A guideline to clinical utility of prostate specific antigen

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ABSTRACT

Prostate cancer has emerged as the most common tumor effecting adult men. In the USA, 300,000 cases each year, and some 40,000 deaths per year are expected from this disease. Once prostate cancer gets to an advanced stage, one cannot prevent its progression and cure is no longer possible. Thus, to effect the course of prostate cancer and to diminish the death rate from this disease, it should be detected at its early stages. The prostate specific antigen serum test is the best tumor marker present but it is certainly not perfect. The proper utility of prostate specific antigen testing, and analysis of prostate specific antigen parameters, will allow us to detect prostate cancer at earlier stages, and prevent progression and death rates from this disease. In this manuscript, we review the current status of prostate specific antigen testing for early detection and staging of prostate cancer, as well as its role for monitoring response to various forms of therapy.

Keywords: Prostate cancer, prostate specific antigen, prostate specific antigen density, prostate specific antigen velosity, prostate specific antigen for monitoring therapy.

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The prostate specific antigen (PSA) has had an enormous impact on the diagnosis and management of prostate cancer. Use of PSA and its widespread application in clinical practice has increased the diagnosis of prostate cancer. PSA is a 34-kDa 240-amino-acid glycoprotein produced exclusively by prostatic epithelial cells. It is a serine protease, and has a high sequence homology with human glandular kallikerin. In the serum it is present mainly in a complex form with alpha-1 anti-chymotrypsin. It is secreted in the seminal plasma and is responsible for liquefaction of the seminal coagulum.[1]

Elevated serum levels of PSA occur in about 20% to 50% of patients with benign prostatic hyperplasia (BPH), (depending on the epithelial volume of the adenoma and the degree of bladder outlet obstruction it causes), in patients with prostatitis, and in 20% to 92% of patients with prostate cancer, depending on tumor volume and to a lesser extent tumor differentiation.[2,3] A major drawback to PSA-based prostate cancer detection is the appreciable false positive rate. Methods that have been used to improve clinical utility and specificity are many: PSA density (PSAD);[4] PSA velocity (PSAV),[5] PSA age-specific reference range[6] and measurement of different PSA molecular form ratios (free-to-total PSA).[7] The past several years have witnessed major advances in the use of PSA. This article will focus on the clinical issues facing the urologist and primary care physician with respect to the use of PSA for early detection and staging of prostate cancer, as well as for monitoring response to various types of treatment. We have attempted to address the clinically important issues relevant to PSA testing and summarize the currently accepted concepts on

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Table 1 - Determined age specific serum PSA reference ranges.

Age	PSA range[19]	PSA range[6,28]
40-49	0.0-1.5	0.0-2.5
50-59	0.0-2.5	0.0-3.5
60-69	0.0-4.5	0.0-5.0
70-79	0.0-7.5	0.0-6.5

interpretation of PSA results.

Use of PSA as a screening test for prostate cancer. The use of PSA testing for the early detection of prostate cancer is controversial.[8] Serum PSA was studied as a screening test extensively in multiple series.[9-11] Advantages of this simple measurement include reproducibility, objectivity, low cost and high patient acceptance. But the disadvantages are significant: low positive predictive value with a high false positive rate for prostate cancer detection. This is driven by the variable and unpredictable volume of BPH and the relative stromal epithelial composition of BPH within the prostate, thus limiting the use of PSA alone as a screening test for prostate cancer. In 1995, Gann et al showed in a prospective study that a simple PSA measurement has a high sensitivity and specificity for detection of prostate cancers that arose within 4 years.[12]

PSA density. The ratio of PSA and prostate volume as determined by transrectal ultrasound (TRUS) was introduced by Benson et al[4] to improve the performance of serum PSA testing for the detection of prostate cancer. The main disadvantage with this technique is that TRUS-determined prostate volume is often inaccurate and difficult to reproduce, and the limitations caused by the marked variations in stromal and epithelial elements contributing to the hyperplastic gland. Kalish et al demonstrated improved use of PSAD if the TRUS-determined volume of the transitional zone was used.[13] The proposed indications of PSAD is to distinguish BPH from prostate cancer for men with a normal digital rectal examination (DRE) who have serum PSA levels within the intermediate range (4.0 to 10.0ng/ml). A cut-off lower level for PSAD was determined to be 0.15ng/ml, below which the possibility of malignancy was low. By contrast, Richie et al reported that use of PSAD > 0.15ng/ml for men with a serum PSA in the range of 4.0 to 10ng/ml would have overlooked half of the cancers.[14] A recent study by Zlotta et al evaluated the sensitivity of PSAD of the transitional zone in patients with PSA less than 10.0ng/ml.[15] The results were promising in this category of patients, with a cut-off value determined to be 0.35ng/ml above which the chance of malignancy increased significantly. The authors recommended prospective studies in order to draw definitive conclusions.

PSA velocity. This concept was introduced by Carter et al,[5] who determined that a PSAV of 0.75ng/ml/year or greater is indicative of prostate cancer. The authors recommended that at least 3 measurements are necessary to calculate PSAV. Other values for PSA that suggest cancer was reported by others: eg Brawer et al concluded that an increase of 20% or greater is indicative of cancer[5,16] while Oesterling et al confirmed that the appropriate cutoff point for PSAV is to use at least 3 separate values taken over an interval of greater than 6 months and less than one year.[17] Kadman et al re-evaluated the role of PSAV in a group of patients from a prostate screening program and found a significant inter-assay variability that must be interpreted when dealing with PSAV.[18] These authors recommend an observation period of at least 2 years before considering PSAV as abnormal.

PSA age-specific reference ranges. These have been proposed by Oesterling.[6] The theory behind the use of age-specific reference ranges is based on the fact that age may affect PSA production, secretion and prostatic volume. Age-specific serum PSA reference ranges have been determined (Table 1) and have the potential to make PSA a more sensitive tumor marker for men less than 60 years of age and a more specific tumor marker for men greater than 60 years of age. Anderson et al re-evaluated the normal age distribution of serum PSA and concluded that the previously published age-specific references did not adequately account for the increasing variability of PSA with age[19] (upper limits too high for men younger than 60 years of age and potentially too low for men aged 70 to 79 years, (Table 1). In addition, the use of age-specific PSA values is limited by the possible ethnic variations proposed by many authors[20-22] therefore more prospective studies are needed to re-evaluate this parameter.

Free to total PSA ratio. This concept was introduced after the discovery that PSA in the serum exists in different molecular forms. The ratio of free to total serum PSA is suggested to be of greatest utility in distinguishing men with prostate cancer from those with BPH and is independent of patient age.[23] A major part of PSA in serum appears in complex with alpha 1-antichymotrypsin, and the

Table 2 - Biochemical recurrence following radical prostatectomy.

Number of patients	PSA cut-off
3170[36]	0.2 ng/ml
955[25,34,37]	0.2 ng/ml
407[38]	0.3 ng/ml

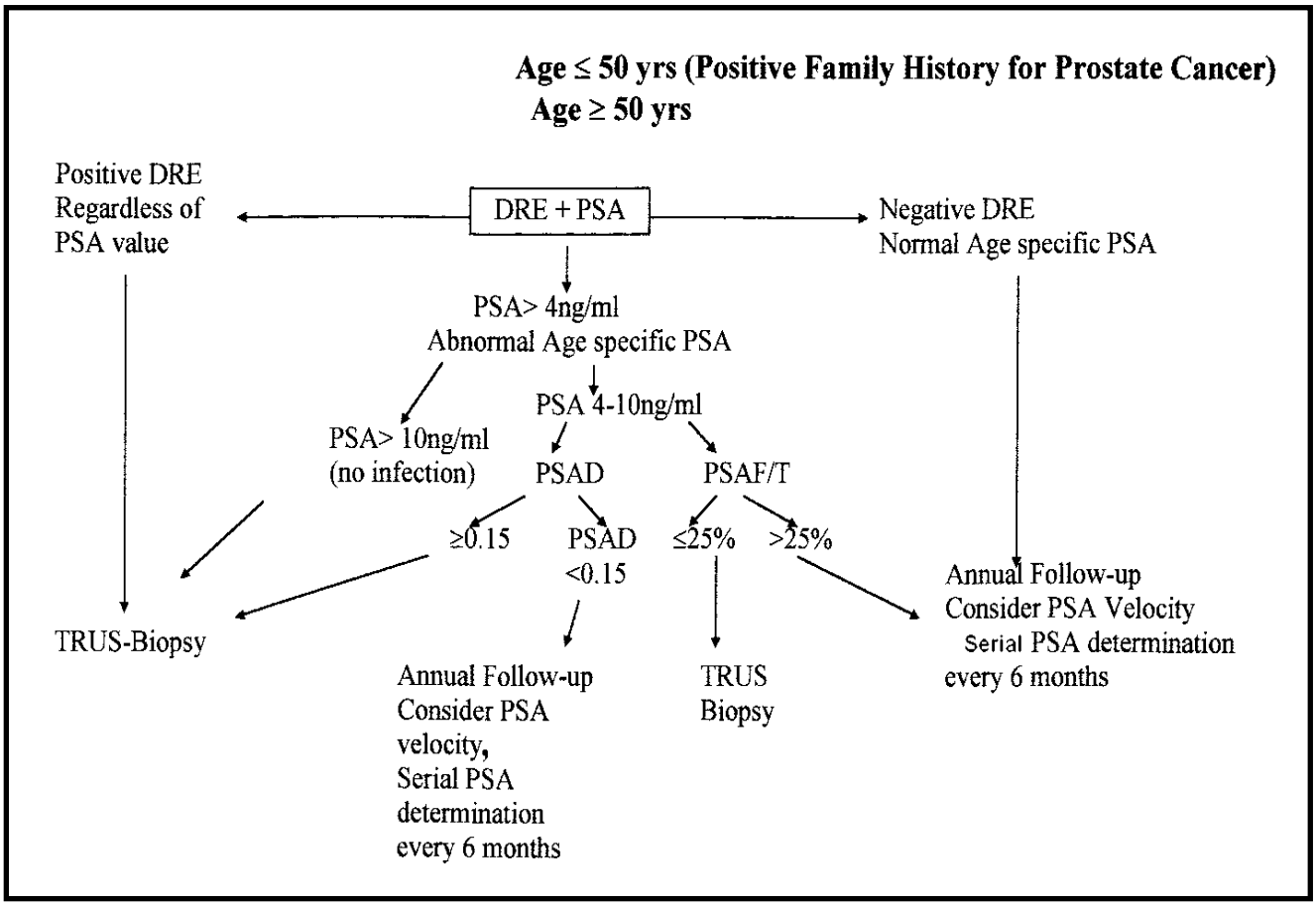

Figure 1 - Clinical use of PSA parameters. (DRE: Digitial Rectal Examination, PSAD: PSA density, TRUS Biopsy: Transrectal ultrasound guided biopsy).

proportion of this complex form is higher in patients with prostatic cancer than in those with benign prostatic hyperplasia. To evaluate the best range of total PSA for using percent free PSA, Vashi et al examined all combinations of lower and upper limits between 2ng/ml and 20ng/ml, and reported that proportion of free PSA contributed the greatest utility to the PSA test for values between 3 and 10ng/ml with a cutoff point for percent free PSA of 19% for values of PSA between 3 and 4ng/ml and 24% for values between 4.1 and 10ng/ml.[24]

Use of PSA to predict the stage of prostate cancer. PSA alone is not specific enough to allow accurate staging for the individual patient due to the unpredictable contribution of BPH and the decreasing production of PSA by higher grade lesions. Partin et al[25] showed that 75% of the men with serum PSA levels less than 4.0ng/ml had organ confined disease, whereas if serum PSA was between 4.0 and 10.0ng/ml only 53% had organ-confined disease and most men with serum PSA levels greater than 50ng/ml have positive pelvic lymph nodes at surgery. The use of PSA to stage prostate cancer preoperatively can be enhanced by considering other preoperative variables, such as tumor grade, digital rectal examination, and transrectal ultrasound-guided biopsy.[25-27] Nomograms are devices derived from statistical or mathematical models which are used to predict outcomes for an individual patient. Partin et al were the first to propose a nomogram to predict the pathologic stage of prostate cancer using clinical stage, gleason grade in the biopsy specimen, and preoperative PSA serum levels.[25]

Use of PSA to monitor therapy of prostate cancer. 1. PSA following radical surgery. Almost invariably, serum PSA becomes undetectable following radical surgery. With a half-life of PSA estimated to be 3.2 days, the baseline level is usually reached by 3 to 4 weeks after surgery.[28] There are some exceptions and a few anecdotal reports of local and distant recurrences following radical prostatectomy with undetectable PSA.[29-31] Vessela and Lange identified 0.1ng/ml as the threshold PSA value after radical prostatectomy above which there is a high risk of persistent disease.[32] Ultrasensitive and second generation PSA assays with detection power below 0.01ng/dl are available, but their clinical usefulness is limited by higher rates of false positive results.[33] Timing of PSA recurrence and PSA velocity are helpful in distinguishing local

recurrence from distant disease. Partin demonstrated a 60% progression rate for men who had detectable serum PSA levels within the first postoperative year following surgery, 71% with distant metastases and 29% with local recurrence.[34] Danella et al found a PSA doubling time of 4.1 months for patients with bone metastases versus 11.4 months for patients with no clinical evidence of disease or local recurrence only.[35] Also, patients who never achieve an undetectable PSA following radical prostatectomy have a high risk of unrecognized metastatic disease and are likely to develop subsequent distant failure.[35]

Although investigators have used various PSA cut-offs to identify patients with biochemical recurrence after radical prostatectomy the hallmark of biochemical failure after radical prostatectomy is a rising PSA level.[36-38] (Table 2). Any significant increase in the serum PSA should be confirmed by repeating the PSA test.

2. PSA following radiotherapy. Goad and associates found that 93% of patients had a PSA less than 4.0ng/ml by 12 months post-irradiation, and 37% eventually reached PSA levels less than 0.5ng/ml at a mean interval of 15.3 months following treatment.[39] Several studies investigated the rate of decline and magnitude of change in serum PSA levels after radiation therapy.[40-42] Hancock et al evaluated the utility of PSA in assessing control of prostate cancer after irradiation; 38% of prostatic cancer of various stages and grades were controlled durably with irradiation with no evidence of accelerated growth of tumor after irradiation.[43] Hanks et al showed that the actuarial survival with biochemical freedom from disease (PSA <1.5ng/ml) at 5 years was 44% for all patients, and that PSA doubling times after radiation failure were variable, with 42% greater than 12 months and evidence that irradiation accelerates the growth of prostate cancer.[44] Cancer control after radiation therapy was confirmed in most men by a PSA reference range of 0.0 to 2.0ng/ml while cancer activity was diagnosed in all men with levels above this range.[45] The risk of biochemical recurrence following radiation therapy is associated with pretreatment serum PSA, tumor grade, and clinical stage.[46] Hanks et al reported only 4 of 118 patients (3.4%) with pretreatment PSA > 20ng/ml to be free of PSA recurrence at 48 months.[47]

The currently recommended approach for detecting early cancer of the prostate is as follows (Figure 1), if PSA is normal for age, then we follow the patient with another value in 6 months to assess PSA velocity. For those patients who have an elevated age specific PSA, or PSA value between 4 and 10ng/ml, we evaluate the F/T PSA ratio, if the latter is less than 25% we proceed to TRUS-guided random biopsies. If F/T PSA ratio is greater than 25%, patients may be spared the biopsy, and the PSA density could help in this setting. If the total PSA is more than 10ng/ml in the absence of prostatic inflammation or infection, biopsies are taken. The well established premise that patients with abnormal digital rectal examination should undergo TRUS guided prostate biopsies continues to hold.

Utilizing the above guidelines, the physician will not only detect prostate cancer at an early and potentially curable stage, but will also spare elderly patients unnecessary interventions, especially in the presence of comorbid conditions, for example coronary artery disease, pulmonary disease and others.

In Lebanon, patients with advanced prostate cancer are being diagnosed to a greater degree than patients with localized disease (AUH experince unpublished data). This fact alone confirms the importance of appropriate work-up and screening of middle aged and healthy men, in an effort for early detection of prostate cancer. When this goal is achieved, it will have an enormous impact on the success and outcome of treatment of prostate cancer in our region.

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