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Is Prostate Specific Antigen Still The Best Tumor Marker for Prostate?

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Abstract **Prostate Specific Antigen (PSA) has been climically utilized in prostate cancer for more than a decade. Because of the overwhelming benefit of PSA, the previous markers for prostate cancer were abandoned. Even though PSA is not organ specific agent, but importantly, its function as an organ specific remains in all clinical situations. PSA significantly involves not only in screening for early detection but also in all clinical spectrums of prostate cancer. Never before had the tumor marker played such a significant role in all purposes of clinical utilizations for prostate cancer as same as PSA did. The answer to the title of this article is absolutely positive. Nevertheless, the question that whether PSA has an impact in decreasing the mortality rate of patients with prostate cancer is yet to be answered. In Siriraj Hospital, though PSA has been available since 1991, the majority of patients registered with the advanced stage of disease and their treatment outcomes are still not satisfactory. Since the prognoses of patients with an early stage of disease appear excellent, to improve the mortality of Thai patients with prostate cancer, screening with PSA for early detection should be introduced and widely used.**

Currently, prostate cancer incidence in Thailand is increasing.[1] Tumor markers for prostate cancer have played a significant role in the care of porstate cancer patients for more than a decade. There are 3 markers commonly used: acid phosphatase (AP), prostatic acid phosphatase (PAP), and prostate specific antigen (PSA).[2] Recently, several investigators indicated that AP and PAP are no longer utilized since the overwhelming advantage of PSA had been addressed.[2] Today, PSA appears to be a popular issue in prostate cancer known as the PSA era. This review will discuss the biochemical characteristics and the update of the clinical utilization of PSA for prostate cancer.

Biochemical Characteristic

PSA was firstly isolated from seminal plasma in 1971.[3] It is a single chain glycoprotein which consists of 240 amino acids and 4 carbohydrate side chains.[4] Depended on the different analysis methods, the molecular weight is approximately 26,000 to 34,000 d.[5] The gene that is related to PSA is located on the long arm of chromosome 19.[6] PSA is synthesized in the acina and ductal epithelium and subsequently secreted into the lumen of prostatic duct and eventually becomes a component of the seminal fluid.[7] Physiological function of PSA is to liquefy the coagulum and

break down the seminal clot through proteolysis of the gel-forming proteins into a small soluble fragment.[8] This subsequently causes releasing of spermatozoa. PSA has a role of promoting cell growth as well.[9] Base on the structure and function characteristics as well as the gene location, PSA is classified in the human kallikrein family known as hK3.[6]

Different molecular forms of PSA have recently been discovered. The predominant forms are a PSA complexed to α1-antichymotypsin (PSA-ACT), a free (unbond) PSA, and a PSA complexed to α2-macroglobulin (PSA-MG).[10] Other forms such as PSA-PCI, PSA-AT, or PSA-ITI are either only a tract component in the serum or a minor component in the seminal fluid. At present, only the PSA-ACT and free PSA are measurable by immunoassays. Generally, the word "PSA" alone means a total PSA which composes of the free PSA plus the PSA-ACT. The total PSA assays have been introduced for a clinical used since 1980s' while the assays for the free PSA are just available.[12] There are many assays to measure PSA in the serum and the PSA value is dependent on each assay. These variations are results of the difference in the test methods such as monoclonal or polycolonal antibody; type of solid phase; sandwich or competitive; pH; incubation time; the composition of the diluent used; PSA isoforms used to generate the PSA antibodies; specificity of the antibodies; the composition of the calibrator or the PSA values assigned to the calibrator.[13] Thus, the results reported by laboratories should include the identity of assay used. However, there are good correlations among some assays such as the Hybritech Tandem-R and Abbott Axsym assays.[13,14] Most PSA assays indicated that the normal level is between 0 and 4.0 ng/ml for the clinical used. The timing for drawing serum to measure PSA is very important because several prostatic conditions or urological manipulations such as prostatitis, cystoscopy, or prostatic biopsy could affect the value of PSA level in the serum.[27] The half life of PSA is 2-3 days.[28] Thus, PSA should be measured approximately 4 weeks after these events. However, several investigators suggested that an increase of PSA level due to digital rectal examination (DRE) is clinically insignificant.[29]

PSA is no more an organ specific agent in the experimental data because it was found in several organs even in women such as aprocrine sweat gland, salivary gland tumors, periurethral gland, endometrium, or breast cancer.[11] Despite found in other organs, PSA is still an organ specific marker for all clinical situations. PSA is not cancer specific marker because it is produced by both normal epithelial cells and malignant cells.[15] Many investigators showed an overlap of PSA level between men with benign prostatic hyperplasia (BPH) and prostate cancer.[2,17] Despite not a cancer-specificity, PSA has been utilized in all clinical situations for prostate cancer.

Clinical Utilizations

Total, PSA has been used in all spectrums for prostate cancer; screening for early detection; diagnosing; staging; predicting the prognosis; and monitoring after treatments. In Siriraj Hospital, PSA has been clinically utilized since 1991.

Screening

In the United State, screening with PSA testing and DRE has been widely used since 1990. Neither PSA nor DRE is a perfect method for the screening. Many studies reported a large proportion of missing prostate cancer and an underestimating the volume and the local stage by DRE.[16] In addition, there is an overlap in serum PSA level between men with BPH and those with prostate cancer.[2,17] The use of PSA alone to detect cancer could miss 14 per cent of the patients with prostate cancer due to their normal PSA (<4.0 ng/ml).[2] In two large screening trials (n=31,953 and 6,630), PSA had a higher positive predictive value than a DRE (30% versus 25%) but the combination of PSA and DRE admitted the highest result (48%).[18,19] For these reasons, the American Cancer Society recommended that all men between 50-70 with ten year life expectancy should undergo annual screening by PSA testing and DRE. Nevertheless, the necessity of annual screening in men with a normal PSA (<4 ng/ml) is skeptical. One study (n=6842) determined the risks of developing prostate cancer within the next three years in men with an initial PSA level of 0-1, 1.1-2, and 2.1-4 ng/ml were 0.34, 0.97 and 6 per cent, respectively.[20] Men who have an initial PSA level of 2 ng/ml or less appear not to be necessary for an annual screening within the next three years while those with an initial PSA of more than 2 ng/ml do need. Because of the overwhelming using the screening programs by PSA testing and DRE, prostate cancer has become the most

common cancer in American men but a lot of significant localized cancer has become the most common cancer in American men but a lot of significant localized cancer were early detected and cured.[21] In addition, the mortality rate of prostate cancer is not the first rank among cancer death.[21] In Thailand, prostate cancer incidence in Siriraj Hospital is increasing despite the limited screening. However, the majority of the patients in Siriraj Hospital registered with an advanced disease and their treatment outcomes are not satisfactory[1]. Thus, to improve the mortality rate of prostate cancer in Thai patients, screening by PSA testing and DRE should be introduced and widely used. However, some urologists would debate against the cost effectiveness issue.

Diagnosis

PSA is an important test to detect prostate cancer in men by performed a prostatic biopsy if their PSA values are more than 4 ng/ml. Since a substantial overlap of PSA between BPH and prostate cancer, the grey area is between 4.0-10 ng/ml. To improve the specificity and sensitivity of PSA testing, four methods were introduced; PSA density (PSAD), PSA velocity (PSAV), age specific reference range (ASRR), and free to total PSA ratio (F/T PSA).

PSA density is defined as the ratio between a value of PSA and a prostatic volume. It was observed that patients with prostate cancer have PSAD approximately 10 times than those with BPH[2,22]. Several investigators suggested that a PSAD of 0.15 might increase the detection of prostate cancer patients who have a total PSA of 4.0-10 ng/ml[23]. However, contrast results were subsequently reported by others[24,25]. Recently, a large multicenter analysis in thousands men indicated that a cutoff PSAD for detection prostate cancer is limited. This is because the prostatic volume calculated by transrectal ultrasound is a subjective and an examiner dependent method. The differences among the examiners may mislead the interpretation.

PSA velocity is defined as the rate of PSA level changing over a time period. Men who have a rising PSA would be suspicious for prostate cancer. Many studies suggested that the rising PSA cutoff value of 0.75 to 0.8 ng/ml per year showed the maximized sensitivity and specificity for predicting cancer in 70 year-old men or younger[30,31]. However, other studies showed that 12.5 per cent of men without prostate cancer had a rising PSA more than 0.75 ng/ml/year over the 2-year period and suggested that a 2-year follow-up is needed before using PSAV to make a decision for a biopsy[32]. Nevertheless, many urologists feel that if PSA continuous rising, it is unnecessary to wait for two years to biopsy the patients. At present, PSAV can increase the predictive value and be widely utilized for detection of new prostate cancer.

ASRR was introduced because the PSA value in men without prostate cancer increases with age. The older patients are, the higher PSA is. Several investigators are studying the levels of ASRR.[33,34] A PSA cutoff abnormal value is lower than 4.0 ng/ml for the younger men while it is higher than 4.0 ng/ml level for the older men. ASRR seems to be more specific in men whose age is higher than 60 and more sensitive in men whose age is lower than 60. However, the data showed that a 4.0 ng/ml cutoff PSA is superior to ASRR in all age groups for early detection.[35] In a large study (n=116,073), despite higher specificity as well as higher positive predictive value, ASRR has a lower sensitivity than a 4.0 ng/ml cutoff PSA value especially in older men which is the majority of prostate cancer patients.[36] Thus, most screening programs still prefer a 4.0 ng/ml cutoff PSA value for early detection.[36] At present, ASRR appears to be clinically useful for men who are younger than 60 years old only.

Free/total ratio PSA has been recently utilized since the observation that the fraction of free PSA is low in men with prostate cancer compared to men without malignancy. Several studies reported the cutoff ratios of 0.14 to 0.28 with the sensitivities and the specificities ranged of 71-100 per cent and 19-92 per cent, respectively.[37] The variations might be the results of the differences in the study designs, analysis methods, or biological factors that influence their outcomes. At present, the best cutoff point of using free/total ratio PSA to discriminate prostate cancer from other benign conditions is yet to be solved. Nevertheless, men who have a total PSA level of 4.0 to 10 ng/ml combined with a low F/T PSA ratio are strongly recommended for a biopsy. Today, free PSA has not yet available in Siriraj Hospital.

Staging

Importantly, PSA level is roughly correlated with the volume of intracapsular carcinoma at a rate of 3.5 ng/ml/gm cancer.[2,22] In addition, it increases linearly

when the clinical stage of prostate cancer increases.[38] With the PSA levels less than 10 ng/ml, most tumors will be confined in the prostatic capsule and bone metastases as detected by bone scan are exceedingly rare.[39] At the PSA level of 50 ng/ml or greater, seminal vesicle invasion and pelvic lymphadenopathy are predominent.[40] However, PSA levels between 10 and 50 ng/ml are unpredictable. At the lower PSA levels, organ confined disease is more likely. In the other hand, stage T3 or C disease is more frequent at the higher PSA levels. Obviously, PSA levels above 100 ng/ml are associated with metastatic disease. Several investigators attempted to calculate the probability of lymphnode metastasis with a statistical model using PSA, Gleason score, and clinical stage by DRE.[41] Some urologists would not perform lymphadenectomy if the PSA and Gleason score is low in stage T1C patients (negative for DRE).

Currently, the reverse-transcriptase polymerase chain reaction (RTPCR) of PSA mRNA has been utilized to detect a metastatic prostate cancer cell in the peripheral blood and bone marrow samples in the patients who had micrometastases that undetected by conventional methods such as total PSA or bone scintigraphy.[42] The detection rate of prostate cancer cells in metastatic patients was high (88%) while the false positive rate was low.[43] It may provide the best prognostic indicator for improving the accuracy of staging metastatic disease. However, due to the variation of different laboratories, at the present time, some investigators suggested that clinical decisions should not depend on the RTPCR results only.[44]

Prognostic Indicator

PSA has also been used as a prognostic indicator in prostate cancer. Pretreatment serum PSA is an important predictor of the results of definitive treatments for clinically localized prostate cancer. Data suggested that 3-5 year rates of biochemical failure stratified by pretreatment PSA < 4 ng/ml, 4-10 ng/ml, >10-20 ng/ml, and > 20 ng/ml were approximately 8, 17-16, 45-55, and 55-80 per cent for radical prostatectomy series and 0-31, 10-56, 11-73, and 20-87 per cent for radiotherapy series.[45] However, there were the varieties of the outcomes and the definitions of biochemical failure among those series. Thus, its value for predicting prostate cancer should be interpreted cautiously. Nevertheless, the combination of pretreatment PSA with other prognostic factors such as clinical stage, Gleason score, tumor volume, DNA ploidy, P53, bcl-2, or Ki-67 could improve the prognostic accuracy.[46]

Monitoring

To determine the treatment outcomes as well as to follow-up prostate cancer patients, urologists monitor their patients with several parameters. But the most important parameter is PSA which mostly used in term of biochemical failure PSA failure, PSA recurrence, or PSA progression. It is usually more sensitive than other parameters such as symptoms or radiological investigations. PSA monitoring is utilized not only in a localized disease but also in a locally advanced or an advanced disease. After the radical prostatectomy in a localized disease, serum PSA level should decline to the undetectable levels (PSA<0.2 ng/ml) within three weeks and should stay undetectable indefinitely.[47] Whenever the PSA level dose not decline to the undetectable level or increase after its nadir level, it means that there may be somewhere of residual disease or tumors progress, respectively. Data suggested that PSA recurrence rates are correlated to the pathological stage of disease. Ten year likelihood of PSA progression free rates after radical prostatectomy were approximately 71-90 per cent in stage T1 or T2, 58-82 per cent in stage T3a, 21-43 per cent in stage T3b, and 0 per cent in N1.[48] Several urologists use the PSA failure as an indication for adjuvant therapy such as adjuvant radiation therapy or hormonal therapy especially in aymptomatic patients. For the definitive radiotherapy in a localized prostate cancer, PSA should decline to the normal level within 6 months after therapy in many patients.[49] However, it dose not imply disease-free status in the future.[50] Thus, PSA monitoring after definitive therapy is very important. For an

Table 1 New classification in metastatic prostate cancer.

Metastatic stage	Definition
D1	Pelvic lymphnode metastases
D1.5	Rising PSA after failed local treatment
D2	Bone and/or other organs metastases
D2.5	Rising PSA after nadir level
D3	Hormone refractory disease
D3S	Hormonally sensitive
D3I	Hormonally insensitive

advanced disease, PSA also plays a significant role as an indicator for the hormonal treatment. Recently, some investigators used PSA for the new classification of metastatic disease as shown in Table 1.[51] With the new definition, PSA is not only more important for monitoring but also significant to decide treatment options. The rising PSA indicates a disease progression in metastatic prostate cancer treated with hormonal therapy. Thus, the treatment should be reconsidered for the hormonal refractory disease. At present, though PSA monitoring is universal, the pattern for the follow-up is various because it depends on the difference of treatment options in each stage of disease.

Human Kallikrein 2 (hK2)

As stated above, PSA belongs to kallikrein family. Recently, a novel marker known as hK2 has been investigated for prostate cancer. It is also located on chromosome 19 and contains 237 amino acid that 80 per cent of its sequences are as same as PSA.[52,53] Primary data showed that with the use of RT-PCR in human serum, 67 per cent of men with prostate cancer were positive for hK2 and 17 per cent of those men were positive for PSA whereas none of men without prostate cancer were positive for either hK2 or PSA.[54] At present, the utilization of hK2 in the clinical aspect for prostate cancer has not yet been reported. Thus, the role of hK2 need to be further investigated for the clinical benefit.

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