PSA Testing for the Pretreatment Staging and Posttreatment Management of Prostate Cancer: 2013 Revision of 2009 Best Practice Statement

Panel Members:
Peter Carroll, MD, Chair; Peter C. Albertsen, MD, Vice Chair; Kirsten Greene, MD, Facilitator; Richard J. Babaian, MD; H. Ballentine Carter, MD; Pater H. Gann, MD, ScD; Misop Han, MD; Deborah Ann Kuban, MD; A. Oliver Sartor, MD; Janet L. Stanford, MPH, PhD; Anthony Zietman, MD

Explanation of Revised Document

This revised document contains the content of the "Prostate-Specific Antigen Best Practice Statement: 2009 Update" deleting that which pertains to the detection of prostate cancer. An updated guideline, available on the auanet.org website, is the 2013 AUA document "Early Detection of Prostate Cancer: AUA Guideline." Statements related to the detection of prostate cancer have been deleted, such that this revised document addresses only the use of PSA testing for the pretreatment staging and posttreatment management of prostate cancer. No other major changes have been made.

Introduction

PSA is a glycoprotein produced primarily by the epithelial cells that line the acini and ducts of the prostate gland. PSA is concentrated in prostatic tissue, and serum PSA levels are normally very low. Disruption of the normal prostatic architecture, such as by prostatic disease, inflammation, or trauma, allows greater amounts of PSA to enter the general circulation. Elevated serum PSA level has become an important marker of many prostate diseases – including benign prostatic hyperplasia, prostatitis, and prostate cancer, the focus of this document. Prostatic intraepithelial neoplasia (PIN) does not appear to raise serum PSA levels.1,2

The Use of PSA Testing for Pretreatment Staging of Prostate Cancer

Routine radiographic staging, such as with bone scan, computed tomography (CT), or magnetic resonance imaging (MRI), or surgical staging with pelvic lymph node dissection is not necessary in all cases of newly diagnosed prostate cancer (Figure 1).3,4 Clinical criteria can identify patients for whom such staging studies are appropriate.
Figure 1: Staging – Once Prostate Cancer is Diagnosed

1. Pretreatment serum PSA predicts the response of prostate cancer to local therapy.

Accurate pretreatment staging is crucial in prostate cancer management. Serum PSA levels correlate with the risk of extra-prostatic extension, seminal vesicle invasion, and lymph node involvement.

Pretreatment serum PSA is an independent predictor of response to all forms of therapy. Nomograms incorporating pretreatment PSA are statistical models that use important variables to calculate the probability of clinical endpoints, and have been useful in predicting outcomes of prostate cancer treatment.5,6

Pretreatment PSAV is an independent predictor of prostate cancer-specific and overall mortality.
following therapy. For example, men with localized prostate cancer and a pretreatment PSAV greater than 2.0 ng/mL/year may experience a significantly higher risk of cancer recurrence and prostate cancer-specific mortality following surgery or external beam radiotherapy.\textsuperscript{7,8}

2. **Routine use of a bone scan is not required for staging asymptomatic men with clinically localized prostate cancer when their PSA level is equal to or less than 20.0 ng/mL.**

An analysis of 23 studies examining the utility of bone scan found metastases in 2.3\% of men with PSA levels <10.0 ng/mL, 5.3\% in men with PSA levels from 10.1 to 19.9 ng/mL, and 16.2\% in men with PSA levels >20.0 ng/mL.\textsuperscript{9} The authors concluded that low-risk patients are unlikely to have disease identified by bone scan. Accordingly, bone scans are generally not necessary in patients with newly diagnosed prostate cancer who have a PSA <20.0 ng/mL unless the history or clinical examination suggests bony involvement. As metastatic disease is significantly more common in advanced local disease or in high-grade disease, and as some high-grade prostate cancers have lower PSA values, it is reasonable to consider bone scans at the time of diagnosis when the patient has Gleason 8 or greater disease, or stage ≥T3 prostate cancer, even if the PSA is <10.0 ng/mL.\textsuperscript{9,10}

3. **Computed tomography or magnetic resonance imaging scans may be considered for the staging of men with high-risk clinically localized prostate cancer when the PSA is greater than 20.0 ng/mL or when locally advanced or when the Gleason score is greater than or equal to 8.**

Although this guideline is commonly used by the experts in the field, supporting data are lacking. CT scan is not a useful staging procedure for the vast majority of patients with newly diagnosed prostate cancer for whom the estimated incidence of positive lymph nodes is approximately 5\%.\textsuperscript{11-13} CT is rarely positive when the PSA is <20.0 ng/mL and is generally reserved for men whose risk of lymph node metastasis is ≥20\% by Partin table estimation.\textsuperscript{14}

Additionally, several studies have found a correlation between Gleason score and lymphadenopathy detected on imaging; 1.2\% of patients with Gleason score ≤7 have detectable lymph node enlargement on CT scan, compared to 12.5\% in men with Gleason score ≥8.\textsuperscript{9} However, it should be noted that many men with Gleason scores of 8-10 on biopsy, may be downgraded based on examination of radical prostatectomy specimens.\textsuperscript{15} CT scan identification of pelvic adenopathy depends upon lymph node enlargement, and the correlation between nodal size and metastatic involvement is poor.\textsuperscript{16} Although the histologic incidence of positive pelvic lymph nodes is substantial when PSA levels exceed 25.0 ng/mL, the sensitivity of CT scanning for detecting positive nodes is only about 30\% to 35\%, even at these levels.\textsuperscript{12}
For similar reasons, MRI scanning using a body coil is also not a useful staging procedure in the vast majority of patients with newly diagnosed prostate cancer, because sensitivity is again determined by lymph node size. Its sensitivity for detecting nodal metastases, as determined from the analysis of seven studies using MRI, was only 36%. Endorectal coil MRI together with magnetic resonance spectroscopy (MRS) for characterization of cancer stage and volume is still considered an investigational procedure, but has shown promise in preliminary studies.

MRS allows MRI technology to identify functional and metabolic abnormality. However, imaging modalities of various types are being refined and will likely play a greater role in the routine diagnosis, staging, treatment and post-treatment evaluation of prostate cancer in the future.

4. Pelvic lymph node dissection for clinically localized prostate cancer may not be necessary if the PSA is less than 10.0 ng/mL and the Gleason score is less than or equal to 6.

Although pelvic lymph node dissection is often routinely performed in conjunction with radical prostatectomy, its morbidity, even if limited, must be considered. This is especially true in cases where it offers little additional information. A benefit to standard lymph node dissection has not been conclusively shown. Several studies have shown increased sensitivity; in addition, that there may be a recurrence and survival benefit associated with extended lymph node dissection, especially in intermediate- to high-risk patients, even when all nodes are negative. In extended lymphadenectomy, the area of additional dissection involves the region from the external iliac vein to the internal iliac vein medially, and to the bifurcation of the common iliac artery superiorly, rather than to just the obturator fossa. The benefit accruing to this more extended dissection must be balanced against the potential for increased morbidity, however, making careful patient selection critical.

Measurement of pretreatment PSA level, supplemented with clinical stage and Gleason score information, can identify a subset of patients in whom the incidence of nodal metastases is very low (3% to 5%). Patients with a pretreatment PSA level <10.0 ng/mL and a Gleason score ≤6 rarely have nodal metastases, and it may be appropriate to omit lymphadenectomy in this group. These observations have been made in several large series of patients.

The Use of PSA in the Post-treatment Management of Prostate Cancer

1. Periodic PSA determinations should be offered to detect disease recurrence. The early biochemical (PSA) detection of recurrence after definitive local therapy (Figure 2) may prompt further treatment. The optimal strategy for such adjunctive therapy, including time of initiation,
remains uncertain, and it is the focus of ongoing clinical trials and study. Different definitions of biochemical recurrence exist after surgery and radiation, making it difficult to compare recurrence free survival by time period. To date, it is unknown whether survival is altered by using PSA values to time the initiation of salvage therapy. Treatment options for recurrence following radical prostatectomy include surveillance, salvage radiation therapy, other forms of focal therapy, androgen deprivation and enrollment in clinical trials evaluating new therapies. Treatment options for recurrence after radiation therapy include surveillance, androgen deprivation, cryotherapy, additional radiation (i.e. brachytherapy), and salvage radical prostatectomy. Salvage therapies in both instances may be more effective if initiated early, but the overall impact of any form of salvage therapy is currently the subject of much study.

Figure 2: Posttreatment Assessment and Management

2. Serum PSA should decrease and remain at undetectable levels after radical prostatectomy.

A detectable PSA following radical prostatectomy is associated with eventual clinical disease recurrence in some, but not all patients. It may also be due to the presence of benign glands.

The AUA defines biochemical recurrence as an initial PSA value ≥0.2 ng/mL followed by a subsequent confirmatory PSA value ≥0.2 ng/mL. However, a cut-point of 0.4 ng/mL may better
predict the risk of metastatic relapse.\textsuperscript{41} This cut-point was selected as a means of reporting outcomes, however, rather than as a threshold for initiation of treatment. The median interval from PSA recurrence to cancer death is between 5 and 12 years, depending upon the Gleason score and PSA doubling time. The utility of “ultrasensitive” PSA testing has not been established as yet. Although its use seems to distinguish between those who are less likely and those who are more likely to recur, there may be considerable variability and inconsistency of results at low PSA levels.\textsuperscript{42,43}

3. Serum PSA should fall to a low level following radiation therapy, high intensity focused ultrasound and cryotherapy and should not rise on successive occasions.

Following radiation therapy, the PSA value should fall to a low level and then remain stable. PSA values <0.2 are uncommon after external beam radiotherapy, which does not ablate all prostate tissue. A consistently rising PSA level usually, though not always, indicates cancer recurrence. The number of rises needed to define a failure has been a matter of debate, but a consensus is emerging in support of the American Society for Therapeutic Radiation and Oncology (ASTRO) definition of failure: three successive rises above nadir.\textsuperscript{44} More recently it has been recognized that this endpoint is relevant only for external beam radiotherapy and even then it is easily confounded by biological variability.

The change in PSA following interstitial prostate brachytherapy is complex. Over the first year, the PSA level declines, then rises again in the second or third year in up to 40\% of cases, only to fall back to much lower values by year four.\textsuperscript{45-47} Although these rises (or “benign bounces”) are generally small (<0.8 ng/mL), they can, on occasion, be as high as 10.0 ng/mL, and they may last for 6 to 18 months. Their cause is uncertain, but they may correspond to infarction of the prostate occurring as a late vascular effect of the radiation. The principal concern regarding the benign bounce is that it may be confused with failure and lead to the initiation of unnecessary additional therapy. Ironically, bounces may actually predict a particularly good ultimate outcome.\textsuperscript{48} By the fifth year after interstitial prostate brachytherapy, the PSA level is <0.6 ng/mL in 90\% of patients who are clinically disease free. The median PSA level of these patients is <0.1 ng/mL.\textsuperscript{49}

A Consensus Committee was convened in Phoenix in 2005 to reconcile these differences and to produce a universal definition of PSA failure after all forms of radiation therapy, with or without androgen deprivation. The Committee arrived at the following conclusions: that any rise in PSA level of 2.0 ng/mL or more, over and above the nadir, predicted true 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. The
Consensus Committee also determined that the time of failure should not be backdated to the first rise in PSA.\textsuperscript{50,51} This endpoint, the “Phoenix Definition,” was designed to make comparison between any radiation series possible but did not facilitate easy comparisons with surgical series.\textsuperscript{52,53} It was designed as a research tool, rather than as a trigger for a clinical intervention. The Consensus Committee further noted that setting a “target PSA” was not possible after external beam radiotherapy, although for interstitial prostate brachytherapy a PSA level of <0.7 ng/mL at five years would be reasonable. They also commented that the PSA level continues to decline more than five years after interstitial prostate brachytherapy, allowing for even tighter definitions of failure with enough follow-up. Less data exist to document PSA behavior after either cryotherapy or high-intensity focused ultrasound.

\textbf{4. PSA nadir after androgen suppression therapy predicts mortality}

Though it has long been known that achievement of a low PSA nadir after hormonal therapy has prognostic significance,\textsuperscript{53,54} there are now increasing data that quantitatively link this end point to survival. For patients with metastatic disease receiving androgen suppression therapy, failure to achieve a PSA nadir of <4.0 ng/mL seven months after initiation of therapy is associated with a very poor prognosis (median survival: approximately one year) whereas those patients with a PSA nadir of <0.2 ng/mL have a relatively good prognosis (median survival: over six years). For patients with PSA nadirs >0.2 and <4.0 ng/mL, the prognosis is intermediate (median survival of 44 months).\textsuperscript{55}

Additional data to support the importance of PSA nadir following hormonal therapy are derived from studies of patients with nonmetastatic disease. For patients with a PSA rise following radical prostatectomy or radiation and no radiologic evidence of metastases, a PSA nadir of >0.2 ng/mL within eight months of androgen suppression is associated with a 20-fold greater risk of prostate cancer-specific mortality as compared to those patients with a PSA nadir of <0.2 ng/mL.\textsuperscript{56} A PSA nadir of >0.2 ng/mL in the setting of a PSADT of <3 months is an ominous finding. Taken together, these data clearly support the prognostic importance of the value of the PSA nadir after androgen deprivation therapy and suggest that careful PSA monitoring after the initiation of such therapy can effectively identify those patients with a poor prognosis.

For patients with hormone-refractory disease (defined as disease progression despite castrate levels of testosterone), the relationship between PSA decline and prognosis remains controversial. Despite multiple studies indicating that PSA declines of >50% correlate with survival,\textsuperscript{57-59} large well-controlled studies have shown mixed results.\textsuperscript{60-62} Attempts to establish PSA declines as a surrogate end-point for patients in this setting have not been universally accepted and more
investigation is necessary to create consensus. However, PSA kinetics do appear to correlate with outcomes in this group of patients. 63

5. Bone scans are indicated for the detection of metastases following initial treatment for localized disease but the PSA level that should prompt a bone scan is uncertain. Additional important prognostic information can be obtained by evaluation of PSA kinetics.

For patients with a rising PSA level after surgery or radiation for localized prostate cancer, the estimate of total PSA alone is an imperfect predictor of a positive bone scan. In studies where bone scans have been positive in this setting, PSA values have averaged between 30.0 and 140.0 ng/mL. 64-67 For this reason, the lowest PSA value at which bone scans will always be positive is uncertain. Several analyses 67,68 indicate that the rate of PSA change is an additional critical variable in this setting. For men with a PSA doubling time >6 months and a serum PSA <10.0 ng/mL, the probability of a positive scan is extremely low (less than 1%); however for patients with a PSADT of <6 months, there is approximately a 10% chance of a positive bone scan. Nomograms have been constructed which predict the likelihood of a positive bone scan using a combination of PSA kinetics and PSA values. 68 Thus, the use of routine bone scans in the setting of a PSA rise following local therapy is not justified, particularly for those with a PSADT of >6 months and a PSA value of <10.0 ng/mL.

6. The kinetics of PSA rise after local therapy for prostate cancer can help distinguish between local and distant recurrence.

Distinguishing local from distant recurrence is problematic after local treatments as most patients with a PSA rise have a negative physical exam and noninformative imaging tests. A positive biopsy in the prostate (postradiation) or at the anastomotic site (postradical prostatectomy) may not be the only reason for the rise in PSA, as a distant recurrence may also be a contributing factor. Accordingly, other variables are necessary for assessment. Perhaps the best method to assess for local recurrence after radical prostatectomy is to review the prognostic variables associated with durable responses to salvage radiation therapy. Pooled data from multiple centers indicate several variables in the salvage radiation setting that are predictive of a durable response to salvage radiation. 69 These variables include pathology findings at the time of surgery (seminal vesicle or margin positivity), PSA doubling time, PSA level at the beginning of radiation, and Gleason score. The PSA recurrence-free interval and the pre-operative PSA level are not thought to be consequential in predicting durable responses to radiation in this setting. Using these variables, one can risk-stratify patients into those more and less likely to respond to radiation. Of note, a positive post radical prostatectomy anastomotic biopsy does not independently predict
positive responses to salvage radiation, thus calling into question the value of this procedure.\textsuperscript{70}

Even patients with multiple adverse risk factors may respond to salvage radiation, especially those with positive surgical margins receiving treatment when the PSA is low (i.e. 0.5 to 1.5 ng/mL) and slowly rising.\textsuperscript{71} Given that salvage radiation is the only potentially curative treatment in this setting, such patients should strongly consider radiation.\textsuperscript{72} Whether or not radiation administered with concomitant androgen suppression is superior to radiation alone is an unsettled issue.

Predictors of favorable response to postradiation salvage prostatectomy are less well defined compared with those for salvage radiation following radical prostatectomy. Recurrent disease noted on prostate biopsy, PSA less than 10.0 ng/mL (preferably PSA less than 5.0 ng/mL), a clinically localized cancer (ie T1C or T2), and no evidence of metastases on prior evaluation or pre-operative imaging are reasonable criteria for consideration.\textsuperscript{73,74}

Excellent data now indicate that patients with a long PSADT (>15 months) have a low likelihood of prostate cancer-specific mortality over a 10 year period,\textsuperscript{75} and active surveillance may be considered for those with a life expectancy of <10 years. In contrast, patients with a PSADT <3 months have a median overall survival of 6 years following PSA failure, and are likely have distant disease.\textsuperscript{75,76} In addition, patients experiencing a relapse after local therapy may be candidates for clinical trials.

**Methods Used in Best Practice Statement Development**

The AUA convened a multidisciplinary panel for the purpose of developing a resource about PSA testing for urologists and primary care physicians. Panel membership included six urologists, one radiation oncologist, two medical oncologists, one internist and one epidemiologist. Funding in support of panel activities was provided by the AUA. Panel members received no remuneration for their efforts, and each member provided conflict of interest disclosure.

The Panel formulated its policy statements and recommendations by consensus, based on a review of the literature and the Panel members’ own expert opinions. The current policy was based on a reassessment of the previous policy published in 2000. After Panel members agreed on the general areas to be covered, each member took on the task of conceptualizing and writing and/or revising a section of the document in an area where he/she had specific expertise. Every part of the document was thoroughly critiqued by Panel members, both in written comments and in verbal discussions in a series of conference calls. Over the course of successive manuscript revisions, the Panel scrutinized and modified the conceptual framework, reworked the wording of
key statements, and reexamined supporting evidence reported in the literature until Panel members reached consensus.

The Panel did not use any particular methodology to develop its consensus statements. As noted above, these statements are based upon Panel members’ expert opinions and knowledge of the published literature, and are referenced with what the Panel considered to be the most appropriate publications. The Panel also did not address issues of costs or cost-effectiveness in this document, nor did it systematically incorporate patient values and preferences in the analysis. However, the Panel did include ample information in the document to assist patients as well as health care professionals in decision-making regarding the best use of serum PSA for staging and treatment follow-up of prostate cancer.

After the Panel reached an initial consensus, 70 peer reviewers representing the following medical specialties reviewed the manuscript: family practice, internal medicine, radiology, oncology and urology. The panel made numerous document changes based on insight from peer reviewers, Thereafter, the document was submitted for approval to the Practice Guidelines Committee of the AUA and then to the AUA Board of Directors for final approval.

The panel recognizes the limitations of the document and acknowledges that recommendations are likely to change with new information. However, it is hoped the information contained will assist physicians, other healthcare providers and patients in using serum PSA efficiently and responsibly.

References

Urol, 173, 777-80, 2005
2025, 2006
### Abbreviations and Acronyms

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<th>Abbreviation</th>
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<tr>
<td>ASTRO</td>
<td>American Society for Therapeutic Radiation and Oncology</td>
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<td>AUA</td>
<td>American Urological Association</td>
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<td>BPH</td>
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<td>cm</td>
<td>centimeter</td>
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