The Progression of Prostate Cancer to Castration-Resistant Disease

Prostate cancer (PrCa) is the most common cancer found among men in the United States and is the second-leading cause of death for American males. Statistical analyses have projected an estimated 238,590 cases of PrCa among US men in 2013 alone, with approximately 29,720 expected deaths in this population during 2013. In males, the probability of developing invasive PrCa increases with each decade of life, with a risk that rises from 1 in 37 males between 40 and 59 years of age to 1 in 8 males for those who are 70 years and older. Between birth and death, the probability of developing invasive PrCa is estimated to be 1 in every 6 US men.1 Improvements in the early detection of PrCa have led to a substantial reduction in the number of patients who are diagnosed with advanced stages of the disease. Increased rates of screening for levels of prostate-specific antigen (PSA) have led to a notable decline in late-stage diagnoses of PrCa. Analyses of data from the Surveillance, Epidemiology and End Results (SEER) database between 1992 and 2008 identified a 75% reduction in late-stage disease incidence. However, regardless of these improvements in early detection, PrCa continues to be a leading cause of mortality among US males, invariably due to the emergence of hormone-refractory, androgen-independent disease.1-4

Although many patients with PrCa experience disease control after primary therapy, 1 retrospective analysis of patients who had undergone prostatectomy after an initial instance of PrCA found that 34% of patients developed metastatic disease after a median of 5.4 years of follow-up.5 For those men whose disease recurs, the majority will relapse biochemically as evidenced by elevated PSA levels, but the use and timing of androgen deprivation therapy (ADT) for biochemical relapse is controversial.6 Although higher levels of PSA at baseline in a patient is indicative of greater risk for metastatic disease or subsequent disease progression, it should be noted that PSA remains an imprecise marker of risk.7 PSA alone may not predict the onset of metastatic disease. Also, other factors, such as PSA doubling time, patient life expectancy, and comorbidities, may often prescribe when hormonal therapy is utilized. In patients with advanced disease, androgen deprivation blockade, which may be achieved pharmacologically or surgically, leads to the regression of metastatic disease in the majority of patients.8 With
androgen blockade, patients with high-risk, locally advanced, or metastatic disease may experience long-term regressions in disease activity, but advanced PrCa virtually always progresses to castration-resistant PrCa (CRPC), which is also known as androgen-independent PrCa (AIPC). CRPC is clinically detected by recurring symptoms, a rise in PSA levels, progression in soft tissue disease, or progression on bone scan. A significant PSA elevation is typically defined as 3 consecutive rises over its lowest point following treatment. This rise in PSA occurs in the context of the patient having castrate levels of serum testosterone (≤50 ng/dL) following a withdrawal of antiandrogen therapies for at least 4 weeks, despite secondary hormonal manipulations and/or radiologic evidence for disease progression.

The management of CRPC presents a number of difficult clinical challenges. Notably, systemic therapeutic options for this stage of PrCa have been very limited in the past. Historically, for patients with PrCa who failed hormonal therapy, traditional treatments were only approved for, and used primarily to provide, symptomatic benefits. These therapies included: (1) bisphosphonate agents to protect the skeletal integrity in patients with bony metastases; (2) secondary hormonal manipulations, such as ketoconazole combined with hydrocortisone; (3) the addition of antiandrogen chemotherapy; and (4) beta-emitting radioactive isotopes. Over the past decade, however, there have been substantial improvements in the understanding of the biological and genetic bases for the progression of PrCa. This increased comprehension is partially attributable to the development of high-throughput genomic, transcriptomic, and proteomic technologies. The mechanisms of androgen independence in CRPC have been researched extensively, including pathways that are mediated by the androgen receptor (AR), as well as AR amplification/overexpression is considered one of the major causes of disease progression to CRPC, and this overexpression may be attributed to factors such as gene amplification, transcriptional upregulation, translational upregulation, and decreased degradation. Increased expression of AR is required for the transformation of some PrCa cell lines from a hormone-sensitive phenotype to one that is refractory to hormone-deprivation therapy. AR overexpression occurs in most cases of CRPC, mostly due to transcriptional upregulation. A study published in 1995 that examined 23 samples of PrCa lesions found that AR gene amplification was detected in 30% of samples of recurrent tumors, whereas none of the primary tumors demonstrated AR gene amplification. Gene amplification leads to increased AR protein expression, which sensitizes PrCa cells to respond to low levels of androgen ligand.

Mechanisms Surrounding Development of CRPC and Metastatic Disease

Androgen Receptor Signaling and CRPC
Prostate function and cellular differentiation depend upon androgen receptor signaling (ARS), a component that is also critical in the progression of PrCa. The AR is expressed to some degree in almost all primary PrCas, and there appears to be a relationship between the AR on a cellular level, primary prostate tumors and metastatic lesions, and the subsequent progression of disease to CRPC. Androgens mediate their effects by binding to and activating the AR in normal and in cancerous prostate cells. Leuteinizing-hormone-releasing-hormone (LHRH) agonists and antagonists, as well surgical castration, deplete testosterone levels and thus abrogate signaling along the AR signaling axis. While ADT is highly effective, PrCa eventually becomes unresponsive to hormonal treatments, leading to CRPC. CRPC cells are capable of adapting to low circulating levels of androgens, and AR can become hypersensitive and activated by these low androgen levels, as well as through various other cellular mechanisms, which include: (1) AR amplification/overexpression; (2) gain of function AR mutations; (3) intracrine androgen production (the production of androgens by PrCa cells); (4) AR overexpression of AR cofactors that sensitize cells to low levels of androgens; (5) AR activation by cytokines or growth factors; and (6) altered ARs known as messenger ribonucleic acid (mRNA) splice variants that have androgenic activity in the presence of little to no androgen stimulation. Measurement of PSA is the most commonly used evaluation to detect progression of disease, and rising levels of PSA may indicate dysfunctional AR activity in CRPC. However, given the heterogeneity of the disease, patients can progress in bone and in soft tissue disease without a significant rise in PSA. AR Amplification/Overexpression
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static tumors compared with patients who have lower-grade primary tumors or those who have been treated solely with castration. Multiple mutations with different consequences on AR activity have been identified. Most identified mutations are associated with increased functional activity of the AR, leading to a receptor that is more sensitive to low levels of androgen or can be activated by other steroids, such as adrenal androgens, estrogens, and progestins, as well as anti-androgens that are designed to treat PrCa. Constitutive activation (gene expression) without ligand binding may also be observed. In addition to AR mutations, the discovery of AR splice variants has become a significant point of interest in CRPC therapy. These variants tend to exhibit transcriptional activity without the presence of androgens, and may contribute to the progression of CRPC in the presence of a ligand (ie, androgens) for activation.

**AR Coregulators**

Alterations of the balance between AR and its coregulators may also play a role in the progression to castration-resistant disease. Coactivators of AR have been shown to be overexpressed or overactivated in the development of progressive PrCa, with the deregulation of AR activators tending to increase with tumor progression, which is correlated with the aggressiveness of disease, poorer prognoses, and the development of CRPC. Many kinase pathways may enhance the activity of AR through the phosphorylation of coactivators. Oxidative stress can regulate AR signaling by affecting the levels of expression of AR coregulators, which then induces AR target gene transcription.

**AR Activation by Growth Factors/Cytokines**

Many patients with PrCa who do not have AR mutations nor amplification retain active AR signaling even when levels of androgen are reduced with antiandrogen therapy. Proliferation of PrCa can also be regulated via indirect pathways, involving paracrine mediators that are produced by stromal cells, which include insulin-like growth factor (IGF), transforming growth factor-β (TGF-β), fibroblast growth factor (FGF), and epidermal growth factor (EGF). These growth factors have been demonstrated to stimulate the expression of androgen-responsive genes, regardless of androgen levels. In addition, serum elevation of several cytokines has been found in patients with PrCa, and may be associated with more severe, malignant disease. For example, elevations in plasma interleukin-6 (IL-6) and its soluble receptor have been associated with progressive disease and poorer prognoses in patients with PrCa. In addition, the tumor suppressor gene (phosphatase and tensin homolog deleted on chromosome 10 [PTEN])/AKT pathway plays a role with the AR in tumor development and progression. Decreased PTEN expression also correlates with progression of disease. Growth factors and cytokines act together with AR signaling through their downstream intracellular signal-transduction pathways.

**De Novo Intraprostatic Androgen Synthesis**

AR signaling may also be increased in CRPC by the repletion of endogenous AR agonists within the tumor tissue itself. While dihydrotestosterone (DHT) levels may be similar or depleted in CRPC tumors when compared with those of untreated (pre-castration) tumors, intratumoral testosterone levels may be similar to untreated tumors in patients with castration-resistant disease. CRPC tissue can have levels of testosterone similar to that of androgen-stimulated benign prostate tissue, with levels of DHT approximately 10% as high as those found in androgen-stimulated benign prostate tissue. DHT can activate the AR, resulting in PSA expression at similar tissue levels in castration-recurrent and androgen-stimulated disease. Research has demonstrated that following castration, there is a 75% reduction in DHT that is present in prostate tissue, which prompted concern over whether the 25% residual DHT, post castration, can stimulate growth of residual prostate tumor cells. Data have shown that even small amounts of prostatic DHT, such as those that may result from adrenal androgens following castration, may stimulate protein synthesis of tumor epithelial cells. Intratumoral conversion of adrenal androgens and the steroid synthesis/conversion of adrenal precursors are other potential pathways that are implicated in the progression of PrCa to castration-resistant disease, and are currently undergoing investigation.

**Immune-Mediated Pathways in CRPC**

Immunotherapy for cancer is designed to stimulate the immune system of a patient in an effort to restrict tumor growth or to destroy the malignancy. Primarily used for advanced or metastatic stages of cancer, cancer immunotherapy attempts to delay or stop advancing malignancy through numerous mechanisms, such as targeting tumor-associated antigens (TAAs), or disrupting the pathways that support tumor growth. Advanced PrCa is a logical target for immunotherapy for several reasons. Generally, the disease progresses slowly, which allows time for immunotherapy to induce and potentiate T-cell–mediated immunity against the tumor. Slow progression of disease may also prevent the generation of signals that promote an immune response, and thus allow the tumor to evade detection. Immunotherapeutic approaches are also potentially valuable options because immunotherapy does not depend on high cell prolifer-
tion, and its potential targets may include any gene product expressed by PrCa cells. As the prostate is also prone to inflammation and infection outside of malignancy, and the body can produce an immune response when prostate tissue is affected by nonmalignant disease, it is hypothesized that cell-mediated immune responses may be utilized to stem tumor progression. Finally, the development of autoimmunity against prostate-specific TAAs is not likely to negatively affect the body itself, as the prostate is not an organ that is actually essential to life. Known circulating prostate-specific TAAs offer potential targets for immunotherapy, including PSA, prostatic acid phosphatase, and prostate-specific membrane antigen. The primary goal in this type of therapy would be to activate effector T cells that can migrate to developing tumors and mediate the destruction of malignant cells.

**CRPC and the Development of Osteoblastic Metastases**

CRPC is usually diagnosed by 1 or more of the following parameters: a progressive rise in serum PSA levels, an identified progression of preexisting disease, or the appearance of new metastases. Bone is the most common site for metastatic spread of cancer, which can develop whenever cancer cells relocate to the bony skeleton from the primary tumor site, making bone metastasis of special clinical concern in patients with PrCa. Approximately 90% of bone metastases related to PrCa are blastic lesions when visualized radiographically. Bone metastases have a marked impact on quality of life (QOL) for patients with advanced PrCa as they can cause severe pain, hypercalcemia, and increased risk of fracture. Further, metastases to the spine are common, and can lead to spinal cord compression and neurological impairment. In a recent study published in 2011, investigators conducted autopsies on 13 men who had died from PrCa, and the results demonstrated that all 13 cases had evidence of metastatic bone involvement.

The architecture of the human skeleton is determined by a balance between bone resorption, which is mediated by osteoclast cells, and bone formation, which is governed by osteoblasts. A "steady state" of bone metabolism is achieved by coupling these 2 processes. The formation, function, and survival of osteoclasts are regulated by tumor necrosis factors (TNFs), which can either promote or inhibit osteoclast activity. Among TNFs, there are 3, specifically, that constitute a molecular triad which impacts both normal and pathological bone metabolism: (1) RANK, (2) RANK Ligand (RANK-L), and (3) osteoprotegerin (OPG), which functions as a decoy receptor for RANK Ligand. RANK serves as a signaling receptor that is expressed on osteoclast precursor cells and activates osteoclasts, while RANK-L is a mediator of osteoclast formation, function, and survival. RANK-L binds to RANK, stimulating osteoclast precursors to form and differentiate into functioning osteoclasts. OPG is secreted by osteoblasts, and by acting as a decoy receptor for RANK-L, OPG inhibits the binding of RANK-L to RANK, which thereby reduces the half-life of membrane-bound RANK-L. Overall, OPG reduces osteoclast activity by blocking osteoclast differentiation and adhesion to bone surfaces, and by promoting apoptosis of activated osteoclasts. In patients with bone metastases, the equilibrium between the opposing actions of RANK-L and OPG is interrupted, which disturbs the normal rates of bone resorption and formation, ultimately leading to bone architecture abnormalities. This is an effective therapeutic approach despite the fact that the majority of metastases in men with PrCa are osteoblastic. The expression of RANK-L, RANK, and OPG has been found to be high among patients with late-stage PrCa who are refractory to hormone therapy, and the high expression of these factors has also been found to correlate with disease stage and Gleason score, androgen status, and levels of PSA. Because the expression of RANK-L, RANK, and OPG is associated with more aggressive and advanced metastatic CRPC, those TNFs are strong candidates for diagnostic, therapeutic, and prognostic targets in the management of patients with CRPC.

**Biomarkers in CRPC: Moving Beyond PSA**

The therapeutic landscape for CRPC is continuously evolving and has recently experienced a rapid growth in the number of systemic agents that are used to treat advanced disease, such as novel hormonal therapies (eg, abiraterone, enzalutamide), immunotherapies (eg, sipuleucel-T), chemotherapy (eg, cabazitaxel), and drug agents that target the microenvironment of bone (eg, denosumab, radium 223). As treatment decisions to manage patients with CRPC and metastatic disease become more complex for clinicians, there are major clinical and research priorities that surround the investigation of biomarkers to better understand the natural history of CRPC, to identify the individuals who would benefit most from particular therapeutic agents, and to pinpoint early response or progression in an effort to improve targeted treatments and patient outcomes.

Beyond rising PSA levels and the Gleason scoring system, which is the strongest clinical predictor for the progression of PrCa, other prognostic markers are undergoing consideration for the management of CRPC, including the potential evaluation of the tumor microenvironment surrounding tissue invasion and metastasis. Immunologic approaches to detecting circulating tumor cells and also urine and serum...
markers under investigation offer potential sources for tracking disease progression. While prognostic biomarkers chart the natural history of disease, predictive biomarkers can identify the likelihood of benefit from a specific therapy, and may categorize a disease into more defined subsets, which thereby offers more individualized approaches to treatment. Predictive biomarkers under consideration in CRPC include bone turnover markers, alkaline phosphatase, androgen receptor splice variants, levels of androgen precursors, Ras/Raf mutations, and tubulin mutations, among others. These biomarkers are emerging as a potential “platform” for the guidance of therapeutic decisions, and will likely increase in importance over time as they progress in development.

A summary of current biomarkers validated by data was compiled in a study by Armstrong et al, which demonstrated the paucity of options that are currently available for predictive factors and prognosis post treatment (Table 1).

### Classifying CRPC for Optimizing Therapy and Management

While several methods for classifying CRPC have been used over the years, the most recently updated and accepted classification system was published by the American Urological Association (AUA) in May 2013. The clinical practice guideline identified 6 types of “index patients”...
with CRPC and was developed to “provide a rational basis for treatment of patients with CRPC, based on currently available published data.” Those 6 index patients were designed to represent the most common clinical scenarios that are actually encountered in practice when managing patients with CRPC. The models vary according to many facets, such as the presence or absence of metastases, degree of symptoms, performance status, and prior treatment with docetaxel-based chemotherapy or lack thereof (Table 2). The index patients may be further described as having the following characteristics:

- **Index patient 1:** This is a patient with a rising PSA level despite medical or surgical castration and no radiological evidence of metastatic disease. PSA-only failure is defined as a rising PSA level that is greater than 2 ng/mL higher than its lowest point; this rise must be at least 25% over nadir and must be confirmed by a second PSA level obtained at least 3 weeks later. The patient must have castrate levels of testosterone (≤50 ng/mL).

- **Index patient 2:** This patient has a rising PSA level despite castrate levels of testosterone, has documented metastases on radiographic imaging, and has no previous docetaxel chemotherapy treatment. The patient has either no symptoms or mild symptoms attributable to PrCa. If a patient requires regular narcotic medications for pain control, they are not included in this index category.

- **Index patient 3:** This patient has a rising PSA level despite castrate levels of testosterone, has documented metastases on radiographic imaging with good performance status, and has no previous docetaxel chemotherapy treatment. To be included in this category, the patient must have symptoms clearly attributable to PrCa metastases, not another medical condition. This patient should also require regular opioid pain medications to achieve adequate pain control for symptoms caused by metastatic disease.

- **Index patient 4:** This patient has metastatic CRPC (mCRPC), poor performance status, and has not received prior docetaxel chemotherapy. There are few trial data to support specific treatment in these cases, as patients with poor performance status are usually excluded from clinical trials. “However, treatments with acceptable safety profiles do exist and should be considered, even in poor performance status patients.” Such therapy must especially be considered in patients for whom poor performance status may be a direct result of PrCa and whose status may improve with effective treatment.

- **Index patient 5:** This patient has mCRPC, has completed docetaxel chemotherapy, which was often initiated early in the course of disease, and continues to be minimally symptomatic with excellent performance status. The focus of therapy here should be to maintain the performance status without significant toxicity from additional therapy.

- **Index patient 6:** This patient has mCRPC and is symptomatic, with poor performance status and previous docetaxel chemotherapy. Any treatment must focus on QOL for these patients, concentrating on symptom management. As treatment given in the last months of life may hinder access to end-of-life care and increase costs, patients with poor performance status should usually not be offered further treatment.

The ultimate goal of this guideline update is to provide classifications for evidence-based recommendations in the treatment of CRPC. It should be implemented in conjunction with recent, systematic literature reviews, as well as a complete understanding of each individual patient’s treatment goals. It must be noted that these patient indices are based upon clinical parameters that are predominantly used for drug approval (ie, symptomatic vs asymptomatic, visceral vs nonvisceral) and do not reflect whether an individual patient may be more or less responsive to a given type of treatment.

### Table 2. American Urological Association Guidelines for CRPC: Identified Index Patients

<table>
<thead>
<tr>
<th>Index Patient</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Index Patient 1</strong></td>
<td>Asymptomatic, non-metastatic CRPC</td>
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<tr>
<td><strong>Index Patient 2</strong></td>
<td>Asymptomatic or minimally symptomatic mCRPC without prior docetaxel therapy</td>
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<tr>
<td><strong>Index Patient 3</strong></td>
<td>Symptomatic mCRPC with good performance status and no prior docetaxel therapy</td>
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<tr>
<td><strong>Index Patient 4</strong></td>
<td>Symptomatic mCRPC with poor performance status and no prior docetaxel therapy</td>
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<td><strong>Index Patient 5</strong></td>
<td>Symptomatic mCRPC with good performance status and prior docetaxel therapy</td>
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<tr>
<td><strong>Index Patient 6</strong></td>
<td>Symptomatic mCRPC with poor performance status and prior docetaxel therapy</td>
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CRPC indicates castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer. Adapted from Cookson MS, Roth BJ, Dahm P, et al. *J Urol.* Published online May 9, 2013.

### Conclusion

CRPC presents serious challenges to both the patients suffering from this advanced form of PrCa and the clinicians managing these patients. Clinicians are often faced with
providing comprehensive diagnoses and assessments of the mechanisms that cause disease progression in an effort to guide appropriate and individualized treatments. By improving our understanding of the pathophysiological basis of CRPC and metastatic disease, and by identifying appropriate therapeutic and prognostic markers, the potential clinical benefit of targeted therapy is increased, and clinicians are enabled to better managed CRPC, improve the QOL for patients, and enhance clinical outcomes.

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REFERENCES


