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Precision Oncology

Review

Androgen deprivation therapy for prostate cancer: from mechanism of action, complications and challenges to future prospects

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ABSTRACT

Prostate cancer ranks among the most prevalent malignancies in men, with disease progression driven by sustained androgen receptor (AR) signaling. Androgen deprivation therapy (ADT), which suppresses androgen synthesis and AR activation, serves as the standard treatment for advanced disease. ADT modalities include surgical castration, gonadotropin-releasing hormone agonists/antagonists, anti-androgens, and androgen synthesis inhibitors. Despite initial efficacy, long-term ADT is frequently complicated by the emergence of castration-resistant prostate cancer (CRPC) and multi-system toxicities involving metabolic, cardiovascular, and skeletal systems. CRPC arises from AR reactivation via gene amplification, mutation, splice variants and crosstalk with oncogenic pathways. Contemporary treatment intensification combines ADT with next-generation AR inhibitors, chemotherapy, and immunotherapy. Predictive biomarkers such as AR variant 7 and homeobox B13 facilitate patient stratification and individualized treatment decisions. The aim of this review is to summarize the role of ADT in prostate cancer management, with particular emphasis on androgen metabolism, AR signaling, mechanisms of castration resistance, ADT-related complications, and emerging therapeutic strategies. Based on systematic literature retrieval from PubMed and Embase (2018–2025), this review synthesizes current knowledge on androgen metabolism, AR signaling, CRPC mechanisms, ADT-related complications, and emerging therapeutic strategies to optimize long-term outcomes.

Key Words: castration-resistant prostate cancer; androgen receptor signaling; treatment complications; precision oncology; predictive biomarkers

MeSH terms:

PROSTATIC NEOPLASMS, CASTRATION-RESISTANT — DIAGNOSIS

PROSTATIC NEOPLASMS, CASTRATION-RESISTANT — PHYSIOPATHOLOGY

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Introduction

Prostate cancer (PC) is the most prevalent malignancy in the male urogenital system, ranking the second most common cancer globally and the fifth leading cause of cancer-related deaths [1]. In 2022, it was estimated to have over 1.46 million new cases and more than 396,000 deaths [2]. This significant increase compared with historical incidence and mortality rates is driven by global demographic shifts, including an ageing population and rising life expectancy, particularly in lower- and middle-income countries. In addition to racial characteristics, risk factors for developing PC include genetic predisposition, chronic inflammation in prostate tissue known as prostatitis, environmental, professional and dietary factors, including high fat diet, smoking and excessive alcohol intake [3]. For clinically localized PC, radical prostatectomy and radiation therapy are standard, with adverse effects including incontinence and erectile dysfunction [4]. Active surveillance is an option for low-risk disease to avoid overtreatment [5]. For locally advanced disease, adding long-term androgen deprivation therapy (ADT) to local treatment improves outcomes, with chemotherapy added in high-risk cases [6]. ADT is standard for metastatic disease and is used as neoadjuvant approach in high-risk localized disease [7, 8]. Having outlined PC staging and treatment strategies, understanding its pathogenesis is key to optimizing ADT. PC development involves complex genetic, epigenetic, and metabolic alterations, with androgen signaling as a central driver.

The novelty of this study lies in the systematic integration of PC pathogenesis, androgen signaling, ADT mechanisms, castration resistance, and ADT-related multi-system complications. Rather than focusing on single therapeutic strategies or separate molecular mechanisms, this paper bridges the gap between basic hormone regulation and the clinical application of different ADT regimens, while also addressing long-term adverse reactions and tumor drug resistance. It is important to note that the presented logic linking fundamental research and clinical practice allows us to focus attention on the frequently encountered problems of long-term anti-androgen therapy.

The aim of this review is to summarize the role of ADT in PC, address its associated complications and resistance mechanisms, and provide an updated overview integrated with recent clinical evidence and international guidelines. A literature search was performed in PubMed and Embase from 2018 to 2025 using key terms including “castration-resistant prostate cancer”, “androgen receptor signaling”, “treatment complications”, “precision oncology”, and “predictive biomarkers”. Where necessary to clarify specific aspects of the publications under review, earlier studies were also considered. Only clinical trials, high-quality reviews, and mechanistic studies in English were included, except for selected Russian- and Chinese-language sources used in specific cases, while case reports were used selectively when relevant to rare complications or unusual clinical scenarios. The following section focuses on how dysregulated androgen metabolism and receptor signaling contribute to tumor initiation and progression.

Prostate cancer pathogenesis androgen signaling and molecular pathology

The clinical classification and corresponding treatment strategies for prostate cancer are summarized in Table 1. The pathogenesis of PC is complex and involves a combination of lifestyle factors, genetic mutations and epigenetic changes [9, 10]. These factors, including diet and obesity, can interact with inherited genetic predispositions in epithelial cells and lead to the disease development [11, 12]. Common genetic alterations in PC include androgen receptor (AR) amplification/mutation, phosphatase and tensin homolog (PTEN) loss (which activates the prosurvival phosphoinositide 3-kinase / protein kinase B / mechanistic target of rapamycin [PI3K/AKT/mTOR] pathway), and *MYC* overexpression driving uncontrolled proliferation and genomic instability [10, 13]. A recent study by Boufaied N. et al. shows that obesity, coupled with a diet high in saturated fats can initiate PC with *c-MYC* gene amplification [14].

Table 1. Clinical classification and corresponding treatment strategies for prostate cancer

Cancer staging	Core treatment principles	Key treatment approaches	Therapeutic goal
Clinically localized prostate cancer	Radical cure	Radical surgery (prostatectomy), radical radiation therapy, low-risk individuals can be actively monitored	Complete tumor removal and cure
Locally advanced prostate cancer	Primary and adjuvant	Radical surgery, radiotherapy, plus long-term androgen ADT (or combined with chemotherapy)	Reduce the risk of recurrence and prolong the disease-free survival
Metastatic prostate cancer	Control, survival	ADT, second-generation anti-androgens, chemotherapy, targeted, and immunotherapy	Delay progression, relieve symptoms, prolong survival

Note: ADT — androgen deprivation therapy.

PC belongs to hormone-sensitive tumors, as cancer cell proliferation is initially dependent on external signals in the form of androgens [15]. During normal prostate development, the AR is highly expressed in stromal cells and absent in epithelial cells. However, as PC progresses, stromal AR expression declines but epithelial AR becomes dominant [16]. While androgens normally regulate prostate cell growth via AR, PC is driven by aberrations in androgen biosynthesis, metabolism, and AR function, which promote tumor progression and castration resistance. Understanding these alterations is therefore essential for elucidating disease mechanisms and advancing targeted therapies.

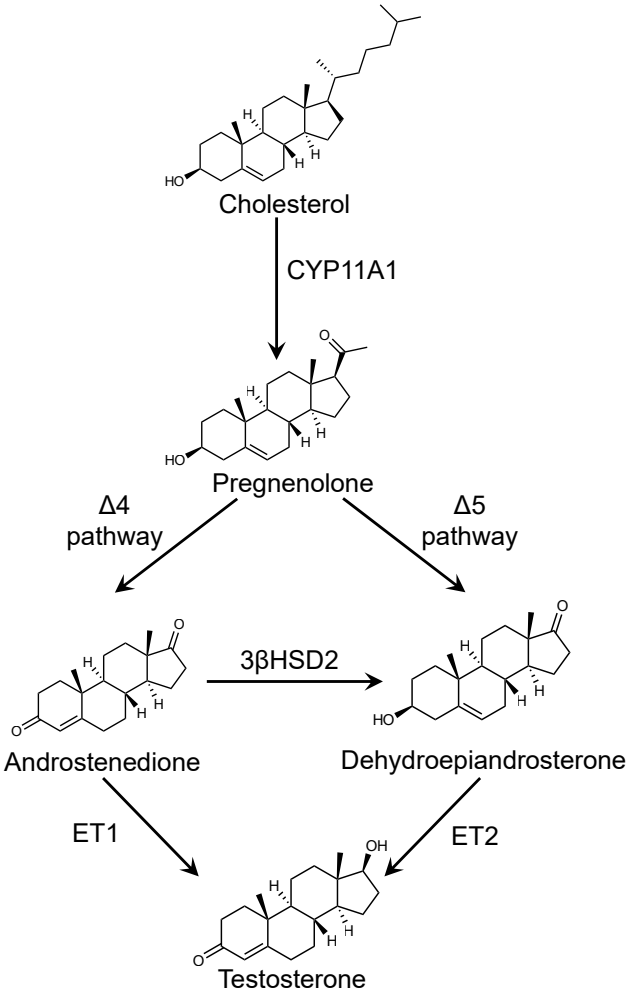
Androgen synthesis and metabolism

Androgen synthesis and metabolism maintain normal prostate physiology. In PC, these pathways are often dysregulated and reprogrammed, promoting tumor progression and ADT resistance. A clear understanding of these processes is critical to revealing how cancer cells reshape the androgen microenvironment to evade treatment.

Androgens in the human body are primarily synthesized in the testicular interstitial cells of males and the ovarian and adrenal cortex of females. The core androgen biosynthetic pathway begins with cholesterol, which is catalyzed by cholesterol side-chain cleavage enzyme (CYP11A1) to form pregnenolone [17]. This pregnenolone then undergoes two intermediate pathways — Δ5 and Δ4 — yielding dehydroepiandrosterone (DHEA) and androstenedione, respectively.

After several enzymatic reactions DHEA and androstenedione are eventually converted to testosterone [18] (Figure 1).

FIG. 1. Androgen synthesis pathway

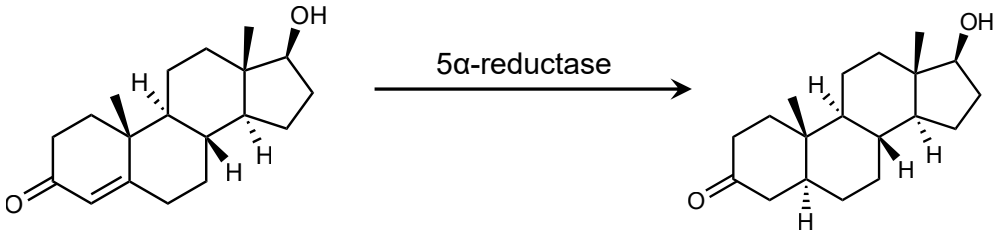


Note: CYP11A1 — cytochrome P450 family 11 subfamily A member 1; 3βHSD2 — 3β-hydroxysteroid dehydrogenase type 2; ET1 — several enzymatic reactions required for androstenedione to get converted into testosterone; ET2 — several enzymatic reactions required for dehydroepiandrosterone to get converted into testosterone.

Androgens in the human body are metabolized by enzymes in the liver and peripheral tissues. As the most abundant cytochrome P450 (CYP) enzyme in the liver, CYP3A4 is responsible for the metabolism of numerous exogenous substances and the synthesis and transformation of endogenous substances [19]. For androgens, the CYP family primarily employs CYP3A4 and CYP2C9/19. The former mainly catalyzes hydroxylation reactions of androgens such as testosterone, converting testosterone into 6β-hydroxytestosterone while participating in reduction and hydrolysis processes. The latter assists in the oxidative metabolism of androgens, serving as a compensatory mechanism when CYP3A4 activity is limited to ensure complete metabolic processes [20].

In peripheral tissues, androgens are either converted into the more active dihydrotestosterone form or locally inactivated, achieving tissue specificity [21]. The primary enzyme involved in the conversion (Figure 2) is 5α-reductase (5AR), which has two subtypes in humans: 5AR1 and 5AR2. The former is mainly distributed in the skin [22], while the latter exhibits higher activity in the prostate and visceral fat, responsible for converting testosterone into dihydrotestosterone (DHT).

FIG. 2. Peripheral metabolism of androgens



Testosterone Dihydrotestosterone

Recent studies indicate that gut microbiota metabolize conjugated hormones into free DHT via β-glucuronidase [23]. The concentration of DHT in feces can be over 70 times higher than in serum, creating a unique high-DHT microenvironment, which provides an additional source of androgens for PC lesions [23]. More importantly, after ADT, the DHT synthesis involving gut microbiota remains unaffected. This may allow DHT to reach PC through bloodstream, thereby promoting tumor growth. Meanwhile, the high DHT microenvironment can disrupt microbial balance, triggering chronic inflammation that further accelerates tumor progression [24].

Structural and functional aberrations of the androgen receptor

Central to the PC pathophysiology is the AR, a nuclear receptor that mediates the biological effects of androgens, primarily testosterone and DHT. AR is a modular protein composed of several distinct structural domains that play crucial roles in its function. N-terminal domain (NTD) is responsible for transcriptional activation by binding to co-activators, such as p160 family, to initiate downstream gene expression [25]. NTD contains activation function (AF)-1, a modular region with key transcriptional activating units 1 and 5, which work in cooperation with AF-2 of the ligand-binding domain (LBD) for full gene activation, controlling downstream protein interactions and signaling [26]. The C-terminal LBD, responsible for binding with androgens, undergoes conformational changes, presents AF-2 at the surface to interact with coactivators, which further stabilizes the AR-DNA complex to promote transcription initiation [27]. The DNA binding domain recognizes and binds to androgen response elements (ARE) on target genes via a conserved zinc finger structure [28]. Each of these domains contributes to AR's ability to regulate gene expression in response to hormonal signals, highlighting its role as a key player in PC biology.

In PC cells, abnormal activation of AR involves both traditional DNA-binding actions and rapid non-genomic signaling interaction with PI3K/AKT/mTOR and mitogen-activated protein kinase / extracellular signal-regulated kinase (MAPK/ERK) pathways, thereby driving continuous cell division, preventing cell death, and maintaining tumor growth [29, 30]. The traditional activation of AR signaling pathway involves ligand binding, conformational activation and associated release of heat shock proteins, leading to AR nuclear translocation, where it forms a dimer and binds to ARE to initiate transcription [31]. In treatment-naïve locally advanced PC, AR acts as a master regulator of the G1-S phase transition increasing the activity of cyclin-dependent kinases, phosphorylating retinoblastoma protein to release early region 2 binding factor, and reducing the cell cycle inhibitor p27, which ultimately promotes

DNA replication and cell proliferation [32]. Apart from this mechanism central to PC progression, the transcriptional activity of AR could be also modulated via coregulators that do not bind to DNA but enhance or repress transcription via chromatin remodeling [33, 34]. Among all AR coregulators, Forkhead box protein A1 is a crucial pioneer acting as a gatekeeper that binds to condensed chromatin, remodels nucleosomes to create accessible sites for AR binding, thereby controlling hormone-driven gene expression of PC [35].

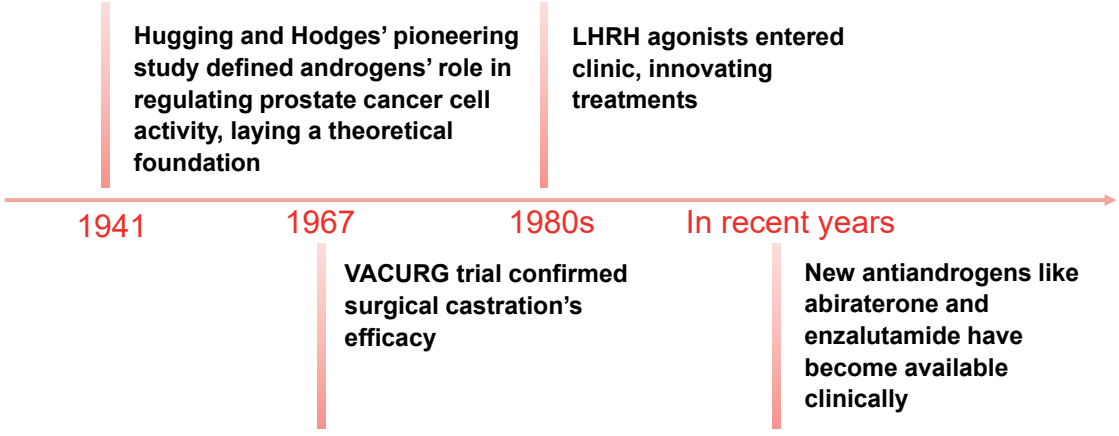
The complexity of AR signaling is further underscored by the existence of AR splice variants (AR-V) and AR gene amplification, that are significant players in PC progression and therapy resistance apart from the canonical full-length AR [36]. AR-V7 lacks the C-terminal LBD of the full-length receptor and functions as a constitutively active, ligand-independent transcription factor that stimulates tumor growth [37]. Additionally, missense mutations in the AR gene can alter ligand affinity and cause agonist-like activity by changing the shape of the LBD, particularly helix 12, allowing the receptor to bind to anti-androgens and activate the AR pathway instead of blocking it [38]. The common mutations include H874Y, F876L, T877A, W741L/C [39] that are the key drivers of resistance to ADT and treatment failure. Collectively, all these factors function as crucial intermediaries that dictate the strength and outcome of AR signaling in PC progression.

Androgen deprivation therapy and castration resistance

Androgen deprivation therapy modalities and clinical application

In 1941, Charles Huggins and Clarence V. Hodges pioneered a groundbreaking study that has identified the effects of androgens on the activity of PC cells [40] (Figure 3). This discovery established the androgen-driven model for PC, using serum phosphatases as biomarkers of PC, and laid the foundation for hormonal therapy, for which Huggins received the Nobel Prize in 1966 [41].

FIG. 3. The development of androgen deprivation therapy



Note: LHRH — luteinizing hormone-releasing hormone; VACURG — Veterans Administration Cooperative Urological Research Group.

The rationale behind ADT is based on the dependence of PC cells on androgens, and when androgen stimulation is lost, AR signaling pathway is inactivated, resulting in the inhibition of tumor cell growth and proliferation [40]. This includes surgical castration (orchiectomy) or pharmacological castration with agents that suppress hormone production (gonadotropin-releasing

hormone (GnRH) agonists / antagonists, androgen synthesis inhibitors) or block AR (anti-androgens). The overall information about available ADT methods is summarized in Table 2.

Table 2. Comparison of androgen deprivation therapy methods

Treatment category	Representative drugs/methods	Pharmacological effects and mechanisms	Key clinical features*	Notes and limitations*
Surgical castration [42]	Orchiectomy	Directly remove testicular androgen source to rapidly lower testosterone.	Advantages: rapid onset (within 24 h), permanence, low cost, no medication adherence issues. Indications: patients needing rapid testosterone reduction with advanced diseases.	Irreversible, psychological impact, persistent somatic side effects (e.g., hot flashes, osteoporosis).
GnRH agonists [43]	Leuprorelin, goserelin, triptorelin	Stimulate pituitary GnRH receptors for desensitization, inhibiting LH/FSH secretion and reducing testosterone synthesis.	Features: presence of "flare-up phenomenon" (transient testosterone elevation in the initial 1–2 weeks). Dosing: 1/3/6/12-month formulations. Flare-up management: concurrent use of antiandrogens (e.g., bicalutamide) for 2–4 weeks with the first dose to block flare-up risk.	Mainstream ADT option, monitor cardiovascular risks and long-term bone loss.
GnRH antagonists [44]	Degarelix	Directly block pituitary GnRH receptors, rapidly inhibiting LH and FSH secretion without testosterone flare-up.	Features: faster onset, no "flare-up phenomenon". Dosing: Loading dose 240 mg, maintenance 80 mg/month. Comparison: Efficacy comparable to agonists, but injection site reactions are more common, and anaphylaxis risk requires attention.	Patients need immediate, rapid testosterone reduction and intolerant to flare-up risk.
Antiandrogens [45]	First-generation: flutamide, bicalutamide Second-generation: enzalutamide, apalutamide, darolutamide	Competitive AR blockade. First-generation: AR LBD targeting. Second-generation: LBD blockade and AR nuclear translocation inhibition.	Features: monotherapy preserves testosterone/sexual function but inferior to castration. Application: often combined with GnRH analogs (CAB). Combined therapy or intermittent ADT.	Enzalutamide (high BBB permeability; monitor fatigue/falls); darolutamide (low BBB permeability; fewer central side effects).
Androgen synthesis inhibitors [46, 47]	Abiraterone, ketoconazole	Irreversibly inhibit CYP17A1 enzyme, blocking androgen synthesis in testicles, adrenal glands, and tumors.	Feature: potent systemic androgen suppression. Dosing: concurrent use with prednisone (5 mg, twice daily) to prevent mineralocorticoid excess. Indication: metastatic CSPC, non-metastatic CRPC.	Ketoconazole (early agent) is largely replaced by abiraterone due to significant hepatotoxicity and modest efficacy.

Note: * — Unless otherwise cited, the content in these columns reflects the authors' interpretive summary of the literature and does not constitute verbatim statements from individual references; GnRH — gonadotropin-releasing hormone; LH — luteinizing hormone; FSH — follicle-stimulating hormone; ADT — androgen deprivation therapy; AR — androgen receptor; LBD — ligand-binding domain; CAB — combined androgen blockade; BBB — blood-brain barrier; CYP17A1 — cytochrome P450 family 17 subfamily A member 1; CSPC — castration-sensitive prostate cancer; CRPC — castration-resistant prostate cancer.

First-line options for ADT involve reducing testosterone levels through surgical castration or pharmacological castration with GnRH antagonists or GnRH agonists combined with anti-androgens [48]. Surgical castration, orchiectomy, involves the removal of one or both testicles, leading to a significant reduction in testosterone production. While testosterone level below 50 ng/dL has long defined as "castration" in PC treatment, clinical studies suggest that reaching testosterone levels below 20 ng/dL as a result of bilateral orchiectomy leads to more profound androgen suppression, delaying disease progression and improving biochemical relapse free survival of patients [49, 50]. Orchiectomy is particularly effective in advanced PC as it offers immediate hormonal control, providing a rapid relief for patients

with metastatic disease. However, this definitive treatment is associated with psychological impacts, loss of libido, infertility and erectile dysfunction [51]. GnRH agonists, such as leuprolide and goserelin, act by overstimulating the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [52]. This therapy initially causes a testosterone flare, with peak serum testosterone at days 2–3, returning to baseline by days 7–8. Sustained overstimulation downregulates pituitary GnRH receptors, leading to castration levels of testosterone by approximately 2–3 weeks [53]. This mechanism makes GnRH agonists effective in reducing androgen levels over time, but the initial flare can exacerbate bone pain and spinal cord compression in patients with metastatic disease, necessitating a concurrent administration of anti-androgens to block the action of testosterone during the first few weeks of treatment [54, 55]. This combined approach, termed maximal androgen blockade, manages the initial surge, though GnRH antagonists could offer rapid androgen deprivation without flare and microsurges. Unlike GnRH agonists, GnRH antagonists provide a distinct approach by competitively binding to GnRH receptors in the pituitary gland and decreasing LH and FSH secretion [56]. Degarelix, most common GnRH antagonist, provides a rapid disease control, resulting in castration levels of testosterone within the first 3 days of therapy [57]. This makes GnRH antagonists particularly advantageous for PC patients who may experience complications from testosterone flare during the initial treatment phase with leuprolide [58]. First-generation antiandrogens, flutamide and bicalutamide, are non-steroidal molecules that prevent androgen binding to AR, thereby competitively inhibiting AR in PC cells and leading to tumor regression [59]. These antiandrogens are often used in conjunction with castration therapies, GnRH agonists, to enhance therapeutic efficacy. However, prolonged treatment with flutamide or bicalutamide is associated with side effects and most importantly, can lead to the development of castration-resistance [60]. Notably, the clinical role of non-steroidal antiandrogens (NSAAs) remains controversial. According to the European Association of Urology (EAU) guidelines, combined androgen blockade using NSAAs confers only a small survival benefit (< 5%) compared with ADT monotherapy, and this modest advantage must be balanced against increased adverse events. Given the superior efficacy of newer combination regimens, NSAAs are generally recommended only when other standard combination therapies are not available [61, 62].

Castration-resistant prostate cancer: definition and resistance mechanisms

Castration-resistant prostate cancer (CRPC) develops after loss of sensitivity to the initial ADT. As a result, PC relapses as the hormone-refractory disease, in which tumor cells are able to survive and proliferate despite the castration levels of testosterone [63]. Clinical criteria for the CRPC diagnosis include biochemical relapse or radiographic progression, evidenced by newly formed metastatic lesions, that develop at the serum testosterone concentration maintained below 50 ng/dL. Biochemical progression involves three consecutive serum prostate-specific antigen (PSA) increases with each 50% higher than the previous lowest point, separated by at least one week, and a final PSA level exceeding 2.0 ng/mL [64]. In 90% of cases with metastatic CRPC, bone metastases are developed, reducing the median survival of patients to 1.5-2 years [65]. One of the key events driving CRPC involves reactivation of AR signaling, when PC cells acquire advantageous adaptations for overcoming ADT. The mechanisms of hormone-refractory PC

growth include amplification or mutation of the AR gene, alternative splicing of AR and formation of AR-V7, increased synthesis of endogenous androgens from cholesterol or progesterone, activation of AR by non-androgen ligands such as glucocorticoids and antiandrogens acting as agonists [66]. It has been shown that AR-V7-mediated castration resistance in PC is attributed to reactivation of genes involved in lipid biosynthesis with fatty acid synthase being associated with poor prognosis and disease relapse [67]. The principal metabolic difference between CRPC and androgen-sensitive tumors is enhanced *de novo* lipogenesis controlled by Sterol Regulatory Element-Binding Proteins (SREBP), which are transcription factors activating a number of genes involved in lipid biosynthesis [15]. SREBP-1, encoded by the *SREBF1* gene, is overexpressed in advanced stages of PC and in androgen-independent tumors [68]. Hyperexpression of the gene, encoding SREBP-2, was detected in tumor tissues of patients with metastatic cancer, and in *in vivo* model systems of CRPC, nuclear expression of this factor increases threefold compared to androgen-sensitive tumors [69]. There is evidence of increased activity of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the most important enzyme of the mevalonate pathway of sterol biosynthesis, in PC cells resistant to AR inhibitors [70]. Therapy resistance of PC could be also driven via alternative tumor activation pathways, when AR suppression triggers androgen-independent mechanisms. Several growth factors including insulin-like growth factor 1 and epidermal growth factor can activate tyrosine kinase Src or lipid kinase PI3K that directly phosphorylate tyrosine residues on the AR, thereby triggering ligand-independent activation of AR [71]. Another important mechanism underlying progression of CRPC involves overactivity of oncogenic signaling pathways MAPK and PI3K/AKT that switch cancer cells to alternative survival routes independently of AR [29]. Finally, the tumor microenvironment plays a significant role in the hormone-refractory prostate tumorigenesis and immunosupression. It was identified that under ADT, tumor-associated macrophages deliver cholesterol to PC cells, thereby stimulating the synthesis of endogenous androgens. This metabolic cooperation triggers AR signaling pathway and ultimately leads to the progression of CRPC [72].

In addition to dysregulated lipid metabolism, glucose metabolism and glycolytic reprogramming also play critical roles in PC progression. Increased expression of monocarboxylate transporters (MCT) 1 and 4 contributes to enhanced glycolysis and lactate export in tumor and stromal cells, and high stromal MCT4 expression is significantly associated with biochemical recurrence and poor prognosis in patients with aggressive PC [73]. MCT1 and MCT4 promote glycolytic reprogramming and malignant progression in PC by mediating lactate transport between tumor and stromal cells. Their overexpression is closely associated with poor patient prognosis, supporting the rationale for developing targeted therapies against metabolic pathways [74].

Contemporary treatment strategies for castration-resistant prostate cancer

For patients with CRPC, standard treatment consists of next-generation AR inhibitors, often combined with chemotherapy, targeted therapy, or immunotherapy to improve survival. Second-generation antiandrogens, enzalutamide and abiraterone, have been developed to overcome resistance mechanisms associated with first-line therapies [75]. Androgen synthesis inhibitors like abiraterone acetate target the enzymatic pathways involved in androgen production. By inhibiting CYP17A1 enzyme, abiraterone decreases the production of not only testosterone but also deplete residual non-gonadal

androgens [76]. This dual action is particularly beneficial for CRPC, in which cancer cells may adapt by utilizing alternative sources of androgens for growth. The use of abiraterone has been associated with significant improvements in overall survival when combined with prednisone, corticosteroid agonist [77]. The concurrent administration of abiraterone and glucocorticoids is standard to suppress the hypothalamic-pituitary-adrenal axis manage side effects such as hypokalemia, hypertension and fluid retention related to mineralocorticoid excess as a result of CYP17A1 inhibition [78]. Second-generation AR antagonists, enzalutamide, apalutamide and darolutamide, not only block the LBD of AR, but also inhibit its nuclear translocation, DNA binding and coactivator recruitment, leading to a more comprehensive blockade of androgen signaling [79]. Recent clinical trials in chemotherapy- and hormone-naïve metastatic PC show that enzalutamide or abiraterone, either used alone or in combination with ADT, could significantly improve metastasis-free and overall survival, suggesting the necessity to use these agents as the first-line options for high-risk advanced cases for better disease control and patient outcomes [80]. The landmark LATITUDE study proved that combining abiraterone with ADT significantly improves overall survival and radiographic progression-free survival in newly diagnosed high-risk metastatic castration-sensitive PC, reducing mortality by 38% [81]. Similarly, the ARCHES trial demonstrated long-term survival advantages for enzalutamide combined with ADT in metastatic hormone-sensitive PC, reinforcing the benefit of intensified AR pathway inhibition [82].

The clinical data presented in this section, including drug dosing, treatment regimens, and clinical recommendations, have been reviewed and aligned with the following international clinical practice guidelines: the EAU Guidelines on PC (2024 Update) [61], the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Prostate Cancer (Version 3.2026) [83], the European Society for Medical Oncology Clinical Practice Guidelines for Prostate Cancer (2020) [84], and the American Society of Clinical Oncology Guideline on Systemic Therapy in Patients With Metastatic Castration-Resistant Prostate Cancer (2025 Update, Living Guideline Version 2026.1) [85, 86]. Where discrepancies between sources exist, the recommendations reflect the consensus across these major guideline bodies.

Common side effects and complications of androgen deprivation therapy and their management

According to clinical data, approximately 50% of PC patients receive ADT during their disease course [87]. However, long-term ADT causes significant adverse effects due to disrupted hormonal homeostasis, including sexual dysfunction, metabolic disorders, cardiovascular diseases, osteoporosis, and anemia, which severely impair quality of life and may become life-threatening in severe cases [88]. Notably, ADT-related complications are also pathophysiologically associated with tumor microenvironment remodeling and therapeutic resistance.

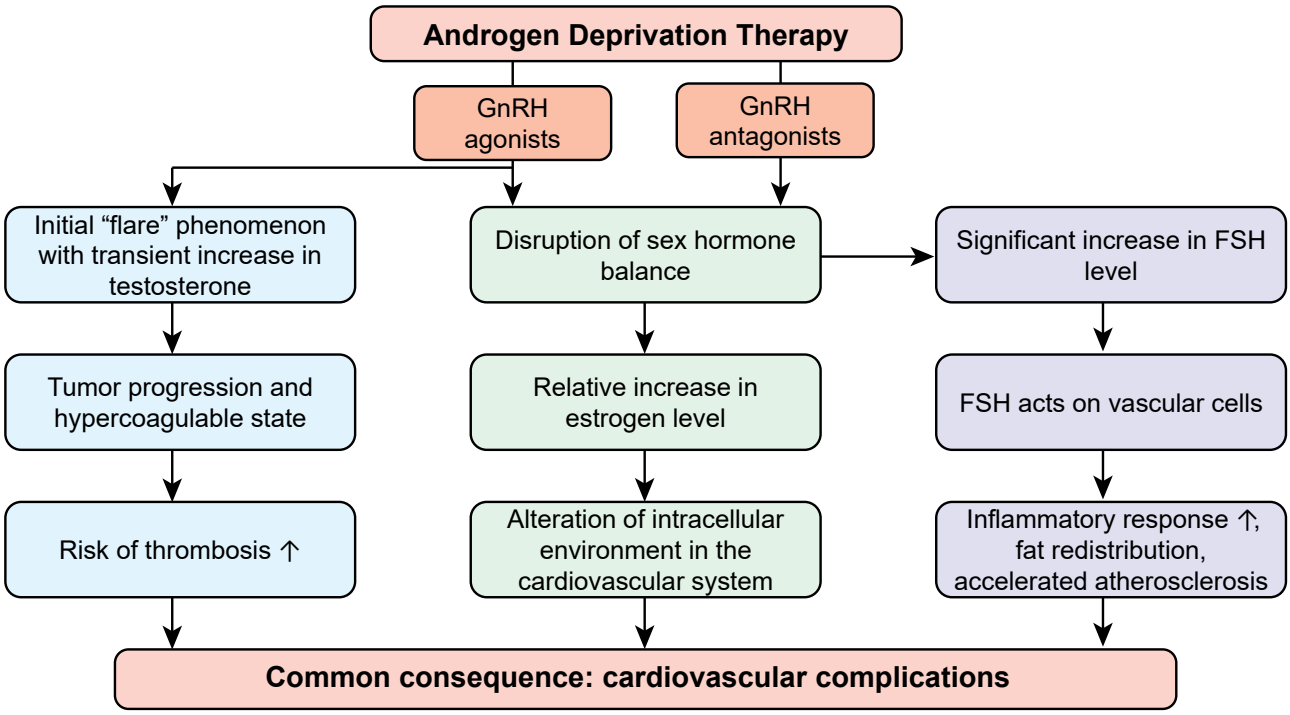
Cardiovascular diseases

According to prospective multicenter studies, PC patients receiving ADT increase the risk of developing major adverse cardiovascular events (MACE) [89]. A study in China showed that the overall prevalence of cardiovascular diseases in this group reached 27.0%, with 7.2% being multiple cardiovascular diseases. Additionally, the prevalence of hypertension was as high as 43.1%, and half of the patients had poor blood pressure control, further exacerbating their cardiovascular risks [90]. In PC patients with a history of heart failure,

myocardial infarction or arrhythmias, a risk of cardiovascular death during ADT treatment significantly increases [91].

FSH binds to its receptor on vascular endothelial cells and activates the PI3K/AKT/mTOR/NF-κB (Nuclear factor-κB) signaling cascade, which further upregulates the expression of vascular cell adhesion molecule-1 and E-selectin, thereby promoting endothelial inflammation and atherosclerosis [92]. As a result, this triggers inflammatory processes and accelerates the progression of atherosclerosis, thereby establishing a mechanism for plaque rupture and greater risk of cardiovascular diseases [93]. The disruption of hormonal homeostasis during ADT also contributes to hypercoagulable state and substantially increases the risk of thrombosis in PC patients [94]. Meanwhile, ADT-induced disruption of androgen–estrogen balance further alters the internal environment of cardiovascular system, becoming another significant factor affecting cardiovascular risk. These mechanisms collectively reveal the multifaceted pathophysiological basis of ADT's cardiovascular toxicity (Figure 4). Evidence from clinical trials suggests that GnRH antagonists exhibit significantly better cardiovascular safety than agonists [95]. Analysis of the side effects of GnRH agonists versus antagonists suggests that degarelix is associated with lower incidence of MACE, myocardial infarction and stroke compared to agonists, particularly for patients with pre-existing heart disease [96].

FIG. 4. Core diagram of mechanisms underlying cardiovascular complications associated with androgen deprivation therapy



Note: GnRH — gonadotropin-releasing hormone; FSH — follicle-stimulating hormone.

A systematic risk assessment strategy for ADT-induced cardiovascular complications involves thorough baseline cardiovascular evaluation and continuous monitoring during treatment [97]. In terms of intervention strategies, lifestyle modifications, including individualized dietary approaches for effective weight management, regular physical activity and smoking cessation, remain the cornerstone in mitigating ADT-induced adverse cardiovascular effects. At the pharmacological level, statins not only regulate blood lipids but may also

exert additional protective effects through the anti-inflammatory mechanisms. For PC patients with comorbid hypertension and diabetes, enhanced blood pressure and glucose control are both critical in cardiovascular prevention [98–100]. Optimal cancer treatment requires multidisciplinary collaboration between oncologists and cardiologists to balance antitumor efficacy and cardiovascular safety, defining cardio-oncology as a key component of modern comprehensive cancer care [101].

Metabolic syndrome and diabetes

AR signaling plays the critical role in metabolic homeostasis by enhancement of insulin sensitivity and direction of lipid metabolism in muscle tissues and liver, thereby preventing fat gain and promoting lean mass [102]. This is the reason why androgen deficiency under ADT is the key driver of metabolic syndrome and the progression to type 2 diabetes mellitus [103]. Clinical evidence suggests that ADT is significantly associated with dyslipidemia (total cholesterol increased by 7–10%, triglycerides by 26%), altered body composition (visceral fat accumulation with muscle loss), insulin resistance, and elevated fasting blood glucose levels [104]. These effects increase diabetes risk in PC on ADT, while also significantly raising the risk of liver pathology [105].

Sarcopenia and physical decline

The underlying mechanism of ADT-induced muscle loss, termed as sarcopenia, is associated with reduced androgen-supported muscle protein synthesis [106]. As a result, PC patients on ADT lose lean muscle mass while gaining fat mass, ultimately developing sarcopenic obesity, which increases risks for type 2 diabetes mellitus, MACE, bone fractures, and reduced physical function [107]. Clinical management for preserving muscle mass during ADT requires a multifaceted approach, which includes resistance-based exercises coupled with protein, vitamin D and calcium supplementation alongside monitoring mass changes [108, 109].

Osteoporosis and bone fracture risk

Androgens maintain bone metabolic balance through both direct effects, activation of osteoblast AR receptors, and indirect pathways, conversion into estrogen and muscle-skeletal coupling [106, 108, 110]. As a result of ADT, a significant loss of bone density develops in PC patients within the first 6–9 months of therapy [111]. After 2 years of ADT, 42.9% of men develop osteoporosis, and the proportion rises to 80.6% with ≥10 years of ADT, which features trabecular bone destruction and bone resorption greater than bone formation [112]. Therefore, bone-protective agents such as bisphosphonates, which trigger osteoclast apoptosis and denosumab, a monoclonal antibody against receptor activator of NF-$\varkappa$B ligand that prevents osteoclast formation, are used to improve bone mineral density in PC patients receiving long-term ADT.

Anemia

Physiologically, testosterone raises erythropoietin levels and stimulates erythropoiesis, promoting the differentiation of bone marrow haematopoietic stem cells into erythroid cells, a process disrupted by ADT [113]. ADT increases the risk of iron deficiency anemia in men with prostate cancer. The key underlying mechanism of this side effect involves ADT-induced testosterone deficiency that directly suppresses differentiation and proliferation of erythroid progenitor cells in the bone marrow [114]. The primary therapeutic interventions

aimed to mitigate the anemic syndrome in PC patients on ADT include nutritional support with iron, vitamin B_{12} and folate supplementation along with erythropoiesis-stimulating agents [115].

Sexual dysfunction

The primary cause of sexual dysfunction following ADT is the dramatic decline of testosterone that plays a critical role in maintaining libido and erectile function [116]. Although GnRH agonists may cause the initial testosterone surge, but eventually these pharmacological agents lead to castration levels of androgens via persistent suppression of pituitary function and GnRH receptor desensitization [43, 55]. AR is highly expressed in the smooth muscle cells of the corpus cavernosum. Physiologically, testosterone binding to AR activates nitric oxide (NO) synthase, which promotes NO production and smooth muscle relaxation in corpus cavernosum through the cGMP signaling pathway, thereby maintaining the erection [117]. ADT-associated testosterone deficiency reduces NO availability that impairs vasodilation and reduces penile blood flow, ultimately leading to erectile dysfunction [118]. Furthermore, decline of serum testosterone levels results in reduced stimulation of insula, frontal lobe and thalamus, brain regions involved in sexual desire [119]. This neurological shift serves as the explanation for ADT-associated decreased libido and sexual interest. Treatment typically involves sexual therapy and short-term ADT withdrawal for recovery.

Cognitive decline

Androgens exert crucial regulatory effects on key cognitive brain regions such as the hippocampus and prefrontal cortex through their AR [120]. These mechanisms primarily involve support of neuron survival in the hippocampus, promotion of long-term potentiation and dendritic spine growth, suppression of neuroinflammation. They also increase neprilysin, which is responsible for Aβ clearance and prevention of plaque buildup [121]. Clinical observations indicate that patients undergoing ADT develop widespread cognitive impairment after six months of treatment characterized by significant decline in multiple cognitive domains including attention, memory and executive functions [122]. From the perspective of pathophysiology, these cognitive impairments are closely related to the reduced neurogenesis, impaired synaptic plasticity, aggravated neuroinflammatory response and imbalance of neurotransmitter system, which need to be managed and treated in cooperation with neurologists and psychiatrists [123].

Future prospects

Therapeutic intensification

ADT remains a cornerstone of advanced PC management, with diverse strategies adapted to individual patient and disease characteristics. Since each approach has distinct benefits and drawbacks, treatment selection should account for tumor stage, patient preference, adverse effects, and progression risk [124]. Although ADT continues to be a foundational component in the treatment of metastatic PC, its limitations necessitate a shift towards combination therapies that leverage synergies with other treatment modalities, aiming to improve survival outcomes [125]. Recent evidence from ARASENS and PEACE-1 trials suggests that addition of docetaxel and second-generation antiandrogens to ADT, termed as triplet therapy, provides greater survival benefits for patients with metastatic castration-sensitive PC by intensifying

initial treatment beyond the ADT alone [126]. It has been shown that the triple therapy darolutamide + ADT + docetaxel reduces the risk of cancer-related mortality by 31% [127]. This treatment regimen has been recommended at the highest level (Grade I) in the Chinese Society of Clinical Oncology Prostate Cancer Diagnosis and Treatment Guidelines and has become an important clinical choice in oncological practice [128].

Immuno-metabolic synergy

The integration of immunotherapy approaches such as immune checkpoint blockade, adoptive cell therapy and tumor vaccines with ADT represents a promising avenue for enhancing treatment outcomes [129]. Immune checkpoint inhibitors have revolutionized the treatment of various malignancies, but their role in PC is still evolving with modest results as single agents but displaying durable responses in combinations with hormonal agents, chemotherapy or poly adenosine diphosphate ribose polymerase (PARP) inhibitors [130]. Preclinical mechanistic studies in PTEN-deficient PC models demonstrate that combining programmed cell death-1 (PD-1) inhibitors with ADT (degarelix) and pan-PI3K inhibition (copanlisib) significantly improves treatment response rates over single or dual therapies. Mechanistically, this triple combination upregulates major histocompatibility complex II on immunosuppressive PD-1^{hi} macrophages, enhances their phagocytic activity, remodels the tumor microenvironment, and boosts therapeutic efficacy [131]. Evidence suggests that ADT could increase the number of circulating naïve T cells, stimulate T-cell infiltration into the prostate tissue and decrease immune tolerance to PC cells, making it a rationale for combining androgen ablation with therapeutic vaccines for augmented effector T-cell responses [132, 133]. Furthermore, recent studies highlight the potential link between the gut microbiome and the efficacy of ADT. The composition of gut microbes may influence ADT response by modulating systemic immune status, offering new avenues for improving prognosis through microbial regulation [134]. Thus, the synergy between these immunotherapeutic approaches and ADT could potentially overcome therapy resistance in PC, resulting in durable responses and improved clinical outcomes of patients.

It is now becoming clear that treatment of advanced PC patients and the complications of ADT represents a serious economic and clinical challenge, requiring significant expenditure of the healthcare budget, particularly in patients with existing comorbidities [135, 136]. The existing interplay between AR signaling and aberrant lipid metabolism of PC suggests that reprogramming lipid uptake, synthesis and accumulation in cancer cells could enhance the efficacy of ADT while mitigating its adverse effects, including dyslipidemia and obesity [137]. Experimental studies have shown that ADT in combination with inhibitors of HMGCR, a key enzyme in the mevalonate pathway of sterol biosynthesis, significantly suppresses the growth of enzalutamide-resistant PC [70]. Clinical evidence that combination of HMGCR inhibitors, statins, with ADT mitigates cardiovascular risks associated with long-term hormonal therapy while potentially enhancing anti-tumor efficacy [138]. Pharmacological reprogramming of key metabolic rearrangements in PC could be potentially achieved by combination of ADT with SREBP inhibitors targeting *de novo* lipogenesis.

Innovative technology and support

In the context of advanced PC, drug repurposing offers a pragmatic approach to therapy discovery. It capitalizes on the known safety profiles of existing medications to provide new options for patients with limited choices [139].

For instance, thermoreversible self-assembling polymers can be completely dissolved at low temperature and then spontaneously assemble into uniform-sized nanovesicles, when the temperature rises to body temperature. This serves as the ideal platform for intelligent encapsulation and on-demand release of drugs, particularly into the most vulnerable cell populations responsible for PC metastasis and therapy resistance [140–142].

Finally, systemic support for PC patients on ADT, particularly those with comorbidities, remains equally vital. The supplements and natural products with pharmacological activity can mitigate ADT-induced side effects such as anemic or metabolic syndromes and improve overall nutritional status, thereby supporting overall health during long-term disease management [123].

With the emergence of next-generation hormonal agents, chemotherapy and immunotherapy, combination regimens have produced substantial gains in survival for PC patients with high-risk or metastatic disease, signaling a shift toward more intensive and biologically guided treatment paradigms. Looking ahead, advances in precision medicine, supported by genomic, molecular and metabolic profiling of PC patients are expected to refine the balance between efficacy and tolerability of the therapy. Deep understanding of the complex interplay between androgen signaling, metabolism and PC biology holds a significant potential for developing novel targeted approaches that can be effectively combined with ADT to overcome castration resistance.

Predictive biomarkers

This dual approach, which refers to blocking androgen dependence and disrupting the key metabolic support system of the tumor simultaneously, may achieve synergistic effects by blocking androgen dependence while disrupting key metabolic support system of the tumor [143]. Precision medicine in CRPC has been further advanced by the identification of key molecular markers and regulatory mechanisms. Among these, AR-V7 and homeobox B13 (HOXB13) have emerged as promising predictive biomarkers with potential to guide individualized treatment [144].

In the PROPHECY study of 118 metastatic CRPC patients, AR-V7 positivity was associated with significantly shorter progression-free and overall survival (adjusted hazard ratio 1.9–2.4 and 3.5–4.2, respectively), with PSA response rates of 0%–11% versus 26–28% in AR-V7-negative patients [145]. Moreover, AR-V7 detection is influenced by circulating tumor cell (CTC) burden: CTC-positive/AR-V7-positive samples exhibit higher CTC counts and tissue AR-V7 expression, yet discordance between CTC and tissue AR-V7 status is common: 63% of CTC-negative patients and 62% of CTC-positive/AR-V7-negative patients had detectable AR-V7 protein in matched biopsies [146].

HOXB13 is a lineage-specific transcription factor and AR coregulator consistently expressed across PC stages. It demonstrates high sensitivity (97%) and specificity (99%) for identifying prostate origin, outperforming conventional markers in advanced metastatic disease. Notably, HOXB13 remains detectable in 84% of AR-negative CRPC and neuroendocrine prostate cancer, supporting its utility as a diagnostic biomarker for confirming prostate lineage, particularly in challenging cases [147]. Furthermore, *HOXB13* abundance correlates with *PSMA* expression and prostate-specific membrane antigen (PSMA) positron emission tomography (PET) standardized uptake values at both mRNA and protein levels, suggesting that PSMA PET may serve as an imaging biomarker reflecting HOXB13 transcriptional activity in aggressive disease [148].

Beyond AR-V7 and HOXB13, other predictive biomarkers have emerged in CRPC. Homologous recombination repair mutations (e.g., *BRCA2*) predict PARP inhibitor sensitivity [149, 150]. These biomarkers reflect the molecular heterogeneity of CRPC and highlight the value of comprehensive genomic profiling.

Conclusions

In summary, the treatment of PC has transitioned from simple androgen deprivation to a multimodal paradigm combining targeted, immunological, and metabolic approaches. This review focuses on mechanistic and pathophysiological insights relevant to ADT action, and associated adverse events. This review provides a comprehensive overview of key pathophysiological processes, although emerging targeted therapies, novel immunotherapies, or real-world evidence are not extensively covered owing to scope limitations; molecular biomarkers such as AR-V7 and HOXB13 are briefly introduced. Future progress requires a deeper understanding of the crosstalk between androgen signaling and the tumor microenvironment. By integrating ADT within precision-guided frameworks, we can optimize therapeutic efficacy, mitigate complications, and ultimately improve long-term patient outcomes.

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