

Implications of Prostate Specific Antigen and its Molecular Derivatives in the Management of Carcinoma Prostate

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Abstract

Carcinoma prostate is the second leading cause of cancer-related deaths in men. In clinical practice prostate, specific antigen (PSA) estimation has been the gold standard for determining the presence of prostate cancer (PCa). Its elevation may indicate the presence of prostate disease but not always prostatic carcinoma. Identification of disease-specific molecular derivatives is the rational approach to addressing the current clinical challenge of whom to biopsy, whom to offer interventional therapy, and to plan the therapeutic strategies. The normal serum level of PSA is between 1.0 and 4.0 ng/ml, in men. The measurable PSA found circulating in the blood exists in complexed (cPSA) or bound form and free form (fPSA). Development of new monoclonal antibodies specific for fPSA and cPSA has allowed more accurate measurement of different molecular forms of PSA and their ratio in serum. Food and drug administration (FDA) has approved the measurement of fPSA in the diagnostic gray zone of 4.0-10 ng/ml. It can also be used as a decision-making tool for repeat biopsy. Measuring the ratio of [-2] pro PSA to total PSA further improves the specificity since they are raised in PCas. Same is true for the ratio of intact to fPSA. Volume based parameters and PSA velocity are other parameters which further refines the decision-making exercise. The present study is a focused review of these parameters of PSA, their implications, limitations, and use in the management of carcinoma prostate.

Key words: Carcinoma, Prostate specific antigen, Prostatic cancer

INTRODUCTION

The carcinoma prostate is the second leading cause of cancer-related deaths in men. Consistent elevation of total prostate specific antigen (tPSA) in serum, as well as a marked decrease in apoptosis and tissue differentiation, are a key factor in the progression of prostate tumor to advanced disease. In clinical practice tPSA has been the gold standard for determining the presence and/or staging of prostate cancer (PCa). As varying amount of tPSA value are found in patients with normal prostate functioning,

benign prostatic hyperplasia (BPH), and PCa. High serum tPSA levels are not diagnostic of the presence of prostatic cancer. There is no linear relationship between PSA and PCa stage and metastasis.

PSA is the most notable biomarker and is a member of Kallikrein family. It is also designated as hk3. It is an androgen-regulated protease.

Serum PSA becomes detectable at puberty, with an increase in luteinizing hormone and testosterone. PSA levels vary with age, race, and prostatic volume. Its elevation may indicate the presence of prostate disease, but not all men with the prostatic disease have elevated PSAs. Furthermore, PSA is an organ specific antigen and not cancer specific.

The PCa prevention trial has concluded that there is no PSA concentration that rules out cancer. The controversy that surrounds the use of this marker is currently being

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debated, because it is unclear whether PSA screening has led to a decline in mortality due to prostatic cancer or it has led to over diagnosis and over treatment of carcinoma prostate.

A recent large multi-institutional randomized trial looking at the relationship between PSA screening and PCa mortality published in the *New England Journal of Medicine* (NEJM) demonstrated that PSA-based screening reduced the rate of death from PCa by 20% but was also associated with a high risk of overdiagnosis.

This article discusses the implications of various molecular derivatives of PSA, relevant to carcinoma prostate (PCa) as a diagnostic tool.

CARCINOMA PROSTATE/THE CHALLENGES

PCa is the second leading cause of cancer-related death in men.¹ In the United States (US) approximately 240,000 men are diagnosed with PCa.² The prevalence of PCa increases with age. The chances of detecting PCa, in a 50-year-old man, are as high as 60%.³ The vast majority of men diagnosed with clinically localized PCa are treated with interventional therapies despite studies demonstrating that even without treatment, PCa specific mortality, is low.^{4,5} Early detection of PCa relies on the estimation of serum PSA, digital rectal examination (DRE) and ultrasonography.

Although the routine use of serum PSA testing has increased detection of PCa, it has also led to over diagnosis and over treatment, because of its lack of specificity, resulting in high negative biopsy rates.⁶

There is ever increasing need to find out an appropriate biomarker to address these challenges. The prostatic carcinoma is both biologically and clinically a heterogeneous disease that develops amid diverse genetic and epigenetic changes.^{7,8} Identification of disease-specific molecular biomarker is a rational approach to addressing the current clinical challenge of whom to biopsy, whom to offer certain interventional therapy, and whom to alter therapeutic strategies.

The National Cancer Institute defines a biomarker as “a biological molecule found in blood, other body fluids or tissues that are a sign of normal or abnormal process or of a condition or disease.” A biomarker may be objectively measured and evaluated as an indication of normal biologic processes, pathological processes, or pharmacologic response to a particular treatment or condition.⁹⁻¹¹

PSA, THE HISTORY

It was first identified and purified in 1970s, but widespread use in clinical urology did not occur for another decade. Before PSA was discovered, serum acid phosphatase was used as a biomarker for PCa. PSA is a 33 kD glycoprotein that acts as a serine protease.¹² Although it is produced by other tissues also in minute quantities, but for all practical and clinical purposes PSA is organ specific, primarily produced by the prostate luminal epithelial cells.

The Function

This androgen regulated protease liquefies semen through its action on gel-forming proteins, Seminoglobulin within the semen following ejaculation, but at present it is unknown why this clotting and its lysing mechanism is important to reproductive physiology.

Seminoglobulin is the predominant seminal vesicle secreted protein and is one of the physiologic substrates for PSA. The primary release of PSA into the seminal fluid results in 10⁶-fold higher seminal concentrations than levels measured within the serum. The concentrations found in seminal plasma ranges from 0.5 to 5.0 mg/ml whereas the normal serum concentration in man, at the age of 50-80 years, without prostate disease, ranges between 1.0 and 4.0 ng/ml. PSA expression is strongly influenced by androgen hormones.

The Highlights of PSA

1. Used as screening biomarker for Ca prostate
2. PSA-based screening reduced the deaths from PCa by 20% but also associated with high risk of overdiagnosis
3. PSA is not a perfect marker with less than perfect sensitivity and specificity for the diagnosis of PCa. The U.S. preventive social task force no longer recommends PSA screening for healthy men
4. Despite its limitations, the most accepted and frequently used biomarker for prostatic carcinoma is PSA
5. The protein is very specific to the prostate gland but not specific to PCa. In patients who underwent prostatectomy for PCa, PSA measurement is an excellent test for determination of recurrence¹³
6. At present, the PSA is the only approved (in 1986), clinically used serum based, PCa biomarker. Its testing is approved for early detection along with DRE in men over the age of 50.^{14,15}
7. Research conducted in the early 1990s revealed that PSA combined with DRE is the most effective screening and early detection modality in PCa.¹⁶⁻¹⁹
8. PSA levels are normally elevated in older men relative to younger men regardless of presence or absence of Cancer. Therefore, a continuous rise in PSA levels

over time from relatively low levels may be more indicative of cancer than moderately increased PSA that is stagnant.²⁰

9. Although PCa cells do not produce more PSA than benign prostate epithelium, the PSA elevation seems to be due to disruption of cellular architecture within the prostate gland.
10. The loss of barrier of basal membrane and escape from proteolytic process causes elevation of PSA. It is evident from the fact that such increase also occurs in the presence of prostatitis, prostate manipulation, e.g., DRE, prostatic massage, prostate biopsy, etc.

MOLECULAR DERIVATIVES OF PSA

1. Complexed PSA (cPSA):
 - PSA-ACT (PSA complexed to α_1 -antichymotrypsin)
 - PSA-A2M (PSA complexed to α_2 -macroglobulin)
 - PSA-API (PSA complexed to α_1 -protease inhibitor).
2. Free PSA (fPSA):
 - Pro PSA (pPSA)
 - 7- pPSA
 - 4- pPSA
 - 2- pPSA
 - Benign PSA (BPSA)
 - Other fPSA
 - intact PSA (iPSA)
3. Miscellaneous measurements:
 - PSA density (PSAD)
 - cPSAD
 - PSA transitional zone density
 - PSA velocity (PSAV).

Measurable PSA found circulating in blood, exists either in cPSA or bound and fPSA.²¹

cPSA

Complexed form is bound to three proteins:²²

1. ACT: α -antichymotrypsin
2. A2M: α -macroglobulin
3. API: α -protease inhibitor.

The majority of protease that enters the serum is bound (70%) to these proteins. Of the cPSA derivatives found in serum PSA bound to ACT (PSA-ACT) is immune-reactive and found in greatest concentration.

A man with PCa have a greater fraction of tPSA that is complexed with prostate inhibitors than a man without PCa, therefore the measurement of cPSA can be used as the marker of PCa. In the tPSA range of 4-10 ng/ml, the measurement of cPSA provided improved specificity as

compared to tPSA. It provided similar specificity compared to the percentage of fPSA at a sensitivity range of 95%.

fPSA

Although the majority of serum PSA is found complexed to proteases, 5-35% of PSA exists in free form, called fPSA. It (fPSA) is also immunoreactive and, therefore, measurable. Development of new monoclonal antibodies specific for fPSA and cPSA has allowed more accurate measurement of different molecular forms of PSA and their ratio in serum.

The ratio of fPSA to tPSA is greater when comparing man without PCa but have prostate enlargement (BPH) and those with PCa with no prostate enlargement. The role of percentage of fPSA is more applicable to PSA levels < 10 ng/ml, when DRE gives the impression of benign enlargement of the prostate, and PSA level is minimally raised.

Testing percentage of fPSA is approved by the food and drug administration (FDA) in such diagnostic gray zone of 4-10 ng/ml. of PSA.²³ Free to the total cut-off value of 0.18 (18% free to tPSA) significantly improved the ability to distinguish between subjects with or without cancer prostate compared to the use of tPSA alone.²⁴

The percentage of PSA is an independent indicator of presence or absence of PCa over and above the information gained from DRE, age, tPSA, etc., especially in the range of PSA 4-10 ng/ml.²⁵ The fPSA and tPSA both decreases in men receiving finasterides, as both decline, the percentage of fPSA is not altered significantly by these medications.²⁶

The fPSA also gives prognostic information. Longitudinal measurement of % fPSA changes may add in detection and contribute information regarding disease behavior, e.g., aggressive/non-aggressive and help in decision making.²⁷

Limitation of Interpretation of Data

Prostatic manipulations and urethral instrumentation affect the ratio of fPSA to tPSA. The fPSA is cleared more rapidly from serum as compared to cPSA, so PSA estimation is avoided for several weeks following prostatic manipulations such as surgery, biopsy, cystoscopy, etc.²⁸

FDA has approved the measurement of fPSA in the diagnostic gray zone of 4-10 ng/ml. However, this can also be used as a decision-making tool for repeat biopsy²⁹ for an initial biopsy percentage of fPSA ranges from 18 to 25% is commonly suggested.

fPSA and its Isoform/Molecular Derivatives

pPSA

PSA originates with a 17-amino acid chain that is cleaved to yield a precursor inactive form of PSA called pPSA. The precursor form contains: 7-amino acid proleader peptide and 237 constituents amino acids of mature PSA called [-7] pPSA. Once released the proleader amino acid chain is cleaved at amino acid terminus by hK2 converting pPSA to active 33kD PSA form. Incomplete removal of 7 amino acid proleader chain leads to various clipped form of pPSA such as [-2]pPSA, [-4]pPSA, [-5]pPSA with 2, 4, or 5 amino acids.

With cellular destruction, these inactive forms circulate as fPSA in patients with PCa.³⁰

In PCa, these truncated form of pPSA are significantly increased. The decreased PSA processing in PCa may result in a relative increase in pPSA and its cleaved forms particularly [-2] pPSA. Measuring the ratio of these truncated or cleaved forms of PSA to tPSA may serve to differentiate between a man with or without PCa and serve as potential PCa biomarker.

BPSA

Another isoform of fPSA called BPSA is also a cleaved form of PSA that has been identified in tissue from nodular BPH transition zone.³¹

iPSA

In addition to fPSA and BPSA other isoform have been identified in serum. One form of pPSA is found intact and inactive form which does not make a complex with ACT. It is termed as iPSA. It is identified in PCa cells. The ratio of iPSA to fPSA may improve the accuracy of PCa detection.³²

Volume Based Parameters

Volume based parameters have been evaluated to increase the specificity and to distinguish between BPH and PCa. In such studies, the volume of the prostate gland is determined by ultrasound.

These includes:-

- PSAD: PSA divided by prostate volume
- cPSAD: cPSA divided by prostate volume
- PSA transitional zone density: PSA value divided by transitional zone volume.

PSAD

It may help to distinguish between PSA elevations caused by BPH and those caused by PCa. A direct relationship between PSAD and the chance of cancer has been documented. A PSAD of 0.15 or greater has been proposed for recommending prostate biopsy in men with

PSA levels between 4 and 10 ng/ml., and a normal DRE. The usefulness of PSAD in PCa detection has not been confirmed in all studies. An advantage of PSAD is that it has been directly associated with PCa aggression.

PSA/Transitional zone density (volume) is the parameter with the highest sensitivity and specificity for PCa detection between PSA of 4 and 10 ng/ml.

In general, PSA density is an imperfect parameter. They only represent an additional method of risk assessment with potential utility for counseling men with 4-10 ng/ml PSA levels for prostate biopsy or repeat biopsy if the PSA levels are persistently elevated.

PSAV

PSAV is defined as the rate of change, in PSA levels, for the elapsed time between measurements. PSAV > 0.75 ng/ml, per year, is a specific marker for the presence of PCa in men with levels of PSA between 4 and 10 ng/ml.

1. Men with PCa have more rapid rise in PSAV levels than in men with benign disease
2. PSAV may play a role in the prediction of life-threatening PCa
3. A PSA > 0.35 ng/ml/year 10-15 years prior to diagnosis is associated with a 5-fold increased risk of life-threatening PCa more than a decade later
4. A PSAV > 2 ng/ml/year during the year prior to a PCa diagnosis were associated with PCa specific mortality following radical prostatectomy or radical therapy
5. However, a recent meta-analysis suggested that PSAV prior to treatment provided no additional information regarding PCa outcome when compared to PSA alone.

DISCUSSION

The carcinoma prostate is the second leading cause of cancer-related deaths in men. PSA is the most notable biomarker for screening and diagnosis of prostatic disease. It is organ specific but not cancer specific. Its elevation is not always due to prostatic cancer.

Routine use of PSA testing has increased detection of PCa, but it has also led to overdiagnosis and overtreatment. In 1994, PSA was officially approved for cancer screening by FDA and 4.0 ng/ml. was set as the upper limit of normal range. The observed decline in mortality rates both in the US and round the world has been partially attributed to the ongoing screening based on PSA levels. The PSA can be present in free or complexed form. For those with elevated PSA, in the gray zone of, 4-10 ng/ml, patients are more likely to have PCa when the fPSA is less than 20-25% of

total serum PSA levels. pPSA, a precursor form of PSA may serve as an additional indicator in differentiating cancer from the benign process. The ratio of iPSA to fPSA may also improve the accuracy of PCa detection. Volume based parameters such as PSA density can help to determine the timing of prostate biopsy especially in the range of 4-10 ng/ml. The PSA density has been shown to be directly associated with PCa aggression. PSA/transitional zone density is the parameter with the highest sensitivity and specificity for PCa detection in the range of 4-10 ng/ml. PSAV > 0.75 ng/ml per year is a specific marker, for the presence of prostatic cancer in men with levels of PSA in the gray zone. Men with PCa have a more rapid rise in PSAV levels than in men with the benign disease.

CONCLUSIONS

1. pPSA, a precursor form of PSA may serve as an additional indicator in differentiating cancer from the benign process.
2. The ratio of iPSA to fPSA may also improve the accuracy of PCa detection.
3. PSA transitional zone density is the parameter with the highest sensitivity and specificity for PCa detection in the range of 4-10 ng/ml.
4. PSAV > 0.75 ng/ml per year is a specific marker, for the presence of prostatic cancer in men with levels of PSA in the gray zone.

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