Original Article

Role of Complexed PSA in the Early Detection of Prostate Cancer

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Key Words

Prostate, prostatic neoplasm, detection, prostate-specific antigen, complexed PSA

Abstract

Prostate cancer is a clinically significant health care problem in the United States. Total prostate specific antigen (tPSA) is widely used to detect prostate cancer with a significant increase in the incidence of organ-confined disease at the time of diagnosis. The limitations of tPSA are low specificity and positive predictive value. Numerous attempts to enhance PSA's performance based on prostate volume, patient age, patient race, and PSA velocity have shown little clinical improvement. Percent free PSA has proven to be somewhat improved but still limited. Recently, the complexed PSA (cPSA) assay was developed and multisite institutional studies have shown that cPSA has improved specificity over tPSA. Complexed PSA can replace tPSA as a first screening test. (*JNCCN* 2004;2:209–212).

Early detection of prostate cancer is an important health care problem. The prostate-specific antigen (PSA) assay is widely used for the detection of prostate cancer.[1,2] However, the diagnostic value of total PSA (tPSA) for detection of prostate cancer is limited by its lack of specificity. PSA is neither organ specific nor tumor specific.[3] Elevations in PSA may be caused by benign prostatic hyperplasia (BPH), prostatic inflammation, ejaculation, and urologic manipulations as well as by prostate cancer.[4] To improve the specificity of tPSA for detecting prostate cancer, various enhancements have been developed, such as tPSA density (PSAD), PSAD of transition zone (PSAD-TZ), age- and race-referenced PSA, volume-referenced PSA, or percent free PSA (fPSA).[3,5–8] In men with tPSA between 4.1 and 10.0 ng/mL, the 25% fPSA cutoff has been reported to decrease the number of unnecessary biopsies by 20%, while maintaining 95% sensitivity.[8] Another study suggested that percent fPSA can enhance specificity for detecting prostate cancer in men with tPSA between 2.5 and 4.0 ng/mL.[9] However, the clinical effectiveness of the free-to-total PSA ratio is reduced in men with tPSA values between 2.5 and 4.0 ng/mL.[10–12]

Complexed PSA (cPSA) is an alternative approach to PSA testing. Serum PSA exists primarily as either the free "non-complexed form" or as a complex predominantly with alpha 2-macrogrobulin and alpha 1-antichymotrypsin (ACT), and to a lesser degree with α_1-antitrypsin and protein C inhibitor.[13,14] The majority of PSA present in serum is complexed to protease inhibitors with a higher percentage of PSA bound to ACT in men with malignancy compared with benign disease.[14,15] The cPSA assay measures PSA-ACT and other immunoreactive-bound PSA forms, such as PSA-α_1-protease inhibitor.[16] Several studies have shown that cPSA enhances the specificity over tPSA greater than 4 ng/mL or tPSA between 2.6 to 20 ng/mL.[17–19] This article reviews the evidence for the current and future roles of cPSA for early prostate cancer detection.

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cPSA Assay

The basic cPSA assay became available in 1998 as Bayer Immuno 1 PSA and cPSA immunoassays (Bayer Diagnostics, Tarrytown, NY). The Bayer PSA assay uses a monoclonal antibody for its capture phase, and affinity-purified goat polyclonal antibodies linked to alkaline phosphatase for its detection of fPSA and cPSA based

on the properties of the monoclonal antibody used for capture.[18,20] Moreover, the Bayer Immuno 1 cPSA test contains a separate unlabeled antibody specific for fPSA, along with the antibodies used for the detection and capture of tPSA. The additional antibody is used to render fPSA immunologically nonreactive.[16,18]

Recently, the Bayer ADVIA-Centaur cPSA assay (Bayer Medical Limited, Tokyo, Japan) was developed from the Bayer Immuno 1 cPSA assay.[21] Basically, the Centaur cPSA assay uses the same measuring method theory as the Immuno 1 cPSA assay. In the Immuno 1 assay, however, fPSA is prevented from reacting with the tPSA antibodies by incubating the sample with an fPSA-specific monoclonal mouse antibody, and the cPSA antibody conjugate was labeled with alkaline phosphatase. In contrast, a light reagent with polyclonal goat anti-PSA antibody with an acridinium eater is applied in Centaur assay.[22] These differences between Immuno 1 and Centaur assay led to a continuous operation and cost-effective workstation consolidation in the Centaur assay. The minimum detection sensitivity of Immuno 1 cPSA is 0.2 ng/mL and that of Centaur cPSA is 0.03 ng/mL. Moreover, sample throughput in the Centaur cPSA and Immuno 1 assays can perform 240 tests/h and 100 tests/h, respectively.

Clinical Trials for Early Prostate Cancer Detection

Several reports have suggested that cPSA could be a better initial test for prostate cancer detection than tPSA. Brawer et al.[17] published the first report showing that cPSA improved the specificity over tPSA and free-to-total PSA ratio. At tPSA ranges of 4.0 to 10.0 ng/mL, the authors reported that, at high sensitivity, cPSA enhanced specificity over tPSA. Similarly, Okegawa et al.[23] reported that free-to-complexed PSA ratio (f/cPSA) enhanced the specificity at high sensitivity among 140 biopsy-confirmed Japanese men whose tPSA level was between 4.0 and 10.0 ng/mL. Stamey and Yemoto,[24] however, showed equivalent or modest improvement in specificity for cPSA relative to tPSA.

In a retrospective multisite institutional study (Brigham and Women's Hospital, The Johns Hopkins Hospital, Memorial Sloan Kettering Cancer Center, the Northwest Prostate Institute and University of Washington, and The University of Texas M. D. Anderson Cancer Center), Okihara et al.[25] reported that cPSA and complexed-to-total PSA ratio (percent cPSA) is equivalent to tPSA for the early detection of prostate cancer. They also reported that percent fPSA outperformed cPSA and percent cPSA performed equivalently to percent fPSA in men with tPSA levels between 2.5 and 10.0 ng/mL.

With tPSA levels between 2.5 and 4.0 ng/mL, a significant number of men will have prostate cancer.[26,27] Previous studies[26–28] have shown that of the men whose tPSA is between 2.5 and 4.0 ng/mL, approximately 22% to 27% will be diagnosed with prostate cancer. Approximately 80% of the patients in this PSA range who underwent radical prostatectomy had clinically significant cancer and were potentially curable.[26]

Okihara et al.[29] reported that cPSA was more specific than f/tPSA when tPSA was between 2.5 and 4.0 ng/mL. Receiver operating characteristic (ROC) analysis showed that cPSA (area-under–the-curve [AUC] = 0.718) had a better performance compared with percent fPSA (AUC = 0.635). They concluded that a 2.2 ng/mL cutoff for cPSA appeared to stratify prostate biopsy results in men with tPSA between 2.5 and 4.0 ng/mL. They also reported that cPSAD and cPSAD-TZ had the best specificities compared with percent fPSA and non-volume-referenced cPSA. They found that volume-referenced cPSA might enhance detection specificity in larger prostates (30 mL or greater).

A recently conducted, 7-site institutional study (Johns Hopkins Medical Institution, New York University, Northwest Prostate Institute, Stanford University, University of Innsbruck, University of Texas M. D. Anderson Cancer Center, and Wyoming Research Foundation) examined several studies. Horninger et al.[30] reported that the use of cPSA as a single test enhanced the detection of prostate cancer over that of testing with tPSA and tPSA indices in men with tPSA values between 2 and 4 ng/mL. Naya et al.[31] reported that cPSA, cPSAD, and cPSAD-TZ enhanced cancer detection in men with tPSA between 2.5 and 10.0 ng/mL, especially when the tPSA was between 2.5 and 4.0 ng/mL. They compared the ultrasound-estimated prostate volume with that of the prostate weight obtained from radical prostatectomy and found the importance of the accurate measurement of the total prostate volume and transition zone volume. They also concluded that 2.2 ng/mL for cPSA was the cutoff value differentiating cancer from benign disease in the tPSA range of 2.5 to 4.0 ng/mL.

Partin et al.[32] reported that the use of cPSA as a single test provided improved specificity over tPSA. Percent

fPSA and percent cPSA offered little to no additional benefit in differentiating benign from malignant disease at clinically relevant cPSA concentrations. Within the cPSA range of 3.2 to 8.3 ng/mL (4–10 ng/mL tPSA range), the percent fPSA and percent cPSA provided a significant improvement in AUC over tPSA and cPSA. However, no differences were seen with AUC results for percent fPSA or percent cPSA across all cPSA ranges.

The European multisite institutional study of Djavan et al.[33] showed that the performance of cPSA was better than tPSA in differentiation between benign disease and prostate cancer, and similar to that of percent fPSA in men with tPSA levels between 4 and 10 ng/mL. They also reported that cPSAD and cPSAD-TZ further improved the specificity of PSA in early detection of prostate cancer.

A recent preliminary study from Japan showed that the novel Bayer cPSA (Centaur assay) could enhance prostate cancer detection in Japanese men compared with tPSA and PSA-ACT.[21] This report showed that cPSA is promising in differentiating malignancy from benign disease in men with a tPSA value less than 4.0 ng/mL.

Conclusions

We reviewed the role of cPSA for early detection of prostate cancer. Using a 2.2 ng/mL cutoff for cPSA enhances prostate cancer detection compared with percent fPSA in the tPSA range of 2.5 to 4.0 ng/mL. Volume-referenced cPSA, such as cPSAD and cPSAD-TZ, appears to enhance prostate cancer detection compared with percent fPSA and percent cPSA. Complexed PSA is measured by one test and the free-to-total PSA ratio requires 2 tests. Therefore, the use of percent fPSA in men with tPSA levels greater than 4 ng/mL clearly increases the assay cost as well as introduces the problems associated with laboratory and biologic variability. Complexed PSA is a better initial test than tPSA for early cancer detection.

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