultimate driver of disease initiation and progression, and inflammation is thought to promote this process.

2.1 Initiation and Progression

The prostate is a reproductive organ consisting of three zones: the central layer, transition layer, and the peripheral layer [12, 13]. While cells in all zones have the capacity to develop cancer, the peripheral layer is the principal region of prostate neoplasms and carcinogenesis, making up about 75% of all disease cases [14]. Morphologically, the major structures of the normal prostate are ducts and acini, with stroma embedded in the entity [15]. Like other organs with ductal structure, the ducts of the prostate contain
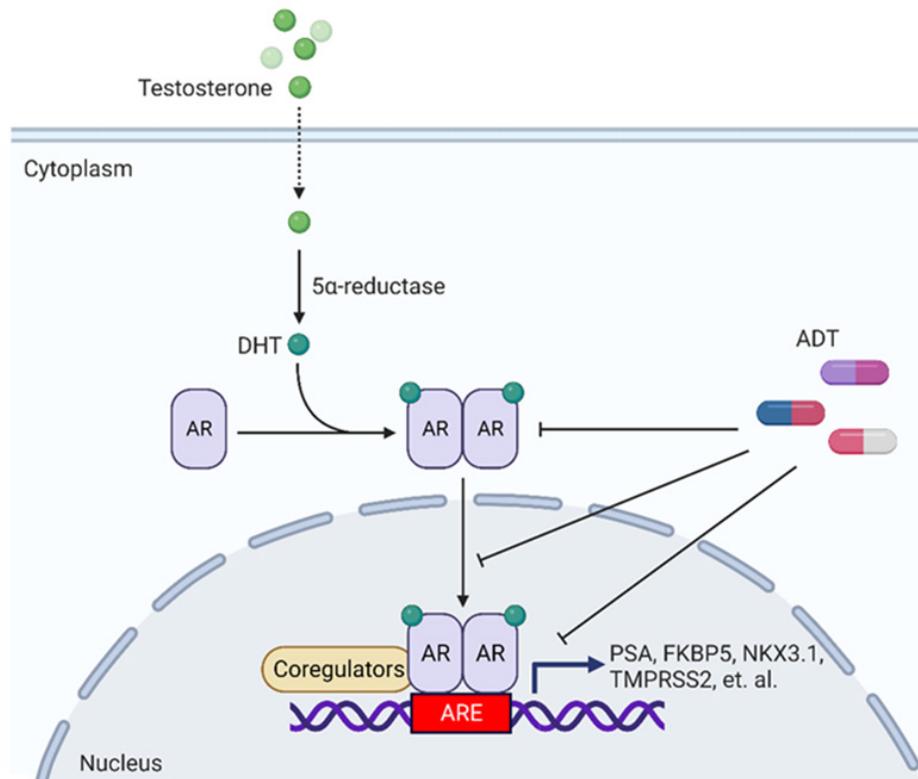
Figure 2. AR pathway and ADT. PCa is strongly associated with the AR pathway. The major androgen in serum is testosterone. It is often converted to dihydrotestosterone (DHT) by 5α-reductase, which is a more potent form of androgen that binds to AR. Without a ligand, AR is mainly located at cytoplasm. Following androgen ligand binding, active AR translocates to the nucleus and forms dimers, where it binds to androgen-response elements (AREs) and initiates the transcription of downstream targets. ADT specifically blocks AR pathways through multiple mechanisms, including inhibition of ligand binding, AR translocation, and the final transcription step. Adapted from "Androgen Receptor Genomic Pathway", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.

luminal cells and basal cells that form the basement membrane. Inside the basement membrane is the extracellular matrix and stromal cells, including smooth muscle myocytes and fibroblasts [16]. The luminal cells are generally accepted as the origin of PCa [17-19]. However, this theory has been questioned by increasing evidence supporting the basal origin of PCa [20-22]. These facts lead to the current hypothesis that both luminal and basal cell types are capable of giving rise to PCa, as supported by other studies [23, 24]. No matter what the origin of the PCa, it is clear that the transformation process must encompass several malignant changes to confer invasive phenotypes to the original cells, which then trigger uncontrolled proliferation and breakthrough of the boundary of the basement membrane. Usually, this process is first observable as proliferative inflammatory atrophy or prostate intraepithelial neoplasia, both of which are considered precursors of PCa and may eventually transform to malignant tumors in the future [25, 26]. In contrast,

benign prostatic hyperplasia, another disease of the prostate that is usually associated with aging, does not provide prognostic value for PCa, in which only non-malignant cell proliferation happens in the transition zone of the prostate [27].

The early onset of PCa accompanies a series of symptoms, such as urethral stricture, and routine screening of PCa for older people has led to most patients diagnosed at an early stage [28]. At this stage, PCa is curable with surgery or radiation therapy. Those who are unlikely benefit from curative treatment due to metastatic disease can be well-managed for a long time. AR is the most important target at this stage due to its dominant role in the survival of PCa. Without the binding of its ligand, androgens, AR is predominantly located in the cytoplasm. Upon binding to androgens, AR translocates to the nucleus where it binds to the androgen response element of its target genes to initiate transcription and drive tumorigenesis (Fig. 2). This is the basis of ADT, which aims to deplete endogenous

androgens to control disease progression. At the beginning, patients respond well to ADT, so the disease is termed castration-sensitive PCa (CSPC). However, even though early diagnosis of PCa has a good prognosis under current management, a substantial portion of patients will experience biochemical recurrence or disease progression, which is usually concomitant with an elevated AR activity and serum prostate-specific antigen (PSA) levels, making patients unresponsive to ADT and thus termed CRPC. Progression to CRPC is frequently marked with visible metastasis to bone marrow due to the bone tropism of PCa [29, 30], and this event is the major cause leading to 90% cancer death [31]. Major steps of metastasis include detachment from cell-cell and cell–matrix contact, invasion and intravasation into the nearby blood vessels, survival through the physical force and immune system in the circulation system, extravasation to reside at the new site, and finally formation of metastatic lesions [32]. This is a multi-step process that is poorly understood [33]. Most often, cells must possess the ability to digest extracellular matrix, which is achieved by secretion of matrix metalloproteinases, and evade the immune system all the time, which might be achieved through the immune-suppressive feature of PCa [34]. Newly formed metastatic CRPC marks the failure of ADT and leads to SREs and symptoms, including bone pain, bone fractures, and spinal cord compression [35]. These complications negatively affect the normal bone remodeling cycle and patients' quality of life. The metastatic event of PCa is a big issue, not only because of the bad outcome associated with it, but also the bad impact on the prognosis of treatment. Since occult metastases might be undetected at diagnosis, patients with invisible lesions will unavoidably experience therapeutic failure [36]. As a result, how to effectively detect occult metastases is under investigation.

2.2 Genetic Landscape

Accumulation of harmful mutations over the long term is thought to account for the carcinogenesis of PCa. These alternations of normal genomes, either in oncogenes or tumor suppressors, gradually render malignant phenotypes to normal prostate cells and slowly transform them into cancerous counterparts. According to the TCGA database, mutations mainly affect cell proliferation and death pathways, as well as the DNA damage response (DDR) pathways, which might be further explored for targeted therapies [37, 38]. Of note, none of them can distinguish

aggressive PCa from indolent ones, which suggests that the onset of PCa is not owing to a dominant driver. Instead, large-scale genomic alterations are prognostic features of non-indolent PCa, suggesting that the progression of PCa is due to the joint efforts of multiple mutations [39]. Indeed, very few genes are targetable, and this is a big challenge for early disease management. Hence, a deeper understanding of the genomic profile will likely guide the treatment strategies of PCa with different features and prognosis.

The mutation landscapes among various stages of PCa display a significant difference. In patients with localized PCa, gene fusions between family members of ETS transcription factors and AR-targeted genes are seen in more than 50% of localized PCa [40, 41], of which the most common one is the fusion of ERG with TMPRSS2. Whole-genome sequencing of the primary tumor also indicates other minor mutations that deserve attention, including the loss-of-function mutations in E3 ligase SPOP and gain-of-function mutations in transcription factor FOXA1 [42]. Increasing evidence suggests that mutations of these two genes have a predominant role in the disease progression. As an E3 ligase, impaired function of SPOP promotes the stabilization of many oncogenic proteins and rewiring of downstream pathways, such as DEK, SRC3, and BRD4 [43-45]. FOXA1 is an AR cofactor that increases the transcriptional ability of AR to promote cancer progression [46, 47]. Furthermore, these mutations could jointly lead to progression by interacting with each other. For instance, it has been reported that fusions of ERG with TMPRSS2 are resistant to SPOP-mediated degradation [48]. Considering the tumor-promoting effect of SPOP mutation, the co-occurrence of two distinct mutations may further increase the likelihood of disease progression and recurrence after treatment. Future studies will need to address similar questions by evaluating the predictive values of a single prominent mutation or its combinations.

Progression from localized PCa to metastatic PCa is coupled with deregulation of several genes. Alterations of the PI3K pathway are frequently seen with gain-of-function mutations in PIK3CA, PIK3CB, and the downstream kinase AKT1 [49, 50]. PTEN, the phosphatase that negatively regulates the PI3K pathway, also frequently encounters deletion and loss-of-function mutations, which are displayed in about 20% of primary tumors but increase to 50% in CRPC [51]. Another important event is the activation of the WNT signaling pathway in CRPC, which

may account for the disease progression [52]. This happens as the mutations of APC and CTNNB1 that directly activate canonical WNT signaling, which are observed in about 20% of CRPC patients [53], or mutations in inhibitory components such as RNF43 and ZNRF3 [54]. Besides, activation of noncanonical WNT signaling is also observed in CRPC, which deserves further exploration [55]. The well-known oncogene c-Myc is also implicated in PCa progression [56]. c-Myc is highly expressed at every stage of PCa through regulations by other genes, which itself stimulates an embryonic stem cell-like signature to drive proliferation and therapy resistance [57, 58]. These significant mutation events in disease progression deserve further attention, and clinical trials to test potential drug candidates that targeting aforementioned pathways should considered in the future.

In CRPC, perhaps the most common genetic alterations are around AR. This important target in PCa undergoes various types of mutations. Mutations most often happen in the form of amplification or gain-of-function mutations of AR per se, but can also involve its associated co-activators and repressors. FOXA1 is the confirmed co-activator of AR related to progression to CRPC [59]. In addition, inactivating mutations or deletions of repressors of AR transcriptional activity, such as ZBTB16 and NCOR1, are detected in substantial portions of CRPC patients [60, 61]. This is in contradistinction to CSPC patients, in which mutations of AR are fairly uncommon [62]. This phenomenon suggests that mutations of AR are the driving force of progression to CRPC and key determinants of resistance to ADT. Overexpression of AR through gene amplification is both necessary and sufficient to confer PCa resistance to ADT. Mutations in the ligand-binding domain of AR can lead to changes in ligand selectivity, resulting in an antagonist-agonist switch of drugs or promiscuity of ligand binding that enables activation by other structurally similar hormones [63-65]. Alternative splicing of the AR gene results in AR splice variants that remain constitutively active. These AR isoforms lack the ligand-binding domains, so they are not affected by AR-target therapies and contribute to resistance to ADT in clinical situations [66-69]. Considering the importance of AR throughout disease progression, ADT is commonly continued on a lifelong basis, but further understanding of genetic alterations driving resistance to ADT is critical for the long-term efficacy of this therapy.

Another class of mutations is genes involved in DDR, which is a hallmark of metastatic PCa compared to localized disease [70]. Mutations happen in about 10% of metastatic PCa cases, and the most prevalent mutations are BRCA2 and ATM, which are involved in homologous recombination repair of double-strand breaks [71]. Other minor alterations are those involved in mismatch repair (such as MSH2 and MSH6) and nucleotide excision repair (such as ERCC2 and ERCC5). Interestingly, metastatic PCa tends to have a higher mutation burden than localized PCa [72], and AR has been reported to regulate DDR genes [73]. Considering that most biopsy samples were obtained from CRPC patients who had been treated with ADT, the higher mutation burden in the late stage of this disease may reflect the synergistic effect of ADT and DDR mutations. Furthermore, mutations seem to be enriched in CRPC compared to CSPC, indicating that this class of mutations has an important role in promoting disease progression. Of note, cells with defects in the homologous repair pathway deficiency result in increased sensitivity to PARP inhibitors, which is termed synthetic lethality [74, 75]. The idea of synthetic lethality has been successfully applied in the treatment of breast cancer with BRCA2/BRCA1 mutations, and this leads to the motivation to investigate whether this subset of PCa patients may respond to PARP inhibitors. Several large-scale clinical trials are ongoing to test this possibility.

Certain genes may uniquely mark a rare variant of PCa. This subset of PCa morphologically mimics the small cell carcinoma and lacks AR expression. Instead, they are enriched with neuroendocrine markers, including chromogranin A, synaptophysin, and neuron-specific enolase [76]. Thus, they are termed neuroendocrine PCa (NEPC). The most frequent mutations in these tumors are amplifications of AURKA and MYCN [77]. Besides, TP53 and RB1 are frequently mutated in NEPC, which concordantly promote lineage plasticity, metastasis, and resistance to ADT [78-80]. De novo NEPC only accounts for a small subset of all PCa. However, since ADT is the standard treatment for PCa, cells with NEPC features are resistant to ADT and may display a survival advantage over bulky tumors, resulting in selective enrichment of this population and treatment-induced NEPC [81]. Currently, the precise molecular profile of treatment-induced NEPC is still not clear, but the trans-differentiation process is likely involved in this transition [82]. Other possible mechanisms, such as hypoxia signaling or epigenetics, need further vali-

dation [83, 84]. Sadly, because of its aggressive phenotype, very limited treatment methods are available for NEPC. Therefore, more investigations to develop treatment options should be guaranteed in the future.

2.3 Inflammation

Although the precise etiology of PCa is not completely discerned, chronic and repeated inflammation is believed to drive PCa in the long term [85-87]. Due to its specific physiological location and frequent exposure to multiple stimuli, the prostate is susceptible to inflammation, making prostatitis very common among the male population [86]. Of note, major inducers of prostatitis such as bacterial infection, chemical exposure, and obesity have been identified as risk factors of PCa [88-93]. Chronic and persistent inflammation significantly damages the normal epithelial barrier of the prostate. The repair of the epithelial barrier results in PIA or PIN, both of which are considered the pre-cancerous condition of PCa and may transform to malignant tumors in the future [25, 26]. Thus, a deep understanding of the interplay between inflammation and PCa is required to establish the disease model. This will also provide insights into pathogenesis and early prevention of PCa.

While the causes of inflammation and prostatitis are disparate among different people, they all negatively impact the prostate tissue homeostasis in multiple aspects. Inflammation is marked by the infiltration of immune cells and the release of cytokines. These cells and cytokines significantly affect prostate carcinogenesis and disease severity. Upon being recruited to prostate tissue, immune cells will release various pro-inflammatory cytokines to promote the transformation of normal prostate cells. On the one hand, active immune cells often secrete free radicals, which can damage the DNA and cause genetic mutations correlated with the initiation of PCa [94-96]. Cells that harbor certain mutations possess a significant survival advantage over other populations under the inflammatory condition. For instance, loss of tumor suppressor NKX3.1 during inflammation is an early event of tumorigenesis, which dramatically accelerates the progression of PCa and associates with higher Gleason score (GS) [97-99]. Another important tumor suppressor, PTEN, is frequently lost during inflammation, which then potentiates the CXCL8 signaling to sustain the growth and survival of prostate epithelium [100]. Indeed, there are certain links between genetic mutations of PCa and the associated inflammatory condition. However, a thorough understanding of this relationship is still largely unknown. Further investigations will need to establish the correlation between these two important early events during prostate carcinogenesis.

Inflammatory signaling also serves as an accomplice to promote cancer progression, and this is due to the interplay between cytokines and other oncogenic pathways [101]. Common inflammatory cytokines IL-1β, IL-6, IL-8, TNF-α, and IFNγ are all implicated in prostate cancer progression and associated with poor survival outcomes [102-106]. More importantly, the interaction of some inflammatory signaling with the AR pathway is detrimental, as this interplay promotes progression to CRPC that is resistant to ADT. For example, elevated expression of IL-6 increases the nuclear translocation and DNA binding of AR, which is accompanied by activation of STAT3 and MAPK pathways. As a result, PCa can survive in an androgen-independent manner. Another cytokine, IL-23, which is released by myeloid-derived suppressive cells, can also enhance the activity of AR and sustain cell survival under androgen depletion conditions [107]. This convoluted interaction between inflammatory signaling and the AR pathway deserves our attention, as it may render novel methods to overcome drug resistance at the CRPC stage. So far, there is some evidence linking the cytokine signaling with the emergence of resistance to ADT [108, 109]. Further study will have to explore the possibility of targeting inflammatory signaling for PCa treatment.

3. Diagnosis of PCa

The prostate gland is located below the bladder and in front of the rectum. Since the urethra is surrounded by the prostate, most patients will suffer symptoms related to urination, such as dysuria and nocturia. When patients have these complications, and there is a high risk of PCa, a physician will have to investigate it. The standard diagnosis of PCa starts with a digital rectal exam, which is a physical palpation of prostate tissue to assess the condition. However, a digital rectal exam doesn't provide any clues on the histological index of prostate, so prostate tissues are needed to evaluate the disease stage, which is achieved by transrectal or transperineal biopsy of prostate [110]. Pieces of tissue are examined by microscopy to see whether there is any pathological change. To stratify the disease severity, samples will usually be graded with a Gleason Score (GS), which conveys a number to samples based on the pattern of biopsy tissue [111]. A sample will be graded with two

scores. The first score is used to evaluate the dominant pattern of tissue, while the second score is for the minority cell pattern. Both scores have a scale of 1 to 5, so the complete GS of a sample is the sum of the two scores. The higher the GS, the worse the disease and outcome. Currently, the Gleason grading system has been reorganized into the International Society of Urologic Pathologists grade system that separates GS into 5 categories [112, 113]. It denotes GS of 6 and 8 as Group 1 and Group 4, GS of 9 or 10 as Group 5. For GS of 7, it further differentiates GS of 3+4 from 4+3. Since the clinical evidence delineates that patients with GS of 4+3 have obvious worse prognosis [114, 115], patients with GS of 3+4 are defined as Group 2, and those with GS of 4+3 are classified into Group 3.

Another canonical diagnosis method is to measure molecular biomarkers of PCa. Since PCa relies on AR pathways to sustain survival and develop malignant phenotype, detection of serum PSA, which is the downstream target of AR, is another gold standard for the diagnosis of PCa. The introduction of PSA as a diagnostic tool marks an unprecedented event in the history of the PCa field and leads to a burst of patients diagnosed with this disease, especially for younger men who are at the early stage of PCa [116]. Since then, PSA has been widely used in the diagnosis of PCa and the prediction of patients' outcomes. The level of PSA is proportional to the severity of PCa, which indicates that patients with higher PSA is more likely to develop late-stage PCa with a predilection to metastatic disease [117]. In addition, PSA can also be leveraged to predict the efficacy of treatment and the potential recurrence of PCa. Higher PSA level before radiation therapy implies a higher likelihood of treatment failure and mortality [118, 119]. After ADT, the nadir PSA level and time to reach it may help to predict the efficacy of ADT [120, 121]. Indeed, serum PSA is a good benchmark for the possibility of biochemical recurrence after radical prostatectomy [122-124]. Because of various advantages and the convenience of PSA detection, the American Cancer Society provides a guideline that those who are at risk of PCa should be tested for PSA regularly to detect early onset of disease.

Unfortunately, the established diagnosis methods have obvious drawbacks under certain circumstances. While prostate biopsy helps identify bona fide pathological lesions, it frequently avoids the area of PCa and provides a false-negative result [125]. Actually, the detection rate of PCa is fairly low, even though multiple biopsies can somehow improve the discovery rate [126]. A report finds that this method misses nearly one-fourth of all PCa cases and often mismatches the scores with actual disease severity [127]. Regarding the PSA detection, there is a debate about which cutoff value is optimal for clinical practice. A low threshold often results in the overdiagnosis and overtreatment of those indolent PCa that have minimal impact on life [128, 129]. In fact, some studies argue that the overdiagnosis rate of PSA screening can be as high as over 50% [130-132], which is an astonishing number deserving our attention. However, a high cutoff also leads to other potential issues. False-negative rate pops up when a high cutoff is set, as it misses potentially aggressive cases that, when later found, are hard to manage [133]. Besides, high cutoff also produces inferior tracking of disease burden in terms of treatment-induced AR-negative PCa, which accounts for nearly one third of all cases after ADT [134].

Considering the weakness of mainstream diagnosis tools, significant refinement should be made to improve the precision of diagnosis. The advancement of radiography has coined more powerful diagnostic technologies. For example, targeted biopsy, which utilizes multiparametric magnetic resonance imaging to locate potential lesions before biopsy [135], displays superiority over standard prostate biopsy in that it provides a competitive discovery rate of clinically significant PCa while ruling out those insignificant ones [136, 137]. Currently, we are in a predicament of how to point out those clinically insignificant PCa that don't need medical intervention. Whether patients' quality of life will deteriorate due to PCa depends on the aforementioned risk factors and comorbidities [138]. Thus, to avoid overdiagnosis and overtreatment, several PCa risk calculators are designed to help evaluate patients' health conditions and the necessity of treatment [139, 140]. Although most of them still need optimization, these programmed estimators help to define disease from an unbiased viewpoint.

Novel diagnostic tools are emerging to address the accuracy of traditional methods, especially in the field of molecular biomarkers that identify PCa. Since the level of PSA is greatly affected by individual prostate volume and health condition, it lacks specificity and often delivers unreliable results. To refine this method, combinatory detection of multiple PSA proteins or related indices has been popular.

For example, the 4Kscore and Prostate Health Index are two commercially available tests used for decision-making of biopsy and prediction of progression [141, 142]. Detection of PCa antigen 3 in urine samples resolves the issue of specificity for PCa cells and decreases the negative rate of follow-up biopsy [143]. Detection of some genes in biopsy tissues is useful to predict the malignancy of cancer and can be applied to distinguish patients who need intensive medication. For example, the assessment of the Cell Cycle Progression score (Prolaris), which consists of 31 genes, is a reliable tool for doctors to improve prognosis [144]. Representative genes of various pathways can pick out presumably malignant cases that need immediate treatment, despite tumor heterogeneity, multifocality, and limited sampling. Based on this notion, a 17-gene Genomic Prostate Score (Oncotype DX) improves the prediction of pathological outcome and provides a guideline for treatment [145]. The Decipher test, which is based on a 22-gene genomic classifier, has been validated in the clinic to predict early metastatic event after prostatectomy [146].

Huge advancement has also been made to increase the sensitivity of detecting metastatic PCa. Bone scintigraphy using technetium-99m methylene diphosphonate, together with computed tomography and magnetic resonance imaging, is the standard diagnostic tool for staging of metastatic PCa. However, the frequent misses of micro-metastases and occult metastases discourage its reliability [147]. To deal with this problem, several radiotracers have been tested in positron emission tomography [148]. Exemplary reagents, including ^{11}C-choline, ^{18}F-flu-ciclovine, ^{18}F-sodium fluoride, and ^{68}Ga-PSMA-11, are available for the detection of metastatic lesions in lymph nodes and bones [149-152]. As advanced techniques are being created, patients will eventually benefit from these more sensitive and specific diagnosis regimens.

4. Treatment for PCa

Since the overdiagnosis and overtreatment of PCa are very common, whether PCa patients need medical intervention must be carefully deliberated. It should be noted that the 5-year survival of PCa is nearly 100%, and the risk of death not caused by PCa actually greatly exceeds death directly caused by the disease per se [153, 154]. Even a 29-year follow-up of PCa cases finds that merely one-third of all patients die of PCa, with life expectancy gained only 2.9 years in surgery treated groups [155]. In contrast, age and other risk factors are the leading causes of death, with
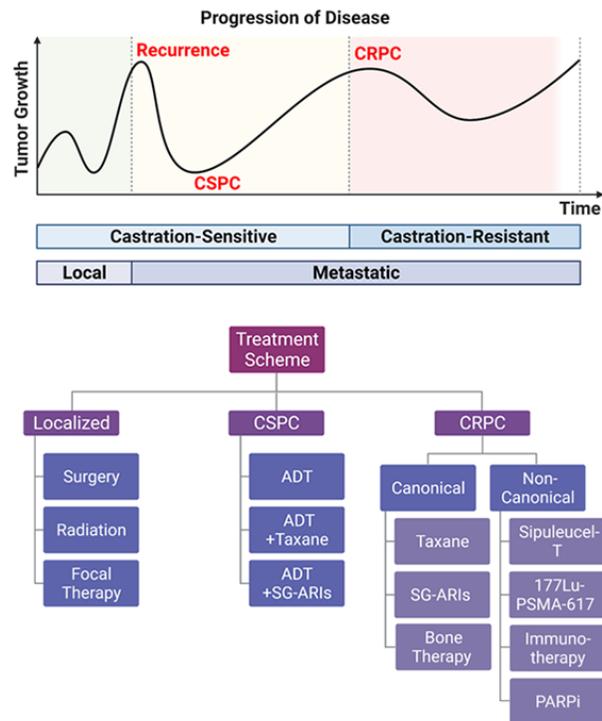

Figure 3. Treatment scheme for PCa. Treatment for PCa depends on the stage of the disease. For localized PCa, the disease is curative with surgery, radiation, or focal therapy, which is a more precise treatment targeting only tumor nodules. However, a substantial number of patients fail the treatment and develop biochemical recurrence accompanied by metastasis. At the CSPC stage, the current treatment modality has been modified, which is usually intensified with combination therapy of canonical ADT plus Taxane or SG-ARIs. However, progression to CRPC is still inevitable, and treatment approaches at this stage are almost the same, except for medicines targeting bone lesions. Some non-canonical treatment is available for a sub-cohort of patients, such as immunotherapy, 177Lu-PSMA-617, and PARP inhibitors. The only available medicine for NEPC is platinum-based therapy, which is not included in this figure. Adapted from "Natural History of Prostate Cancer" and "Flow Chart (5 Levels, Vertical) 6", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.

patients carrying multiple comorbidities having the worst survivorship [156, 157]. Thus, treatment should be deferred unless other risk factors or comorbidities are identified that may negatively impact patients' quality of life and overall survival. Life quality and patients' acceptability should be taken into consideration before any treatment decision is made. Shared decision-making between patients and physicians should be the trend in the future [158]. Nonetheless, men with potentially aggressive cancer should receive treatment to control progression. Depending on the disease features at diagnosis, patients with localized cancer or metastatic cancer have different treatment options (Fig. 3).

4.1 Localized PCa

For patients with localized cancer, there are three treatment options: active surveillance, radical prostatectomy, or radiotherapy [5]. Generally, patients with low-risk PCa are well managed with active surveillance, and the chance of progression and metastasis is negligible [110]. Patients in this category will receive regular PSA screening and biopsy to monitor the disease status. Once a sign of progression is identified, such as a rise in PSA or upgrade of GS, active surveillance should stop, and regular treatment needs to be considered. However, there is an exclusion criterion for active surveillance in patients with low-risk PCa but combined with a cribriform or intraductal pattern of disease, which are associated with aggressive PCa and adverse outcomes [159, 160]. In that case, active surveillance should be avoided [161].

Patients with intermediate-risk PCa are not uniform and should be separated into two sub-categories [162, 163]. Low-intermediate patients tend to have a favorable outcome, so they can be provided with active surveillance after careful evaluation of other risk factors [164, 165]. However, for high-intermediate patients, active surveillance should be denied. Patients may choose to receive radical prostatectomy or radiotherapy combined with short-term ADT.

Patients with high-risk PCa are predisposed to malignant disease and metastasis, so they need immediate medical treatment. The choice is similar with those high-intermediate patients, but more intensive adjuvant therapy may be used to maximize efficacy. To avoid biochemical recurrence, detection of occult metastases is highly recommended before any treatment is applied. Surgery is performed to excise prostate tissue and associated pelvic lymph nodes. Depending on the post-operative PSA level, patients with detectable PSA may receive adjuvant therapy to remove residual tumors, while those with undetectable PSA levels are not recommended to receive further treatment [166, 167]. Instead, salvage radiotherapy is a potential curative approach for those with detectable PSA after surgery [168-170]. If radiotherapy is chosen, a long-term ADT is added to minimize biochemical recurrence. There is no evidence to demonstrate the obvious superiority of one method over another, but patients receiving different therapies may encounter divergent adverse effects. Of note, radiation therapy causes more nocturia and bowel dysfunction compared with radical prostatectomy, which tends worse urinary control and erectile function [171, 172].

Despite the curative outcome of local therapy, the subsequent sequelae may significantly downgrade patients' lives. To address this issue, a more precise approach, dubbed focal therapy, is available for a small subgroup of patients with intermediate-risk, targetable volume of cancer [173]. Focal therapy displays an advantage over conventional local therapy in that it aims to eliminate cancer lesions while keeping healthy tissues intact. Due to this non-invasive feature, focal therapy decreases the risk of adverse outcomes associated with local therapy, such as urinary incontinence and erectile dysfunction [174, 175]. While focal therapy is superior to local therapy, there is no official guideline regarding its application criteria and desired outcome. However, as novel treatment modalities are being added to the armamentarium, focal therapy may eventually be recognized as the standard care for PCa patients [176].

4.2 Metastatic PCa

For patients with metastatic PCa, curative treatment such as radiotherapy and surgery is no longer available. Instead, ADT is the standard care for these patients, which is either achieved by surgical orchiectomy or drugs that deplete or antagonize endogenous androgen. Canonical ADT for CSPC includes luteinizing hormone-releasing hormone analogues that block de novo androgen synthesis or antiandrogen drugs that directly inhibit the effect of androgen [177]. Common side effects include hot flashes, sexual dysfunction, SREs, anemia, and complex metabolic syndrome [178, 179]. Besides, there is an increasing risk of cardiovascular disease in those patients [180-183]. Cognitive problem is a rare side effect but cannot be omitted [184, 185]. To relieve the caveats of continuous ADT, intermittent ADT is an alternative treatment approach for those patients. Marked by cyclical replenishment of androgen in patients, intermittent ADT is supposed to achieve noninferior disease control while reducing ADT-associated adverse effects and enhancing patients' quality of life [186]. Patient selection is crucial for the best results of intermittent ADT, and this needs to be thoroughly investigated before any decision is made.

Unfortunately, nearly all primary treatments for metastatic PCa eventually fail, and the disease progresses to the CRPC stage. Over a long period, docetaxel is the standard treatment for CRPC [187]. For patients who progress after docetaxel treatment, cabazitaxel can provide survival benefits and delay disease progression [188]. However, both drugs only
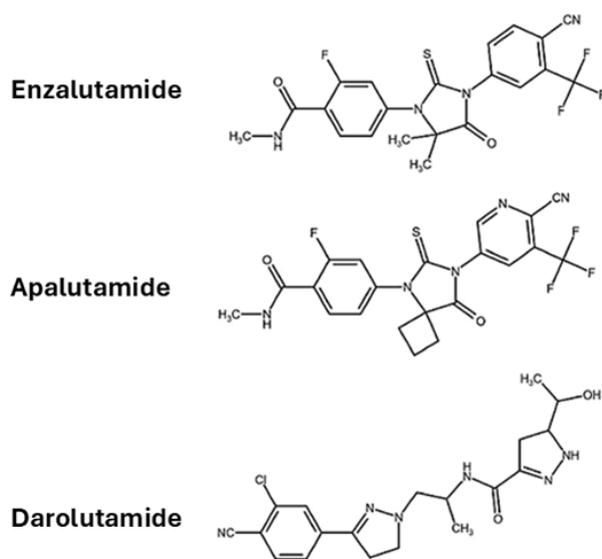
Figure 4. Structure of SG-ARIs. ENZ, APA, and DARO are three SG-ARIs used to treat CRPC patients. As illustrated, ENZ and APA share some structural similarity with similar backbones. However, DARO is distinct from ENZ and APA with some unique functional groups.

have a short-term effect, and cabazitaxel is not an ideal substitute for docetaxel as the first-line treatment [189]. To step out of this predicament, extensive research has been carried out to explore alternative treatments for CRPC. Evidence shows that AR continues to be the major driver of CRPC and thus remains a valid target [190]. Increased de novo androgen biosynthesis due to elevated CYP17A1 is one of the major reasons contributing to CRPC [191], and this finding has led to the application of CYP17A1 inhibitor abiraterone for the treatment of docetaxel-pretreated CRPC [192, 193]. Overexpression or amplification of AR is sufficient to induce CRPC and even alter the response nature of canonical ADT [194, 195]. Based on that, second-generation AR inhibitors (SG-ARIs) (Fig. 4), including Enzalutamide (ENZ), Apalutamide (APA), and Darolutamide (DARO), have emerged as a solution for CRPC patients after docetaxel treatment [196-198]. The emergence of SG-ARIs significantly improves patients' survival. Of note, patients' response to these drugs is somehow mutually exclusive, as indicated by the effectiveness of ENZ and abiraterone after docetaxel treatment, as well as the cabazitaxel after ENZ or abiraterone treatment [192, 193, 196, 199, 200]. This may be beneficial to patients, as different medicines can complement each other to deliver the optimal management of disease. To achieve the best disease control, the

treatment sequence needs to be weighed before decision-making, especially when combining treatment strategies with patients' characteristics. Besides, inherent or acquired drug resistance should be taken into consideration. Identification of molecular biomarkers associated with patients' response before or during treatment will help design and modify treatment regimens.

While these drugs were previously solely used in CRPC, recent studies have demonstrated that early intensified medication with these drugs may provide benefits for disease control, as they may enhance patients' response and delay the emergence of treatment resistance. Accordingly, the current regime of ADT for CSPC has been modified to a combination treatment with Taxane drugs or SG-ARIs. For example, docetaxel plus prednisolone is the standard treatment for CRPC, and the combination with canonical ADT for CSPC can prolong patients' overall survival [201-203]. Likewise, a combination of abiraterone, ENZ, APA, or DARO with canonical ADT in CSPC also shows supremacy over single ADT in several clinical trials [204-209]. However, as all the studies were performed in an era when canonical ADT alone was used as a treatment for CSPC, whether these newly modified treatment strategies can benefit patients who previously received these agents for CSPC is not completely guaranteed, and more studies are needed to address this question.

PCa has a high tendency to metastasize to bone. Once metastases have been identified, nearly 70% of PCa patients will develop bone metastases that are associated with SREs [210]. Because of this specific bone tropism of PCa, therapeutics that improve bone condition are an important component in the treatment regimen of metastatic PCa (Fig. 5). Since osteoclasts are the principal driver of bone effects, drugs that modulate the function of osteoclasts help to alleviate symptoms. Zoledronic acid is a canonical drug for PCa with bone metastases. However, the early administration doesn't delay the onset of bone metastases [211]. A more recent medicine, called Denosumab, is favored to delay the onset of SREs by targeting the receptor activator of nuclear factor κ-B pathway, which is the key signaling in the maturation of osteoclasts [212, 213]. Besides, radiopharmaceutical radium-223 specifically targets the cancer cells residing in bone. Due to its chemical similarity to calcium, radium-223 is enriched in bone where it emits alpha particles to kill metastatic cancer cells. Clinical evidence shows that radium-223 elongates
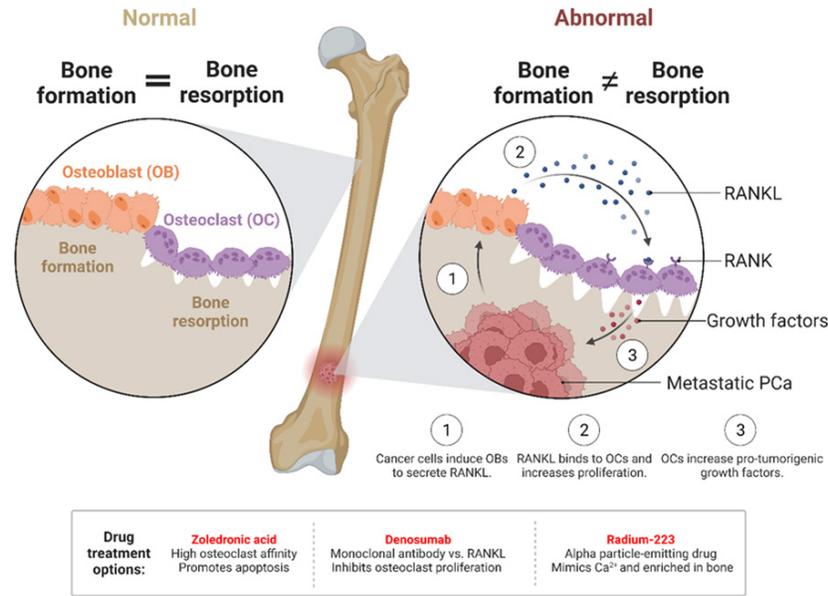
Figure 5. PCa bone metastasis and therapy. PCa has a strong preference for bone metastasis. Normal bone homeostasis is maintained by osteoblasts and osteoclasts, which are responsible for bone formation and resorption, respectively. Under pathological conditions of PCa metastasis, the balance of bone homeostasis is broken. This figure shows the typical osteolytic lesions, in which the bone resorption is enhanced over bone formation, although PCa can also cause osteoblastic lesions. The interaction between osteocytes and PCa promotes the proliferation of tumors and SREs in patients. Multiple therapeutic options are available for patients to relieve the symptoms. Adapted from "Metastasis to Bone Disrupts Bone Homeostasis", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.

patients' overall survival as well as palliates bony metastases-related symptoms [214]. So far, all medicines are only for palliative purposes, and there is still no treatment for preventing bone metastases of PCa. As our knowledge about PCa bone metastasis continues to grow, more options will be available to deal with this common complication of PCa.

4.3 Non-canonical Treatment

While the mainstream therapy for PCa is based on ADT and Taxane drugs, some non-canonical treatment options are available for a small subset of patients. Cancer cells recognized by immune cells are supposed to be eliminated, and this is the central rationale of immunotherapy. While the level of PSA is often used to monitor the activity of AR, it fails to be a good epitope for the identification of PCa cells, as the PSA-based vaccine doesn't convey a survival benefit in PCa patients [215]. The failure of PSA as a valid target stimulates the exploration of other immune epitopes. One immunotherapy vaccine, called Sipuleucel-T, is based on the immunization against the prostatic acid phosphatase and elimination of cancer cells by T cells [216]. Phase 3 clinical trial showed that it could prolong patients' overall survival for 4.1 months, which led to the FDA approval for asymptomatic or minimally symptomatic CRPC patients [217]. Recently, another promising approach has emerged that targets the membrane antigen PSMA of PCa cells. Directed by a cancer-specific PSMA epitope, radioactive compound lutetium-177 can destroy cancer cells with minimal side effects on adjacent tissues. This ^{177}Lu-PSMA-617 radiopharmaceutical has been tested in phase 2 and phase 3 trials, and the results are very exciting. Compared to canonical ADT or Taxane-based therapies, ^{177}Lu-PSMA displays superiority to improve overall survival and quality of life with good tolerance and low toxicity in CRPC patients [218, 219]. Based on these results, the FDA approved this treatment for CRPC on March 23rd, 2022.

As the genetic profiles of PCa patients are being profoundly interrogated, novel therapeutic options have emerged to specifically target the genomic vulnerabilities of cancer cells. The anti-PD-1 or anti-PD-L1 immunotherapy may work for a subset of heavily pretreated CRPC patients with mismatch repair deficiency, which is characterized by microsatel-

lite instability and high tumor mutation burden [220, 221]. Interestingly, the response to anti-PD-1 therapy seems to be unrelated to the expression of PD-L1 [222, 223]. However, this treatment modality fails to provide a substantial effect to control disease progression, as only a subset of patients will benefit from it. Due to this insufficiency, a combination of immune checkpoint inhibitors with docetaxel or ENZ might be a better choice and is still being investigated [224, 225]. Another subset of patients with loss of CDK12 may also benefit from immune checkpoint inhibition, due to the elevated genomic instability, neoantigen burden, and T cell infiltration [226]. Mutations of genes involved in homologous recombination repair consist of about a quarter of the total genetic alterations in CRPC [227, 228]. Among these genetic deficiencies, BRCA2/1 is one of the most frequently mutated genes, which makes up 12% of all lesions. PARP inhibitors that lead to synthetic lethality have been successfully administered in breast and ovarian cancers harboring BRCA2/1 mutations [75]. This inspires the application of PARP inhibitors in CRPC patients. Clinical trials of Olaparib and rucaparib show significant results to control disease progression [229, 230], which leads to the FDA approval of these to treat patients with BRCA2/1 mutations. Together with the tests for BRCA2/1, such as Foundation One and BRAC Analysis, these potent therapeutic approaches further improve the medical care for late-stage patients.

5. Discussion

As one of the most diagnosed cancers, PCa remains a global health burden and challenges the current social healthcare system. In the past decade, significant improvement has been achieved in the field of disease etiology and treatment approaches. Considering the potentially large cases and dynamic changes of disease nature, more technological advances should be accomplished to better manage PCa. Right now, challenges lie in how to establishing a more precise system of risk classification based on clinical features of PCa. This is critical to distinguish those indolent cases, which don't need to be heavily treated, from those that are potentially aggressive, which must be therapeutically intervened. Classification of disease subgroups based on computational histological pattern recognition and prediction of genomic features is now available for prostate cancer prognostication.

Other areas that deserve attention are the increasing number of treatment-induced NEPC, which presents in 10-17% of patients with CRPC [81], and repurpose of immunotherapy in PCa. As ADT and SG-ARIs are now the standard treatment for PCa, this number is expected to increase in the future. However, platinum-based chemotherapy is the only available treatment for NEPC [231], and inhibitors targeting AURKA or MYCN are still under investigation. PCa is a C-class tumor with low mutational burden and few T-cell infiltrations [232]. Most mutations are copy number alterations or gene structural rearrangements without the generation of neoantigen [233, 234]. This serves as a therapeutic barrier to immunotherapy, as a higher mutation burden and immune cell infiltration are associated with a better response rate [235, 236]. To repurpose immunotherapy for PCa, future research needs to clear this barrier, and this can be achieved through either combination therapy or identification of novel immune targets [237, 238].

Several new areas of PCa are being intensively studied, and their role in the disease onset and progression is still largely unknown. For example, senescence and senescence-associated secretory phenotype (SASP) are one of the potential mechanisms to promote cancer growth and metastasis [239]. Senescence and SASP are thought to secrete multiple immunosuppressive factors, which then recruit immunosuppressive cells to the site of the tumor. These immune cells then secrete cytokines and chemokines that lead to malignant phenotypes, preexistence of senescence, or immunosuppressive microenvironment [240-242]. This complex interaction between tumors in senescence and other factors is like a double-edged sword. On the one hand, tumors in a senescence state are dormant and thus stop growing, which is the major mechanism of tumor control by many chemotherapies [243, 244]. However, senescence is distinct from cell death, as tumors are still alive and possess secretory function, which is harmful for the long-term treatment and is responsible for disease relapse through the mechanisms mentioned above. How to navigate the dichotomous feature of senescence to the beneficial side should be considered in the future. Another investigation area is epigenetic therapy. Due to its slow onset and chronic progression, PCa is an excellent candidate for epigenetic therapy [245]. Multiple epigenetic changes, including DNA methylation and histone modifications, are involved in PCa initia-

tion and progression, which are now considered hallmarks of human cancer [246]. There is already an existing epigenetic assay, named DOCUMENT, to help the early diagnosis of PCa [247]. However, whether a similar assay will guide the treatment needs to be verified. A complete and integrative epigenetic taxonomy of PCa under different conditions will help to solve this issue [248-250]. Admittedly, this review cannot cover everything in this field, and many new aspects of PCa are being uncovered. It is promising that in the near future, more therapeutic options will be available for PCa patients to better manage this disease and improve patients' quality of life.

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