Hypotheses and Current Treatment Options For Castration Resistance In Prostate Cancer

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Abstract

Prostate cancer (PCa) is the most common male cancer and is known to affect around one in eight males in the United States. However, it tends to progress slowly and is even curable in the early stages of the disease. Androgen receptor (AR) hyperactivity and overexpression are present in almost all cases of PCa. Targeting AR with androgen receptor signaling inhibitors (ARSIs) has proven effective at slowing tumor progression by chemically castrating the patient. However, this is not a permanent solution, as all tumors treated with ARSIs eventually become castration-resistant PCa (CRPC). This could be due to a myriad of reasons, such as mutated variants of AR, selective pressure from the use of ARSI drugs eliminating cells that express higher AR (AR+), or the activation of alternative pathways.

Additionally, mutated variants of AR may bind to precursors or splice variants of androgens and be unaffected by ARSIs; the tumors themselves may produce more androgens, or the tumor cells may become androgen-independent through the alternate pathways. Further treatment is based on a case-to-case basis depending on various clinical or molecular features, such as the patient's performance status, cancer grade or stage, and dynamic changes in prostate-specific antigen. Options include chemotherapy, intensified androgen deprivation therapy, and targeted therapy for specific molecules. Research for more effective approaches to treating CRPC is currently underway.

Keywords

Biomedical and health sciences; genetics and molecular biology of disease; cancer; prostate cancer; androgen receptor; androgen deprivation therapy; castration resistance.

Introduction

The projected number of new prostate cancer (PCa) cases in 2023 for the United States is roughly 288,000, accounting for 29% of all male cancer diagnoses (Siegel et al., 2023). Despite the large numbers, a majority of PCa cases are diagnosed early in their development due to routine screening procedures **(Schatten, 2018).** However, there will inevitably be tumors that resist first-line treatment. Androgen deprivation therapy (ADT), also known as hormone therapy or castration, is an approach to treating patients progressing to advanced and metastatic PCa (Weiner et al., 2020). ADT is based on the understanding that in the early stages of PCa development, the overactivation of the androgen receptor (AR) dictates the proliferation of the tumor cells in the prostate. In a healthy individual, AR in the cytoplasm binds to androgens, male-specific hormones such as testosterone, eventually inducing sexual development. However, this pathway is hijacked by PCa. The AR and its function are further described in detail in Section 1. In the present day, a variety of medications are available that act as AR signaling inhibitors (ARSIs), either by targeting the synthesis of androgens (leuprolide, degarelix, relugolix) or the binding ability of the AR themselves (enzalutamide, apalutamide, darolutamide) (Desai et al., 2021). All PCa eventually gains castration resistance from ADT, becoming castration-resistant PCa (CPRC) (Tan et al., 2015). Despite the involvement of other

pathways in CRPC, the AR remains arguably the most important driver throughout the progression of PCa (Chandrasekar et al., 2015). This review will briefly describe AR function, thoroughly examine several hypotheses for why castration resistance occurs, discuss treatment options for those with CRPC, and discuss how proposed hypotheses relate to current studies and treatment effectiveness.

1. Androgen Receptor Function

The AR is a ligand-activated nuclear transcription factor belonging to the steroid hormone receptor family and, as such, functions similarly to the estrogen, glucocorticoid, and progesterone receptors (ER, GR, PR, respectively). Because AR signaling plays a central role in the growth of PCa, the entire pathway is a rational target for PCa treatment. To initiate proliferation, androgen-sensitive PCa cells must activate a certain number of ARs (Jacob et al., 2021). Thus, many approaches have been devised to decrease the binding of androgens to ARs as much as possible, collectively known as ADT. Androgen levels can be lowered by surgically removing the testes, known as physical or surgical castration, which produces most of the body's androgens. A more popular option is chemical or medical castration through medication (Weiner et al., 2020).

Regarding the mechanism of action, testosterone and 5α-dihydrotestosterone (DHT) are the AR's native ligands. DHT is converted intracellularly from testosterone by 5α-reductase and binds to the AR. After binding, the heat-shock protein (HSP) disassociates from the AR, which then translocates to the nucleus from the cytoplasm, dimerizes, and binds to the androgen response element (ARE) in the promoter regions to initiate transcription of a variety of target genes, such as prostate-specific antigen (PSA) and TMPRSS2, to maintain the function of a healthy prostate **(Figure 1)**. The transcription of these genes initiates male sexual development and differentiation that would otherwise fail in these hormones' absences. This includes the development of both internal and external male organs (Tan et al., 2015). An illustrated version of an inhibited pathway will be provided to discuss CRPC treatments **(Figure 2)**.

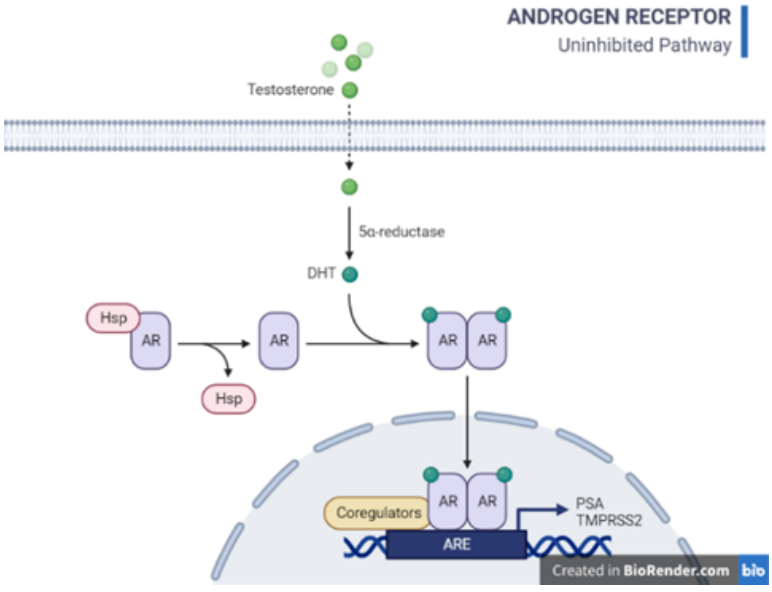

Figure 1. AR pathway action.

Testosterone enters target tissue cells and is converted to DHT by 5α-reductase. The HSP disassociates from the AR while DHT binds to the ligand binding domain. The AR dimerizes and translocates to the nucleus, binding to the ARE with coregulators to initiate a variety of transcription of target genes, such as PSA and TMPRSS. Figure created in BioRender.

2. Hypotheses for Castration Resistance

There are many hypotheses as to why PCa becomes castration-resistant. Considering the complexity and variation within tumors, it is likely that CRPC results from a combination of different mechanisms (Castellon et al., 2022). These mechanisms do not always relate to the AR: thus methods of developing castration resistance may be AR-dependent or AR-independent (Antonarakis & Armstrong, 2011).

2.1 Alternative Pathway Activation

Castration from ADT may encourage PCa cells to rely on alternative signaling pathways (Jamroze et al., 2021). This includes other steroid hormone receptors, such as GR and PR, and other cell growth-related pathways, such as the WNT signaling pathway (Murillo-Garzon & Kypta, 2017). The name, WNT, combines the term “wingless” from a Drosophila gene and “integrated” from a vertebrate homolog (Komiya & Habas, 2008). The WNT proteins secreted by the prostate tumor stroma into the microenvironment promote therapy resistance, and the WNT-β-catenin signals proliferation in prostate cancer stem cells, thereby promoting tumor growth. β-catenin acts as a major force in the WNT pathway, its presence activating canonical (β-catenin-dependent) signals that lead to the transcription of target genes with T-cell factor/lymphoid enhancer-binding factors (TCF/LEFs) such as the B-cell lymphoma nine protein family. To maintain a state of homeostasis, concentrations of β-catenin in cells are closely regulated by a system that ends in β-catenin degradation. Genetic changes in the gene encoding β-catenin (CTNNB1) that activate the WNT pathway are more frequently observed in CRPC than in treatment-naïve prostate cancer. Both a target gene of β-catenin and the transcriptional regulator ERG that is upregulated in roughly half of all prostate tumors, LEF1 has been the focus of most studies on the WNT pathway in prostate cancer as it is upregulated in CRPCn (Murillo-Garzon & Kypta, 2017). One such study draws a direct connection to AR signaling and the downregulation of LEF1, but also that the knockdown of LEF1 restricted cell proliferation in CRCP rather than androgen-dependent PCa (Luo et al., 2020). These results draw direct connections between ADT and shifting dependence on proliferation signaling from ARs to aspects of the WNT pathway.

Another prominent signaling pathway in the development of PCa is the phosphatidylinositol-3-kinase (PI3K), protein kinase B (PKB/AKT), and mammalian target of rapamycin (mTOR) pathway (Shorning et al., 2020). The PI3K-AKT-mTOR pathway is subject to frequent oncogenic activation that facilitates tumor formation, disease progression, and therapeutic resistance in both treatment-naïve PCa and CRPC. Specifically, PI3K activity is stimulated from a large variety of oncogenes and growth factor receptors, with elevated signaling considered by Fruman *et al.* a "hallmark of cancer."(Fruman et al., 2017). PI3Ks are a family of lipid kinase enzymes, and in human cells, they are expressed in three different classes: Class I (further divided into IA and IB), Class II, and Class III. There are three Class II PI3Ks and only one Class III. As heterodimers containing a catalytic subunit and a regulatory subunit, Class IA PI3Ks initiate a wave of signaling events to mediate cell growth, proliferation, autophagy, and apoptosis (Fruman et al., 2017; Shorning et al., 2020). With PI3Ks being only one portion of this complex set of pathway interactions, PI3K-AKT-mTOR poses many points of a possible change in the processes of PCa and castration resistance development. Other examples of points within the PI3K-AKT-mTOR pathway include the deregulation of phosphate and tensin homolog (PTEN) and other phosphoinositide phosphate enzymes, AKT mutation and amplification, and the entire pathway's intersection with different oncogenic signaling cascades, such as RAS/MAPK (Shorning et al., 2020).

The mentioned alternative pathways are not the only possibilities, and many other signaling pathways may be involved in the progression of PCa into CRPC. The complexities of PCa guarantee that no singular reason can be attributed to the development of CRPC.

2.2 AR Variants and Mutations

One particular variant of AR is AR splice variant 7 (AR-V7), which is often found to have an increased expression in CRPC (Castellon et al., 2022). Currently, the second-generation AR antagonist enzalutamide (ENZ) that competitively binds to the AR is an integral component of clinical endocrine therapies for CRPC (Zheng et al., 2022). Similar second-generation AR antagonists commonly used are apalutamide and darolutamide (Chen et al., 2022). ENZ's function is described in further detail in section 3 of this review as a treatment for PCa and CRPC. Considered a key driver in ENZ resistance in CRPC, AR-V7 furthers castration-resistance progression in PCa cells, being ligand-independent and continuously active. It is debated as to whether or not AR-V7 in PCa is dependent on full-length AR (AR-FL) as both are almost always co-expressed in the clinical environment (Zheng et al., 2022). In a model utilizing cistrome and transcriptome studies in CRPC cells, AR-V7 activity mainly depends on AR-FL (Cato et al., 2019).

Conversely, other research has noted that AR-V7 and AR-FL can independently participate in AR transcriptional activity. The production of AR-V7 is also not only limited to the use of ENZ, as a large proportion of high-risk Primary PCa patients were AR-V7 positive, meaning poor prognosis and lower survival rates of those with CRPC after treatment can be at least partially attributed to the generation of AR-V7.(Zheng et al., 2022) Thus, AR-V7 is a notable AR variant for its complete androgen independence, making it a difficult target for treatment.

Alterations in androgen metabolism within tumors, specifically intracrine androgen production, have also been associated with androgen sensitivity (Jamroze et al., 2021). Generally,

androgens are synthesized from cholesterol. However, there are three distinct types of synthesis pathways. The “classical pathway” involves converting cholesterol to DHT through several steps. The “alternative pathway” takes one of the intermediate molecules and converts it to DHT in a separate way. Finally, the “backdoor pathway” takes an even earlier precursor molecule as a substrate DHT synthesis. The alternative and backdoor pathways are activated in CRPC to circumvent the lack of later-stage intermediate molecules in the classical pathway (Zhang et al., 2022). These alternative pathways circumvent several common ARSIs aimed at androgen synthesis inhibition, requiring new avenues of investigation and study.

2.3 Heterogeneity and Cancer Stem Cells

Heterogeneity in the context of tumor cell populations refers to cells of the tumor being diverse in some way, lending a survival advantage. Increasing evidence points to tumors containing a heterogeneous population of both mesenchymal and epithelial cells that cooperate to accomplish a successful metastatic process, increasing the survivability and aggression of the tumor as a whole. The epithelial-mesenchymal transition (EMT) is the main pathway malignant epithelial cells use in carcinomas to switch to expressing a mesenchymal phenotype (Castellon et al., 2022). Tumor cells undergoing EMT acquire mesenchymal characteristics such as increased cell mobility associated with malignant progression and metastasis, increasing tumor cell survival with increased proliferation and regeneration (Chaves et al., 2021). As a common driver (Yang et al., 2021), zinc finger E-box-binding homeobox 1 (ZEB1) is considered a key factor in EMT. It is reportedly involved in androgen synthesis regulation in PCa cells. However, some cells that undergo EMT remain in the intermediary stage and display qualities similar to stem cells (stemness) (Chaves et al., 2021). Cancer stem cells (CSCs) are a small subpopulation of malignant cells with stemness characteristics and increased resistance to apoptosis and drug treatment. CSCs have been identified and characterized in multiple cancers, including PCa, in the last decade. A correlation can be drawn between aggressive and resistant neuroendocrine PCa (NEPC) cells that are AR-independent or AR-negative and CSCs based on the presence of specific cell markers, suggesting that NEPC cells may be associated with or represent a small population of CSCs (Castellon et al., 2022). A tumor dedifferentiated from more specialized cell types and obtains a more mesenchymal phenotype has an increased proliferative and metastatic success, resulting in a correlation between less tumor cell differentiation and worse prognosis (Jogi et al., 2012).

Heterogeneity is also seen in multiple primary tumor foci each at different stages of clonal evolution, thus meaning different areas of the tumor could also express different sensitivity to ARSIs. Tumor foci are cancerous cells differentiated from surrounding cells in some way, usually from when cancer develops simultaneously in the same organ. At the same time, clonal evolution refers to the genetic changes in tumor cells that occur from selective pressure, similar to natural selection among a species. This may arise from genomic alterations or phenotypic differentiation from CSCs, though more likely in combination. Based on healthy mouse prostate studies, it is suggested that in healthy cells, AR functions as a tumor suppressor in the epithelium and as a tumor promoter in the stroma. Thus, AR-deficient prostate epithelial cells exhibit increased proliferation and a loss of differentiation, resulting in larger tumors. With these differences in ARSI sensitivities within the same tumor, Jamroze *et al.* state that under the selective pressure of ADT, AR is known to become overexpressed and hyperactive from

genomic amplifications or sustain point mutations that affect the ligand-binding domain (LBD) that allow for ligand promiscuity. Nearly all AR mutations and structural alteration are suggested to be induced by ARSIs in hormone-targeting therapies, as they are only present in CRPC and not in treatment-naïve tumors (Jamroze et al., 2021). This correlation indicates the difficulty of finding a long-term effective treatment for CRPC. Differences in ARSI sensitivities result in more resistant foci surviving primary treatment and persisting into CRPC development.

3. Treatments for CRPC

Clinically, CRPC is defined as disease progression despite castrate testosterone levels below 50 ng/dL after ADT. Professional associations define disease progression differently; this paper will reference American Urological Association (AUA) guidelines. Thus, disease progression is defined as meeting one or more of the following: biochemical progression, defined as a continuous increase in PSA and a PSA of above 2 ng/mL; radiographic progression of new or pre-existing disease; symptomatic clinical progression (Lowrance et al., 2023).

ENZ, as previously stated, is a second-generation AR antagonist used to typically treat advanced PCa. To inhibit the AR signaling pathway, ENZ acts as a potent competitive binder of androgens, preventing the translocation of the AR to the nucleus to circumvent the transcription of tumor-promoting genes **(Figure 2)**. As part of the second generation of AR antagonists, ENZ exhibits a higher AR binding affinity than its predecessors (Chen et al., 2022). Though castration-resistant, CRPC still expresses AR, often even in excess. In this case, CRPC cells still retain responsiveness to stimulation from androgens, allowing enzalutamide to continue to block these responses (Saad, 2013). In a 2018 study conducted on non-metastatic CRPC (nmCRPC) patients, it was found that ENZ treatment significantly lowered the risk of metastasis or death, with 23% of patients in the ENZ-treated group developing metastatic CRPC (mCRPC) or dying as compared to the 49% receiving a placebo (Hussain et al., 2018). However, CRPC can develop ENZ resistance through various methods (Wang et al., 2021), notably through the emergence of AR-V7 in tumor cells, as described in section 2.2 (Zheng et al., 2022). Other AR antagonists, such as apalutamide and darolutamide mentioned previously, also function as competitive inhibitors (Chen et al., 2022).

Chemotherapy is another treatment option available for CRPC, as it bypasses many restrictions inherent to treating cancer, such as the AR, and thus is a mainstay in various cancer treatments. Docetaxel-based chemotherapy was established as a preferred first-line treatment for mCRPC after the results of the TAX327 and Southwest Oncology Group 99-16 trials in 2004 that showed lengthened overall survival when treatment was administered every three weeks regularly (Seruga & Tannock, 2011). Docetaxel is classified as a taxane, which interferes with microtubules and acts as a mitotic poison, thus inhibiting tumor cell proliferation (Kavallaris, 2010). Similarly to ENZ, PCa, not limited to mCRPC, can eventually develop docetaxel resistance. As stated with ENZ, there are several methods by which resistance to docetaxel can develop, with speculations often on the process of autophagy that acts as a defensive stress mechanism by enhancing cell stress tolerance (Cristofani et al., 2018; Xie et al., 2022).

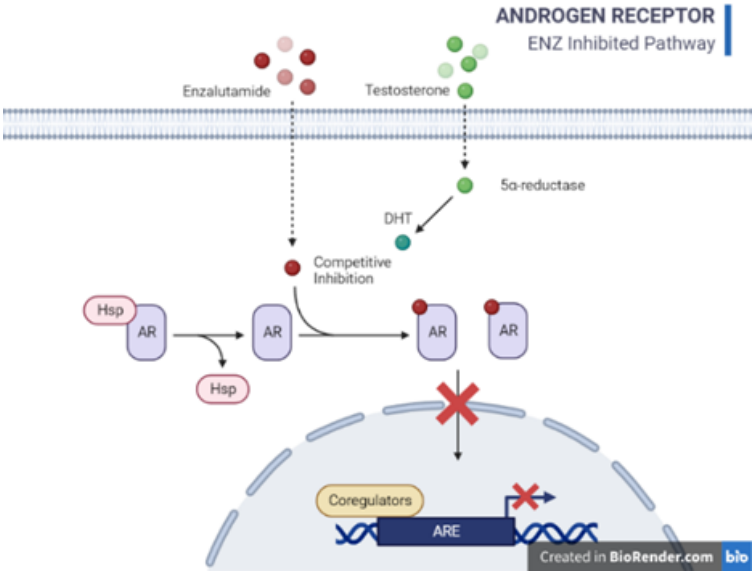

Figure 2. AR pathway action inhibited by ENZ.

Testosterone enters target tissue cells and is converted to DHT by 5α-reductase. The HSP disassociates from the AR while ENZ binds to the ligand binding domain, actively competing with and inhibiting DHT binding. The AR cannot dimerize or translocate to the nucleus, thus also unable to bind to the ARE with coregulators to initiate transcription of target genes, inhibiting cell proliferation. Figure created in BioRender.

4. Decisions on Treatments

The American Urological Association (AUA) has compiled and simplified many guidelines for treating advanced PCa on a case-to-case basis. These guidelines have been recently updated in 2023. Though few remarkably effective treatments for CRPC are currently available, the AUA has outlined the principles by which patients should be assessed and how physicians may proceed with treatment. In this section, guidelines for only CRPC treatment will be discussed briefly.

4.1 Clinical Principles

Generally, clinical principles are the set of ideals that should be upheld before and throughout treatment. When there is suspicion of advanced PCa and the patient has no prior histologic confirmation, clinicians should obtain tissue diagnosis through a biopsy. The patient's well-being and quality of life should be prioritized. Thus, a discussion of treatment options based on factors like life expectancy, other existing medical conditions or diseases, and tumor characteristics should be held, and engagement with professional or community-based resources should be advocated for.

4.2 Non-metastatic CRPC (nmCRPC)

Apalutamide, darolutamide, or ENZ with continued ADT is recommended for those at high risk of developing metastatic disease: for those who do not want or cannot have one of the standard therapies, observation and continued ADT is recommended, especially those at a lower risk for developing mCRPC. Systemic chemotherapy or immunotherapy is advised against, though the certainty in the evidence supporting this claim is limited.

4.3 Metastatic CRPC (mCRPC)

This category is further split based on various criteria. Clinicians make treatment decisions based on prior docetaxel treatment, symptoms, and performance status, typically determined by a patient's ability to self-care and physically strenuous activity (Lowrance et al., 2023). The most common site for metastasis is bone, with roughly 84% of metastatic PCa patients falling into this category. Thus, there is an emphasis on bone health throughout the AUA's guidelines. Other common sites include distant lymph nodes, the liver, and the thorax (Gandaglia et al., 2014).

4.3.1 No Prior Docetaxel

If a patient is asymptomatic or minimally symptomatic, it is recommended to prescribe abiraterone and prednisone, ENZ, docetaxel, or sipuleucel-T (Lowrance et al., 2023), a vaccine against prostate cells (Anassi & Ndefo, 2011). Patients who require regular opioid pain medications or narcotic medications for pain relief should not be included in this category as it could be used to treat comorbid symptoms attributable to metastases.

If symptomatic with good performance status, the same standard treatments are recommended aside from sipuleucel-T. Additionally, radium-223 should be offered by clinicians to patients with symptoms from bone metastases and without known visceral disease.

Because a majority of clinical trials exclude patients that are symptomatic with poor performance status, the confidence in many of the recommended treatments is lower than that of other categories. Thus, the AUA claims that treatments must be individually tailored in these patients after a "careful discussion of risks and benefits with particular attention to patient quality of life." Possible standard treatments include abiraterone and prednisone, or ENZ. Docetaxel chemotherapy may be recommended in select cases where performance status directly relates to cancer. Patients in this category with bony metastasis and no known visceral disease should be offered radium-223. Sipuleucel-T should also not be offered.

4.3.2 Prior Docetaxel

With a good performance status, further treatment focuses on maintaining the current performance status without “significant toxicity from additional therapy” (AUA). Abiraterone and prednisone, cabazitaxel, or ENZ are recommended. If abiraterone and prednisone have been received prior to docetaxel, they should not be offered again. Docetaxel retreatment may also be offered. As with other cases of bony metastasis with no known visceral disease, radium-223 should be provided.

Genetic counseling is recommended for patients who have exhausted all other treatment methods to determine the course of action. If a mutation in a BRCA gene is suspected, clinicians should offer patients a Poly ADP Ribose Polymerase (PARP) inhibitor (D'Andrea, 2018; Lowrance et al., 2023). Lutetium-177-PSMA-617, a new radioligand therapy (Sartor et al., 2021), should be provided to those with a positive PSMA PET imaging study (Lowrance et al., 2023).

With a poor performance status, especially with advanced solid tumors, treatment plans should be focused on increasing the patient’s quality of life and symptom management. In the patient’s final months of life, treatments may increase costs, add unnecessary symptom management, and delay access to end-of-life care. Those only capable of limited or no self-care and are confined to bed or chair for more than 50% of waking hours should not be offered further treatment. Expert opinions suggest palliative care and ENZ or radionuclide therapy for selected patients. Systemic chemotherapy or immunotherapy should not be offered (Lowrance et al., 2023).

5. Discussion

Most PCa cases are diagnosed at an early stage, mainly due to routine screening procedures, such as testing PSA levels and performing digital rectal exams (Schatten, 2018). However, this early diagnosis cannot provide a guaranteed cure for PCa or fully combat the rates of CRPC development. Considering that about 10-20% of PCa patients develop CRPC (Kirby et al., 2011) and the large percentage of males who develop PCa to begin with, there remains a significant need to continue research around mechanisms and treatment.

As stated throughout the hypotheses for castration resistance, the exact processes by which PCa becomes castration-resistant are unclear. Each method has significant evidence, but it currently needs to be determined what factors play important roles and which play supporting roles. Studies and trials to determine more effective treatments are ongoing, with castration resistance being an active area of research.

All current CRPC treatments are not cures but serve as measures to prolong life. PCa shows frequent trends of developing resistance to currently available treatment methods, including hormone therapies, chemotherapy, and even surgical removal. Generally, those with nmCRPC can live up to 14 months longer using recently developed drugs than those without. However, those with mCRPC tend to live for less than two years after developing mCRPC (Moreira et al.,

2017). As research continues, more effective treatments for CRPC and PCa as a whole look to be on the horizon.

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