Overview: Prostate cancer is a leading cause of male cancer mortality worldwide, accounting for 258,000 deaths annually. Prostate cancer is a disease marked by biologic heterogeneity that results in wide variations in clinical outcomes. The optimal management of prostate cancer requires the availability of validated biomarkers that can facilitate appropriate patient selection for therapy. Baseline prognostic factors, including stage, grade, and prostate-specific antigen (PSA) levels, are useful in many clinical disease states; however, additional biomarkers are needed particularly for more advanced stages of progression. One of the most promising predictors of clinical progression is PSA kinetics, or the observed rate of change in serum PSA over time. These have been examined as predictive markers in cancer detection as well as tumor progression. These have also been studied as treatment response markers for multiple therapies, including surgery, radiotherapy, androgen deprivation, and chemotherapy. Importantly, within certain disease states, PSA kinetics strongly predict clinical progression, including overall survival. Additional prospective studies are needed to confirm prior results; however, emerging applications include appropriate selection of patients for potentially toxic salvage therapies and clinical trial design. In summary, PSA kinetics are a powerful predictor of patient outcomes in prostate cancer and add value to currently available outcome models that include traditional staging factors.

Prostate-specific Antigen Kinetics in the Management of Prostate Cancer

By Mark Garzotto, MD

Prostate cancer is the most common visceral malignancy and second leading cause of cancer-related mortality in U.S. males. An important principle in the management of prostate cancer is that clinical outcomes vary widely within multiple disease states. In a study of patients who experienced biochemical recurrence (BCR) who were followed expectantly after radical prostatectomy, the median time to metastases was 8 years and time to death was an additional 5 years. Thus, since the majority of men with BCR are not destined to die of disease, tools that aid in accurate risk assessment are needed to aid clinical decision making.

Several factors, including stage, Gleason score, and PSA, have been repeatedly validated for the prediction of clinical progression, particularly in early-stage disease. Furthermore, these and other factors have been combined to create nomograms and other predictive tools, which further improve outcome prediction. However, the robustness of these tools is limited and improved markers are needed. Early identification of patients at substantial risk of clinical progression—in particular overall survival—is critically important to the appropriate use of potentially harmful salvage therapies. The application of predictive biomarkers to the clinical setting is a promising pathway to improvements in the treatment of prostate cancer.

PSA Kinetics

Clinical application of the PSA test radically altered the ability to identify early-stage, curable prostate cancer. This advance helped usher in refinements to both surgical and radiation therapies as a consequence of the prevalence and stage of the disease. A rise in the PSA after primary therapy may precede clinical recurrence by many years. A number of definitions have been recommended for the monitoring of prostate cancer in the post-treatment setting. In recurrent prostate cancer, an increase in PSA occurs nearly universally. After prostatectomy, BCR is predominately defined as either a PSA 0.2 ng/mL or greater or 0.4 ng/mL on two or more readings. Amling and colleagues showed an increase in PSA to above 0.4 ng/mL after prostatectomy correlated strongly with clinical progression. The European Association of Urology recommends a cut point of 0.2 ng/mL after prostatectomy. After radiation therapy, recurrence is defined as an increase of 2 ng/mL or greater above the nadir PSA obtained after completion of radiation. Used alone, these definitions correlate with increased risk of eventual clinical recurrence; however, time to clinical recurrence varies widely and these cutpoints have not been shown to predict overall survival. Limitations in intersubject discrimination may be due to varied growth rates of prostate cancer, heterogeneous PSA production, or other factors.

More recently, efforts have been made to improve outcome prediction with the use PSA kinetics, or the rate of change in PSA over a period of time. PSA is an extremely sensitive marker in the detection of recurrent prostate cancer; however, alone may not reflect the biologic potential of a cancer. Rate of PSA change is an alternative approach that has shown great promise as a biomarker in numerous clinical settings. In theory, the interval change in serum PSA from baseline values of an individual can be taken to represent growth of tumor mass over time. PSA doubling time (PSADT) and PSA velocity (PSAV) are the primary metrics of PSA kinetics, and have both been extensively studied in various disease states from prediagnosis to the most advanced stages of prostate cancer. There are limitations to its use including the fact that tumor burden alone may not predict adverse outcomes, as some tumors may be fatal despite there being reduced tumor burden. Also, aggressive prostate tumors do not uniformly secrete the PSA protein, which may make serial PSA assessments less reliable. Lastly, some therapies such as hormonal manipulations may specifically affect PSA thus causing dissociation between PSA and tumor status.

Pretreatment PSA Kinetics

PSA kinetics was first studied in a longitudinal population cohort of men without a known diagnosis of prostate cancer. Carter and colleagues analyzed an average of 10 serum samples collected from 18 patients with prostate cancer over a...
PSA kinetics involve evaluating the rate of prostate-specific antigen (PSA) decrease over time. A more rapid PSA velocity (PSAV) before surgery was associated with a 10-fold increase in the risk of death from prostate cancer compared with men with a PSA less than 2 ng/mL/year. In a study of 2,938 patients who had undergone prostatectomy, neither PSADT or PSAV was superior to absolute PSA alone in predicting BCR or metastasis-free survival. In a study by D’Amico and colleagues, a PSAV of greater than 2.0 ng/mL/year was an independent predictor of worse overall survival and cancer-specific survival compared with men with a more rapid PSAV. A PSAV by 2 ng/mL/year before surgery was associated with a 10-fold increase in the risk of death from prostate cancer compared with men with a PSAV less than 2 ng/mL/year. However, in a study of 2,938 patients who had undergone prostatectomy, neither PSADT or PSAV was superior to absolute PSA alone in predicting BCR or metastasis-free survival. In a recent review of PSA kinetics in the pretreatment setting, the authors concluded there is little evidence that PSA kinetics in untreated patients provide predictive information beyond PSA alone.

Active surveillance is another area where biomarkers are needed as an aid in decisions regarding timing of therapy. Because of concerns about potential tumor progression from patients and clinicians, a PSA rise alone in the follow-up period is the most common trigger for treatment of patients on active surveillance. A study by Ross and colleagues examined the ability of PSA change to predict tumor progression in a cohort of 290 patients who were low risk and followed expectantly. In this study, PSA kinetics were unable to predict pathologic tumor progression. It is understood that PSA kinetics have more limited predictive utility in early localized prostate, where benign prostatic hyperplasia, prostatic inflammation, and other factors may commonly induce alterations in PSA values. Despite these limitations, it is not known whether more long-term testing (i.e., 10 years) will provide higher quality data that can serve as an aid to decision making.

**KEY POINTS**

- The development of biomarkers that improve prediction of outcomes and guide treatment decisions are needed to optimize patient care.
- Prostate-specific antigen (PSA) kinetics have emerged as an independent predictor of disease progression and overall survival in certain disease states.
- The application of PSA kinetics is limited in the prediagnostic and pretreatment setting because of PSA fluctuations that occur due to the presence of an intact prostate.
- PSA kinetics are being incorporated into current clinical trial designs and will likely serve as a guide to therapy in the future.

**Post-treatment PSA Kinetics**

Clinical outcomes after treatment of the primary tumor either by surgery or radiation vary widely; thus, variables that allow for accurate outcome prediction are important in decisions to undertake salvage therapies. Numerous studies have evaluated the association of PSA kinetics to adverse outcomes after treatment of the primary tumor. In a study of healthy men treated with prostatectomy alone, the use of PSADT along with other clinical factors was able to strongly discriminate between men at risk for prostate cancer metastases and those who were not. Along with Gleason score and time to recurrence, a PSADT of less than 10 months compared with greater than 10 months allowed investigators to identify groups that ranged from 15% to 82% of remaining metastasis free. In a pooled analysis of patients who had undergone radiation and surgery and who experienced a BCR after treatment, PSADT was examined as a predictor of death from prostate cancer. A PSADT of less than 3 months carried a 20-fold increase in prostate cancer death as compared with men with PSADT of greater than 3 months. However, this subgroup was relatively small and thus not broadly applicable to the majority of patients with a BCR. In a separate study, the PSADT of less than 3 months subgroup comprised only 6% of all patients who experienced a BCR after prostatectomy. Importantly, although a PSADT of less than 3 months carried the greatest risk of mortality, 90% of prostate cancer deaths occurred in men with a PSADT of less than 15 months. In contrast, only 35% of men died from prostate cancer when the PSADT was greater than 15 months. Thus, in the postprostatectomy setting, PSADT is able to delineate graduated risk from clinically significant progression in men who experience BCR.

**Response to Salvage Hormone Therapy**

Use of PSA kinetics has also been retrospectively evaluated on a limited basis as a marker of response to therapy. In a study of patients undergoing salvage androgen deprivation for BCR after definitive therapy, the rate of PSA decline was evaluated as a predictor of survival in a pooled multi-institutional analysis. This analysis showed that the rate of PSA decline was directly related to prostate cancer–specific mortality. In a study by Pinover and colleagues, PSA kinetics was studied as a predictor of response to androgen deprivation after BCR. Men with a pretreatment PSADT of less than 12 months who were initiated on early hormone therapy had a 22% incidence of metastases at 5 years compared with 43% of men who were not initiated on early androgen deprivation. However, in men with a PSADT of greater than 12 months, there was no apparent benefit from early androgen deprivation. In a cohort of 747 men undergoing salvage androgen deprivation for BCR after primary therapy, a pretreatment PSADT of less than 3 months was associated with reduced prostate cancer–specific survival. Consistent with these data, PSA kinetics have been shown to predict treatment response to antiandrogen therapy. Thus, pretreatment PSA kinetics may serve to provide prognostic information as well as a treatment biomarker in the use of androgen deprivation. However, these studies require prospective validation before being widely adopted.

**Castration-resistant Prostate Cancer**

In men with castration-resistant prostate cancer (CRPC), PSA kinetics serve as a valuable predictor of clinical out-
comes. In a study of 201 men with nonmetastatic CRPC followed on the placebo arm of a therapeutic trial, both PSA and PSAV predicted metastatic progression and overall survival. Similarly, in an independent study of 331 men with nonmetastatic CRPC on the placebo arm, predictors of metastases and death were examined. A higher PSSAV was associated with reduced survival and bone metastasis–free survival. Robinson and colleagues examined the power of PSA kinetics to predict clinical disease progression in men with metastatic, new onset CRPC. They found that PSADT was the strongest clinical predictor of death by 9 months.\(^{30}\) PSA kinetics at the time of emergence of CRPC was also able to predict overall survival in a cohort of men subsequently treated with taxane-based chemotherapy.\(^{30}\) Specifically, a PSADT of less than 3 months was associated with a 3-fold increase risk of death compared with men with a PSADT of greater than 3 months. Similar results were reported in a European cohort that was subsequently treated with chemo-

therpay.\(^{31}\) In the chemotherapy treatment setting, PSA responses have been evaluated as a marker of overall survival in men with advanced CRPC.\(^{32,33}\) A PSA decline of 30% or more within 3 months of treatment was associated with a 50% improvement in overall survival.

**Conclusion**

There is a wide spectrum of biologic diversity among individual prostate cancer cases. The optimal treatment for recurrent prostate cancer is rapidly evolving with the increasing number of new agents available for clinical use. These factors present significant challenges to clinicians who are faced with the task of offering optimal and person-

alized treatments. PSA kinetics have emerged as candidate markers with the potential to improve clinical care for patients with prostate cancer and guide clinical trial design for the study of novel agents.

**Author’s Disclosures of Potential Conflicts of Interest**

<table>
<thead>
<tr>
<th>Author</th>
<th>Employment or Leadership Positions</th>
<th>Consultant or Advisory Role</th>
<th>Stock Ownership</th>
<th>Honoraria</th>
<th>Research Funding</th>
<th>Expert Testimony</th>
<th>Other Remuneration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark Garzotto</td>
<td>Centocor Ortho Biotech, Drecodeen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**REFERENCES**


26. Pinover WH, Horwitz EM, Hanlon AL, et al. Validation of a treatment policy for patients with prostate specific antigen failure after three-

dimensional conformal prostate radiation therapy. *Cancer*. 2003;97:1127-

1133.
PSA KINETICS IN PROSTATE CANCER


