Interpreting PSA levels in metastatic prostate cancer

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Introduction

Although prostate-specific antigen (PSA) plays an important albeit controversial role in the screening and diagnosis of prostate cancer (PCa), we will focus on the role of PSA in monitoring for progression across multiple stages of the disease. The variability in how PSA may be interpreted at each stage of the disease is reflected in Table 1. In localized disease, PSA (particularly PSA velocity) plays an important role in risk assessment and treatment decisions. PSA progression following localized therapy is termed biochemical recurrence (BCR), which is characterized by the occurrence of 2 consecutive PSA level elevations following definitive localized therapy. Of note is that currently there is no FDA-approved therapy for BCR. PSA rise in the postoperative patient or following radiation therapy is a trigger to consider local recurrence or the development of early metastatic disease.

Following BCR, the vast majority of patients will have disease that is still androgen-dependent/sensitive (a stage known as castration-sensitive PCa, where the PCa cells still require a certain threshold level of androgens to proliferate). The standard first-line treatment at this stage is androgen deprivation therapy (ADT), which decreases androgen levels or blocks androgen activity to inhibit tumor cell growth. PSA remains a relevant tumor marker for patients on ADT. ADT is given in this setting as a historical adjunct, because there is no documented survival advantage by giving a patient ADT in the setting of BCR. Although approximately 90% of men respond to ADT, resistance inevitably develops, resulting in a transition to castration-resistant PCa (CRPC).

This progression from castration-sensitive to castration-resistant disease is commonly defined by 2 consecutive PSA rises, at least 1 week apart, despite testosterone levels <50 ng/mL. At this point in disease progression, when a patient still has castrate levels of testosterone but is also experiencing rising PSA levels, it is essential to image the patient based on the recommended guidelines to detect metastatic disease as early as possible. Once metastatic CRPC (mCRPC) is identified, the clinician should consider implementing therapies associated with overall survival (OS) advantages and begin shifting the management focus away from PSA response and control. In patients with mCRPC, PSA is a less relevant monitoring parameter, especially in the context of therapeutic agents that have demonstrated a survival benefit with minimal impact on PSA such as sipuleucel-T and radium 223.

Given the evolving role of PSA throughout the various stages of PCa progression, we seek to provide an appreciation of the relative value of PSA at each stage. Our goal is to offer clinicians meaningful context within which to interpret and assess different treatment modalities throughout the PCa disease continuum.

PSA changes in localized disease

Unlike some of the available treatments for mCRPC that can impact OS without affecting PSA, all treatment options for localized disease have a significant effect on PSA levels. As such, PSA is an important tool in monitoring for disease progression in the localized setting. For men with clinically localized PCa, PSA measurements (particularly PSA velocity [change in PSA over time] and age-specific PSA) play important roles in risk assessment. This was evidenced in a study in which men with PCa were evaluated to determine whether PSA dynamics correlated with prognosis. The study showed that PSA velocity greater than 2.0 ng/mL per year was associated with a significantly higher risk of death due to PCa despite having low-risk disease.

Despite its role in risk assessment, PSA measurements have their shortcomings, including the high variability and ambiguity based on patient characteristics, tumor type and grade, and disease heterogeneity. Furthermore, PSA patterns generally differ based on the type of local treatment administered (eg, prostatectomy, radiation therapy, cryotherapy). For example, PSA levels following radiation therapy are typically <0.5 ng/mL. Following prostatectomy, however, the PSA often drops to undetectable levels (<0.1 ng/mL). In such cases, even a small rise in PSA following prostatectomy can be a sign of recurrent disease. Despite these factors, PSA functions as a reliable tumor marker after primary therapy and is therefore routinely used to monitor disease recurrence after definitive therapy.

PSA changes in BCR

Although many men with PCa can be cured with local therapies, 30% to 50% of patients will have evidence of BCR (defined as a rising serum PSA in the absence of signs or symptoms of recurrence) at 10 years after treatment with radical prostatectomy or radiation therapy. BCR is widely accepted as an appropriate endpoint for defining treatment failure in men with localized PCa. As such, monitoring PSA changes in this setting provides clinically useful information, which has implications for treatment decision-making.

For patients who have had a BCR after prostatectomy and have a low PSA (<0.5 ng/mL), early salvage radiation therapy is an appropriate
treatment option. The ASTRO/Phoenix Consensus provides guidelines for PSA failure after all forms of radiation therapy, thereby helping to guide treatment decision-making in this setting. According to these guidelines, 3 consecutive PSA rises or a rise in PSA ≥2.0 ng/mL above the nadir is predictive of treatment failure with great sensitivity and specificity after both external beam radiotherapy and interstitial prostate brachytherapy, irrespective of whether either of these treatments was accompanied by androgen deprivation.

### PSA changes in castration-sensitive metastatic disease

Castration-sensitive metastatic PCa is encountered in approximately 4% to 6% of newly diagnosed patients. It is often believed that local therapy is no longer sufficient to control the disease and a systemic approach is necessary. These PCa cells are “sensitive” to hormonal therapies (ie, ADT) that target the androgen receptor and lower testosterone levels, thereby killing tumor cells that require normal levels of androgens to function.

| TABLE 1 Overview of PSA Interpretation Along the PCa Disease Continuum |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Stage Along Continuum      | Local Disease               | Biochemical Recurrence      | Castration-Sensitive PCa    | CRPC (M0)                   | mCRPC (M1)                  |
| Treatment options:         | RP ± RT                     | RP (if not done earlier)    | ADT Brachytherapy           | ADT                          | Sipuleucel-T                |
|                            | RT +/- adjuvant ADT         | Brachytherapy Observation   | Orchiectomy (castration)    | Docetaxel + ADT              | Docetaxel                   |
|                            | Brachytherapy               |                             |                             |                              | Abriraterone                |
|                            |                             |                             |                              |                              | Enzalutamide                 |
|                            |                             |                             |                              |                              | Cabazitaxel                 |
|                            |                             |                             |                              |                              | Radium-Z23                  |
| PSA Considerations         | XXX                         | XX                          | XX                          | X                           | —                           |
| Clinical utility of PSA for disease monitoring: | | | | | |
| Considerations for interpretation of PSA: | | | | | |
| Pretreatment staging important for newly diagnosed patients with high-risk features to assess if cancer has spread beyond the prostate | | | | | |
| While poorly differentiated PCa tends to produce less PSA than well-differentiated PCa, this is not always the case | | | | | |
| Imaging/scanning considerations: | | | | | |
| RADAR: Scan when PSA reaches 5–10 ng/mL; scan for every doubling thereafter | | | | | |
| RADAR: scan when PSA reaches 2 ng/mL; If imaging is negative, conduct another scan when PSA reaches 5 ng/mL and for every doubling of PSA thereafter | | | | | |
| Patient Considerations      | | | | | |
| Abbreviations: ADT, androgen deprivation therapy; CRPC, castrate-resistant prostate cancer; M0, nonmetastatic; M1, metastatic; mCRPC, metastatic CRPC; PCa, prostate cancer; PSA, prostate-specific antigen; PSADT, PSA doubling time; RADAR, Radiographic Assessments for Detection of Advanced Recurrence; RP, radical prostatectomy; RT, radiation therapy.
ADT is effective in this setting in the vast majority (~90%) of patients.15 Maintaining effective testosterone suppression in men treated with hormonal therapy is an essential strategy in the management of castration-sensitive PCa. Following administration of hormonal therapy, serum testosterone levels should be assessed to ensure that castrate levels are reached.16 A testosterone level <50 ng/dL has been considered the standard castrate level threshold for over 40 years (according to regulatory authorities). As discussed previously, however, testosterone levels after surgical castration are much lower than 50 ng/dL. This has led to questions regarding the appropriate targeted castrate level of testosterone. The European Association of Urology Guidelines outline that testosterone levels should be <20 ng/dL, which is supported by evidence of better clinical results with testosterone levels in this range.17 It has been reported that 25% of men receiving continuous ADT have testosterone levels above the 50 ng/dL threshold and a direct correlation between serum testosterone levels and the time to development of CRPC was observed.18 Additionally, a significant association has been reported between serum testosterone levels 6 months after initiation of ADT and OS.19

PSA should be evaluated in conjunction with testosterone levels for all patients on hormonal therapy to ensure adequate castration is achieved. Although most patients with advanced PCa have an initial response to hormonal therapy, nearly all will eventually progress to a castration-resistant state, which is manifested by rising levels of PSA despite a low testosterone level (20–50 ng/dL).20 The co-testing of serum PSA and serum testosterone becomes particularly important for men on ADT with rising PSA levels. PSA levels often decline following administration of ADT. For those patients whose PSA is still rising, however, there may be a concern for occult micrometastatic disease.21 Traditional staging/imaging modalities have often failed to identify micrometastatic disease.22 Newer modalities may be useful such as NaF positron emission tomography (PET)/computed tomography (CT), and recently, a new diagnostic agent, fluciclovine (Axiumin™), has been approved by the FDA for PET imaging to identify micrometastatic disease in CRPC patients. They suggest the need to develop earlier detection of micrometastases but are not yet widely available in many clinical practices.22

Patients with castration-sensitive disease and high volume of metastatic disease at diagnosis

A small percentage of patients (3%–5%) with castration-sensitive PCa present with a high volume of metastatic disease at time of diagnosis. Findings from a recent trial (LATITUDE) have been published demonstrating that adding abiraterone acetate and prednisone to ADT significantly increased OS and radiographic progression-free survival (rPFS) in this subset of patients.23 Additional trials (Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer [CHAARTED] and Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy [STAMPEDE]) have demonstrated that the early use of docetaxel in this patient population significantly improves PFS and OS.24–26 Docetaxel was added within 2 to 4 months of initiation of ADT in these trials. In addition, the Radiographic Assessments for Detection of Advanced Recurrence (RADAR) II Working Group has recommended that chemotherapy should be initiated early in hormone-naïve, newly diagnosed metastatic PCa patients with a high volume of disease, which is consistent with the CHAARTED study findings.24,27 Of note, chemotherapy has not shown a benefit in hormone-naïve, newly diagnosed patients with a low volume of disease.28

CRPC nonmetastatic (M0)

Men with PCa on continuous hormonal deprivation therapy who have a rising PSA despite castrate testosterone levels are deemed castration resistant. If they are free of any detectable metastatic disease, they are classified as M0. The M0 patient represents an unmet need in PCa therapy. There are secondary hormonal manipulations that can be applied to the treatment regimen, but there is no conferred OS benefit and all patients will likely progress to metastatic disease. Thankfully, multiple clinical trials are ongoing in this space and will hopefully provide an option for these patients in the near future. Until that time, diligence in monitoring for the development of early metastatic disease and enrollment into clinical trials remains the most important objective in treating these patients.

Diagnosis of mCRPC

Over 80% of men with CRPC will progress to mCRPC (which is referred to as M1 CRPC after metastases are identified). Metastatic disease can often be missed, and there is increasing awareness of the presence of metastases in men believed to be nonmetastatic. In an era when clinicians can be discouraged from ordering bone scans or CT scans for newly diagnosed localized disease, more regular imaging should be considered even in the absence of symptoms in the CRPC patient. Support for this can be found in the screening failure rates observed in studies of men with asymptomatic CRPC. In a study (the Endothelin A Use [ENTHUSE] trial, a phase 3 trial of zibotentan vs placebo in patients with nonmetastatic CRPC) that analyzed 2577 patients in 350 hospital-based centers in 39 countries, 32% of men believed to have CRPC had metastatic disease when screened via imaging.29 Another study (Impact of Abiraterone Acetate in Prostate Specific Antigen [IMAAGEN]) reported an even higher screen failure rate of 37%, which was consistent with screen failure data published from other nonmetastatic CRPC trials with similar inclusion criteria for PSA and PSA doubling time (PSADT).30,31

It is pertinent to note that the screen failure rates from these studies were likely underestimated, because imaging was done by traditional bone scans rather than newer more sensitive imaging techniques. Collectively, these studies indicate a high rate of unsuspected asymptomatic metastatic disease in CRPC patients. They suggest the need to improve diagnostic practices and prospectively define risk factors for development of mCRPC to ensure timely identification of metastases and access to effective treatment options that confer OS benefit. Being able to accurately assess the extent of disease in men with CRPC has important implications for treatment decision-making. The PCa RADAR guidelines were designed to optimize imaging of advanced dis-
As previously mentioned, PSA has diminished clinical utility in the metastatic setting. This has been demonstrated in an updated model generated from an analysis of data from 1050 patients with mCRPC receiving first-line chemotherapy. Eight prognostic factors were assessed for survival benefit in patients including Eastern Cooperative Oncology Group (ECOG) performance status (PS), disease site, lactate dehydrogenase, opioid analgesic use, albumin, hemoglobin, PSA, bilirubin, and alkaline phosphatase. Of these prognostic factors, PSA was the most important for predicting survival benefit. Interestingly, 20% of patients that where in the lowest quartile (<22.1 ng/mL) had more than 10 metastatic lesions prior to receiving sipuleucel-T treatment. This post hoc analysis was not powered for statistical significance, and the population within the subgroups was not randomized. Therefore, the findings are limited by their exploratory nature.

**Management of mCRPC**

As previously mentioned, PSA has diminished clinical utility in the metastatic setting. This has been demonstrated in an updated model generated from an analysis of data from 1050 patients with mCRPC receiving first-line chemotherapy. Eight prognostic factors were assessed for survival benefit in patients including Eastern Cooperative

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**FIGURE 1** RADAR imaging recommendations for castration-sensitive PCa and castration-resistant PCa

*Based on PSA testing every 3 months. Abbreviations: PCa, prostate cancer; PSA, prostate-specific antigen. Source: Adapted from ref 32.

For castration-sensitive PCa patients

**FIRST SCAN**

1st scan when PSA reaches level 5–10 ng/mL
- Imaging frequency if negative for previous scan:
  - Scan for every doubling thereafter and evaluate for metastatic disease

For castration-resistant PCa patients

**FIRST SCAN**

1st scan when PSA reaches level ≥2 ng/mL
- Imaging frequency if negative for previous scan:
  - 2nd scan when PSA=5 ng/mL and every doubling of PSA level thereafter*

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*Based on PSA testing every 3 months. Abbreviations: PCa, prostate cancer; PSA, prostate-specific antigen. Source: Adapted from ref 32. 

The timely diagnosis of metastatic disease allows for consideration of treatment modalities beyond the ADT pathway. This is underscored by the fact that multiple available treatments have demonstrated a survival benefit when administered in the early metastatic setting. By implementing the RADAR criteria, clinicians can diagnose metastatic disease in a more timely fashion and allow patients the opportunity for earlier administration of novel therapies. An exploratory analysis of the association between baseline PSA levels and OS benefit with sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial suggested that patients with less advanced disease may benefit the most from sipuleucel-T treatment. In this study, a comparison of patients in the lowest baseline PSA quartile (≤22.1 ng/mL) with those in the highest quartile (>134 ng/mL) revealed a mean survival difference of 13 months with a 49% reduced risk of death in the lower quartile versus 2.8 months survival difference with a 16% reduced risk of death in the highest quartile. These data support the early diagnosis of metastatic disease so that patients may benefit from early therapeutic intervention that results in improved survival. Interestingly, 20% of patients that where in the lowest quartile (<22.1 ng/mL) had more than 10 metastatic lesions prior to receiving sipuleucel-T treatment. This post hoc analysis was not powered for statistical significance, and the population within the subgroups was not randomized. Therefore, the findings are limited by their exploratory nature.
abiraterone acetate, enzalutamide, and radium-223 have all been shown to improve OS in large-scale, well-conducted clinical trials.37 The improvement in OS seen with these novel therapies in patients with metastatic disease is not always associated with changes in PSA.38 Of note, PSA progression alone was not a reason for discontinuation in the pivotal studies of these therapies and the Prostate Working Groups have cautioned that therapies should not be discontinued or changed solely based on PSA results. Two phase 3 studies evaluating sipuleucel-T in mCRPC demonstrated time to progression (TTP) and OS benefits with limited effect on PSA reduction.39,40 Of the 147 patients in the sipuleucel-T arms, only 5 patients had a PSA reduction of ≥25%, for an overall PSA response rate of 4.8%.39 Despite a modest/minimal impact on PSA, sipuleucel-T was associated with significant improvements in OS of over 4 months (23.2 months in sipuleucel-T arm and 18.9 months in placebo arm). Similarly, the alpha-emitting radiopharmaceutical radium-223 demonstrated improved OS relative to placebo but did not improve time to PSA or radiographic progression in the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial.39 In that study, only 14% of patients in the radium-223 group achieved a sustained PSA reduction (defined as >30% reduction in PSA blood levels), while OS was improved by almost 4 months (14.9 months in radium-223 group and 11.3 months in placebo group).41 Taken together, these data reinforce that a lack of effect on PSA does not correlate with a lack of systemic benefit in mCRPC therapies. As previously discussed, in a study examining the association between baseline PSA levels and OS benefit from sipuleucel-T, researchers found that patients with less advanced disease benefited the most from sipuleucel-T treatment with respect to OS.35 Timing is critical in the treatment of mCRPC patients, and immunotherapy may be best used earlier in the course of the disease to reset the immune system, when the disease is lowest. An additional review reinforced this concept by showing that early treatment with immunotherapy boosts the immune system’s ability to fight PCa.42 The National Comprehensive Cancer Network (NCCN) recommends that sipuleucel-T be used first-line for men with mCRPC (if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 months, ECOG PS 0–1 [category 1]), before agents such as enzalutamide, abiraterone, and chemotherapy. The use of first-line sipuleucel-T in mCRPC does not preclude the use of subsequent therapies.43

Communicating with patients and caregivers about the role of PSA

Effective communication is crucial to fostering collaborative decision-making and ensuring patient and caregiver understanding.44 As patients with PCa experience disease progression, they can experience anxiety about their PSA levels in the metastatic disease setting. In fact, a quality-of-life study identified PSA anxiety as the top-ranked concern of patients with mCRPC (receiving an importance ranking of 8/10 among 15 men interviewed).45

In some cases, the lack of impact on PSA may lead a patient, and some inexperienced clinicians, to inappropriately discontinue a new therapy. The urologist plays a pivotal role in educating patients and their caregivers about how to interpret PSA levels in the advanced disease setting. It is important to emphasize that many of the therapies currently available to treat mCRPC do not impact PSA the way that their primary therapies did and this is not reflective of a lack of systemic benefit. Additionally, it can be beneficial to discuss that many factors (beyond PSA levels) will be evaluated to determine the efficacy of a particular therapy. It can be useful to walk patients and caregivers through a theoretical model to explain the potential effect of various types of intervention on tumor volume and tumor burden over time (Figure 2).46

Summary/Conclusion

In the modern era, PSA testing has helped to shape multiple new clinical states of the disease.47 Following definitive therapy with either radical prostatectomy or radiation therapy, regular PSA testing often identifies BCR long before any visible metastases are detected via systemic imaging such as a bone scan, CT scan, or magnetic resonance imaging. Most patients with BCR are treated with ADT and, although most of these patients initially respond to ADT, the majority will experience disease progression to CRPC. Most of these patients will eventually develop detectable metastases and progress on to mCRPC before death.48 With an appreciation of the relative value and significance of PSA at the different stages of disease along the PCa continuum, we have provided context within which urologists can interpret and assess the different treatment modalities now available to treat advanced PCa (Table 1).

Earlier diagnosis of metastatic disease allows for timely treatment intervention with multiple available systemic agents that confer OS benefit. When immunotherapy is used as a first-line treatment for mCRPC, consistent with NCCN guidelines, the survival benefit is likely due to stimulation of the patient’s immune system when tumor burden is lowest and while the patient still has an intact immune system.49–51 This effect on the immune system persists long beyond the 6-week treatment period.52

![Figure 2](Image 324x563 to 342x582)

**FIGURE 2** Model of tumor growth rate over time based on different interventions

Source: Theoretical model adapted from ref 46.
The relevance of PSA, and how it changes as PCAs advances through its various stages, should be communicated clearly with patients and caregivers. With effective communication, the urologist can minimize the patient’s anxiety regarding treatment efficacy in the context of PSA fluctuations. In the early stages of PCAs, PSA plays a role in triggering concerns for the potential development of metastatic disease following definitive therapy. In the later stages of disease, however, patients need to understand that PSA, in isolation, has diminished relevance and a lack of PSA effect does not necessarily mean a lack of systemic benefit from the treatment they are receiving.

REFERENCES

It is important to understand the variability in how PSA should be interpreted at various stages along the PCa disease continuum; consider the following:

- **Track PSA velocity in localized disease** to assess risk and guide treatment decisions.
- Following surgery or radiation therapy; **recognize rising PSA as a flag for local recurrence** or the development of early metastatic disease.
- **Diagnose progression from castration-sensitive to castration-resistant disease** with 2 consecutive PSA rises, at least 1 week apart, despite testosterone levels <50 ng/mL.
- **Image the patient as outlined in RADAR guidelines** to detect metastatic disease as early as possible.
- In patients with mCRPC, **shift the management focus away from PSA response** and toward extending long-term survival.
- To obtain survival benefits, **utilize immunotherapy first-line (when baseline PSA levels are low)** for mCRPC, consistent with NCCN guidelines.
- **Remember that in mCRPC, survival benefits can be observed with minimal impact on PSA levels.**