Prostate specific antigen: an updated review

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SO A, GOLDENBERG SL, GLEAVE ME. Prostate specific antigen: an updated review. The Canadian Journal of Urology. 2003;10(6):2040-2050.

Since its discovery in 1979, serum PSA has revolutionized how physicians manage men with prostate cancer. PSA screening, although currently under much debate, has been recommended by most North American medical bodies, including the Canadian Urological Association, to be performed as a shared-decision making process after discussing with patients the pros and cons of treatment. Although most commonly thought of as a screening tool, serum PSA has also been used to predict tumor volume, stage and prognosis in patients before and after treatment. In this review, we examine PSA testing and its effectiveness in the diagnosis and management of prostate cancer. Further, we also evaluate recent literature regarding the use of PSA derivatives and other prostate cancer markers, such as proPSA, bPSA, and hk2.

Key Words: prostate specific antigen, prostate cancer, screening test

Introduction

With an estimated 18 800 new cases being diagnosed in Canada in 2003,[1] prostate cancer continues to be a significant cause of morbidity and mortality in Canada. Diagnostic strategies including serum prostate specific antigen (PSA) have allowed clinicians to detect prostate cancer earlier in its natural biologic history. For over a decade, clinical experience has identified prostate specific antigen (PSA) as the best tumor marker for prostate cancer and the best overall tumor marker in biology.[2-4] Despite the fact that PSA has revolutionized how physicians manage men with prostatic disease, there is much debate over its validity as a screening tool. Hence, in today's clinical world the serum PSA requires experienced clinical interpretation and judgment in its application to individual patients ("the art of medicine").

PSA was initially identified in human seminal plasma[5] and termed gamma seminoprotein, and it was later used as a semen marker in rape victims.[6] In 1979, Wang et al[7] isolated and purified a plasma protein produced only in prostate epithelial cells (i.e. prostate-specific), distinct from prostatic acid phosphatase (PAP), identical to that found in semen, and termed it PSA. The ability of PSA to diagnose prostate cancer,

Accepted for publication November 2003

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to predict tumor volume and stage, to predict prognosis, and monitor treatment response has been crucial to the improved care of men with this disease.

Biomolecular characteristics and factors that affect PSA levels

PSA is a proteolytic enzyme belonging to the kallikrein family of serine proteases that is produced primarily by human prostatic epithelium.[8] PSA is normally secreted in high concentrations into seminal fluid and functions in the liquefaction of the seminal coagulum[9] and is detectable in normal prostate, BPH, and both primary and metastatic prostate cancer cells.[10]

Total PSA production is determined by the total number of PSA-producing cells, the level of PSA gene expression, the rate of PSA protein secretion per cell, and the degree of "backleak" of PSA from glandular acini into the serum. Serum PSA levels may be elevated from inspissated secretions, distorted architecture, or disruption of basement membrane integrity occurring with prostatic infarction, prostatitis, ejaculation, digital rectal manipulation (DRE) or prostatic instrumentation. DRE has been shown to raise total PSA levels primarily due to elevated free-PSA; hence, complexed PSA appears to be more stable with modest elevations after DRE.[11] Ornstein et al[12] showed that at least 24 hours are needed to allow for PSA to return to "baseline" post-DRE. Cystoscopy can increase serum PSA levels 4-fold while needle biopsies and transurethral resections can temporarily increase PSA levels up to 50-fold[2] all due to an increased "back leak" of PSA into the serum.[13] The relatively long half-life of PSA (2.2 ± 0.8 days), coupled with a slow resolution of inflammation following biopsy or prostatitis, may lead to a delay of several months for serum PSA to reach its baseline after TURP, biopsy, or infection. Ejaculation has been reported to cause greater than a 15% increase in serum PSA within 1 hour[14] and thus can lead to an increase in PSA that could result in a false-positive elevation. After 48 hours, the PSA would be expected to return to baseline levels in most men.[14]

The biological variability of serum PSA ranges from as low as 10% to as high as 50%. In a recent review, Yan summarized data collected from various studies over the last 10 years and established the coefficient of variation at 13.4%.[15] This has very important implications, especially in men with PSA readings near "established" cutoff points. Eastham and Scardino studied yearly PSA fluctuations in 154 men who had initially elevated PSA > 4.0 ug/L. In this group, 30% had PSA values that decreased below the 4.0 ug/L cutoff;[16] this has prompted the authors to advocate "PSA confirmation" at least one time a few weeks after the initial abnormal PSA is found.

Therapy that alters the hormonal milieu of the prostate can also alter the serum PSA levels. Surgical and medical castration, with the use of luteinizing releasing hormone analogues or antiandrogens, has been shown to significantly reduce PSA levels. Finasteride, a 5-a-reductase inhibitor used in the treatment of BPH, also has been shown to decrease PSA levels by 50% in men who have taken the medication for 12 months.[17] In fact, men that start finasteride and do not experience a 50% decrease in their serum PSA should be suspected of having occult prostate cancer. Panneck has shown that free-PSA levels do not rise after finasteride administration, thus producing erroneous percent free-PSA ratios.[18]

PSA in the early detection of prostate cancer

In order to decrease the morbidity and mortality of prostate cancer we must either find better treatment for advanced disease or diagnose the disease at an early curable stage. The role of PSA in the early detection of prostate cancer continues to be the subject of much debate and research. However, most North American medical bodies, including the Canadian Urological Association, American Cancer Society, American Urologic Association, and American Society of Internal Medicine, recommend shared decision-making that includes discussion with patients of the pros and cons of treatment and individualizing screening practices.[19-22]

There is accumulating evidence to suggest that when used as a screening tool in the appropriate population, serum PSA is the single best test for the early detection of prostate cancer and compares favorably with screening tests for breast and cervical cancers. Although PSA lacks adequate specificity to be always diagnostic of prostate cancer, it is useful to stratify men into groups with a high risk of having prostate cancer who should undergo definitive testing with prostatic biopsy, and those with a low risk of having prostate cancer who can be reassured and followed without immediate additional testing.[23-26]

Using the prostate biopsy as the reference standard and a PSA of 4 ug/L as a cutoff point, the sensitivity of PSA testing ranges from 63% to 83%.[27,28] These same studies also show an overall specificity ranging from 81%-90%. Interestingly, specificity decreased in older age groups: 98% in men between 50 and 60 and 81% in men between 70-80.[28] This difference is due to the increasing PSA production by BPH tissue as a confounding variable in older men.

Cross-sectional studies involving tens of thousands of men from several countries have been published and show very similar results regarding the ability of PSA to predict the presence or absence of cancer upon TRUS-guided biopsy of the prostate. Cooner et al[12] reported that the positive predictive value of a PSA between 4-10 ug/L was 20% when DRE was normal and 45% when DRE was abnormal, which increased for PSA levels >10 ug/L to 31% when DRE was normal and 77% when DRE was abnormal. The overall detection rate in this urological (i.e. non-primary) practice was 14.6%, which illustrates that the detection of prostate cancer can be increased by combining DRE, PSA, and TRUS.

Recent data by Punglia and Catalona supports using age-standardized cutoffs for PSA testing.[29] Initially described by Oesterling,[30] specificity in older men can be increased by using higher PSA cutoffs in older men. The Punglia study showed that lowering the threshold for biopsy from 4.1 to 2.6 ug/L in men younger than 60 years would double the cancer-detection rate from 18% to 36%, with the specificity only falling from 98% to 94%. They state that if biopsies were performed when PSA was > 4.0 ug/L, 82% of cancers would be missed in men younger than 60.

Fang and Carter have suggested using a PSA test at age 40 to identify men at risk of CaP. Men aged 40 to 49.9 with a PSA > 0.6 ug/L had a relative risk of 3.7 to develop prostate cancer within 25 years compared to those men with PSA < 0.6 ug/L.[31] Furthermore, they suggest that if early baseline testing is normal, only biennial PSA testing after the age of 50 is required, allowing for more cost effective screening. What these studies do not elucidate, however, is whether lowering the PSA cutoffs increases the rate of detection of clinically insignificant tumors.

In 1993, Andriole and Catalona[32] published the Washington University experience results from a screened population of 20 000 men. Overall, about 10% of screened men older than 50 years of age had a PSA greater than 4 ug/L, and one third of these were found to have cancer on subsequent biopsy, for a cancer detection rate of 3%. When PSA was the only abnormal parameter, cancer was diagnosed in 20%. However, when both PSA and DRE were abnormal 31% of men had cancer, and when PSA, DRE, and TRUS were abnormal 56% had cancer.[25] Interestingly, the detection rate of prostate cancer using PSA in community-based populations was 3%, which is approximately twice that when DRE alone is used[25,26,33,34] and approximately 2-3 times the detection rate of breast cancer using mammography-based screening programs.[35,36]

PSA should not be used alone to exclude the possibility of prostate cancer but is rather a useful adjunct to DRE in the early diagnosis, permitting a rational guide to use TRUS and biopsy. When used together PSA and DRE detect 27% more cancers than would be detected by PSA alone, and 34% more than by DRE alone.[25,26] For example, in a screening study of 6630 men using PSA and DRE, 18.2% of cancers detected were in men with normal PSA levels.[37,38] The positive predictive value of an abnormal DRE when PSA is normal is 10%; conversely, the positive predictive value of an abnormal PSA when DRE is normal is 20%-30%.

Currently, only one randomized trial of PSA screening has been published and it suggests a reduction of up to 70% in prostate cancer mortality in the screened men.[39] However, this study has been criticized for its randomization procedures, sub-optimal patient acceptance rates, and lack of intent-to-treat analyses.

Despite a lack of definitive RCT data, there is abundant indirect evidence, such as epidemiologic data, to support PSA screening. The US Surveillance, Epidemiology, and End Results Program (SEER) data showed that the rising incidence of prostate cancer from 1989 to 1992 and subsequent decline from 1992 to 1994 paralleled trends of prostate cancer specific mortality. Interestingly, the SEER data are consistent to the data from Quebec and Ohlmsted County.[40,41] These results have been suggested by some as evidence for the effectiveness of PSA screening.[42] However, many also claim that other variables, such as diet and lifestyle modifications, attribution bias, and earlier administration of androgen ablation in men diagnoses with advanced disease are important factors contributing to the decline in prostate-cancer specific mortality.[43,44]

Further indirect evidence of the benefits of PSA screening was shown by Bartsch et al[46] in their study of men from the Austrian state of Tyrol. Men from this state were offered free PSA screening that was not available to others in Austria. These authors reported 33% reduction in prostate cancer mortality, compared to the expected rate, in the state of Tyrol between 1996 and 1999 in men aged 40–79 years. These results have been suggested by the authors to represent evidence of the reduction of prostate-cancer specific mortality due to PSA screening.[46]

The benefits of PSA screening on overall disease specific mortality rates will not be fully answered until large RCTs are completed within the next decade, including the European Randomized study of Screening for Prostate Cancer (ER-SPC) and the

Prostate, Lung, Colorectal, Ovarian (PLCO) cancer screening studies.

Does PSA predict for clinically significant cancers?

The goal of early detection is to identify patients who have clinically significant cancers, that is, cancers that are localized and curable. The recently published Holmberg[47] randomized trial confirmed that prostate cancer treatment improves disease-free survival when disease is localized to the prostate.

Gann et al provided some insight in the value of PSA in detecting clinically significant tumors in their Physicians Health Study.[4] In this case-control study, one PSA measurement was performed on frozen serum samples in 366 cancer cases at baseline to evaluate the detection prostate cancer. In this population, cancers were detected by DRE after baseline blood sampling before the availability of PSA testing. PSA measurements on frozen samples revealed that a PSA cutoff of 4 ug/L could have detected 73% of the cancers that arose within 4 years of PSA measurement, and a specificity of approximately 90%. Interestingly, 75% of the 366 men with prostate cancer in this study eventually died of prostate cancer. This longitudinal data suggest that a PSA detected tumors at cutoffs of 4ug/L may have validity in detection of prostate cancers that are clinically significant.[4]

Past autopsy studies have shown that one in three men over the age of 50 have histologic evidence of prostate cancer. However, up to 80% of these were microscopic in size and probably not clinically significant. For this reason, statistics show that only 3% of men will actually die from prostate cancer. The actual tumor volume considered to be critical and likely to impact on survival is not known but has been thought to be 0.5 cc in an earlier study.[48] PSA testing may be sensitive enough to detect the clinically aggressive cancers whose natural history may be altered by early detection and therapy, but perhaps not sensitive enough to identify the highly prevalent very small volume, likely indolent cancers. Evidence thus far suggests that less than 16% of PSA-detected cancers in this latter category.[23,49-51] Conversely, more than 95% of the cancers detected in the University of Washington screening study were localized to the prostate (about two-thirds had pathologically organ-confined disease[32]), and a majority of T1c patients in a radical prostatectomy series were "clinically significant".[52]

However, a recent intriguing study by Stamey et al is challenging the very definition of pre-operative PSA risk levels that was published by the same author 15 years ago.[55] In his cohort of 875 men who underwent radical prostatectomy, preoperative PSA poorly correlated with tumor pathological grade and probability of postoperative biochemical failure.[53] Within this group, 784 of 875 men had a PSA of 2 to 33 ug/L, and correlation was only seen in men with very large tumors and a PSA of greater than 22 ug/L.[53] In another study, Stamey showed no relationship between serum PSA in the range of 2-10 ug/L and volume of all Gleason grades.[54] These studies showed that PSA values, and corresponding lower cancer volumes, may not be as good in predicting "clinical" significance as was previously thought.[55] Both Epstein et al[56] and Salomon et al[57] have shown in a multivariate analysis that tumor volume is not an independent predictor of tumor progression. Further, in both studies, tumor volume does not add any additional information to tumor grade and stage in defining risk of progression in patients. Currently, the definition of clinically significant prostate cancers is still unknown.

Enhancing the positive predictive value of PSA

Urologists recognized early on that the substantial overlap in serum PSA levels in men with early prostate cancer and those with BPH resulted in a lack of sufficient specificity for PSA to be considered an ideal screening test. Consequently, research efforts have been focusing on the development of methods that improve the ability of PSA to predict for the presence of clinically important early prostate cancers, while minimizing the number of false positive results.

Age-specific PSA reference ranges

Oesterling et al[58] and Dalkin et al[59] established normal levels of PSA for 95% of men without clinical evidence of prostate cancer. Based on this data, the upper limit of normal for serum PSA in each decade of life is 2.5 ug/L during the 5th decade, 3.5 ug/L during the 6th decade, 4.5 ug/L during the 7th decade, and 6.5 ug/L during the 8th decade. The use of age-specific ranges to guide to biopsy will help increase the sensitivity of PSA as a tumor marker in men under 60 years of age (increase the detection rate of early cancers), and improve its specificity in men older than 60 years (decrease the number of negative biopsies).

Serial PSA / PSA velocity

Serial PSA measurements over time in individual men,

termed PSA velocity, is a better reflection of longitudinal biological changes within the prostate and increases both the positive predictive value of PSA and the likelihood of diagnosing cancers while they are organ-confined.[60] Based on the retrospective, longitudinal study by Carter et al,[60] a PSA velocity of greater than 0.75 ug/L was predictive of the presence of prostate cancer. Specificity increased to 90% when PSA velocity was >0.75 ug/L over 1 year, compared to 60% for a single cross-sectional serum PSA over 4.0 ug/L. Differences in PSA velocity between BPH and prostate cancer patients were apparent as early as 9 years before the diagnosis of cancer was made. Catalona et al[49] concurred that a PSA velocity of 0.8 ug/L per year helped distinguish between BPH and cancer patients. In their study, the mean velocity for men with cancer was 2.18 ug/L, compared to 0.48 ug/L for men without cancer.

Despite these optimistic results, PSA velocity is not always reliable because of the individual variation in serum PSA levels from one determination to another. Many questions regarding the number of determinations, the intervals between testing, and the influence of aging on the interpretation of PSA velocity remain poorly defined.

PSA density and transition zone density

Another method that has been suggested to improve PSA specificity is PSA density, which is equal to serum PSA divided by prostate gland volume. The concept of PSA density is based on the fact that cancer, on a gram for gram basis, will increase serum PSA levels more than BPH or normal prostate tissue will do. Early studies suggested that PSA density helped differentiate between BPH and early nonpalpable cancer[61] especially at serum levels of 4 to 10 ug/L. However, PSA density fails to provide more information than PSA alone in many men due to difficulty in obtaining accurate and reproducible TRUS volume determinations of the prostate gland, the heterogeneous stromal and epithelial composition between prostate glands which leads to marked variation in the amount of PSA produced per gram of prostate tissue, and biopsy sampling error (larger prostate may hide small cancers).[62] Presti et al have suggested that PSA density may actually miss significant numbers of cancers in patients with PSA values between 4 and 10 ug/L, normal DRE and normal TRUS.[63] Transitional zone measurements, used to improve the specificity of the PSAD, are also subject to high inter-observer variability of TRUS measurements.[64]

"Complexed" vs "free" PSA

A considerable amount of investigation has focused on the measurement of bound and free PSA. When enzymatically active PSA leaks or is secreted into the serum (as occurs in Gleason grades 4 and 5 cancers) its proteolytic activity is immediately neutralized by binding to alpha-1-antichymotrypsin (ACT) or a-2-macroglobulin[65,66] Figure 1. PSA complexed with a-2-macroglogulin is not accessible for immunodetection, while that bound to ACT has a sufficient number of antigenic epitopes exposed to interact with anti-PSA antibodies. The PSA-ACT complex (cPSA) is the major molecular form of PSA in serum, while a small portion exists in a free, non-complexed form. Initial data suggests that BPH is more efficiently differentiated from cancer by the free-to-total serum PSA ratio (%fPSA), which is higher in men with BPH than in patients with prostate cancer.[67-71] Using a %fPSA cutoff of 25%, the specificity of screening improves such that 20% of unnecessary biopsies are avoided while still detecting 95% of cancers.[72,73] Catalona et al have reduced the biopsy rate by 18% when %fPSA to age – specific PSA cutoffs.[74] In men greater than 60 years old and with total PSA between 4-10 ug/L, the sensitivity of % fPSA exceeded that of age-specific PSA cutoffs.[73] Thus, fPSA may help to identify early, curable cancers in healthy men with PSA levels of less than 4 ug/L.[73,74]

The in-vitro instability of fPSA may present a problem at those centers unable to perform the test locally. Paus et al[75] showed that after storage at 4ºC over seven days, fPSA and %fPSA significantly decreased; thus storage time of even refrigerated serum presents a confounding

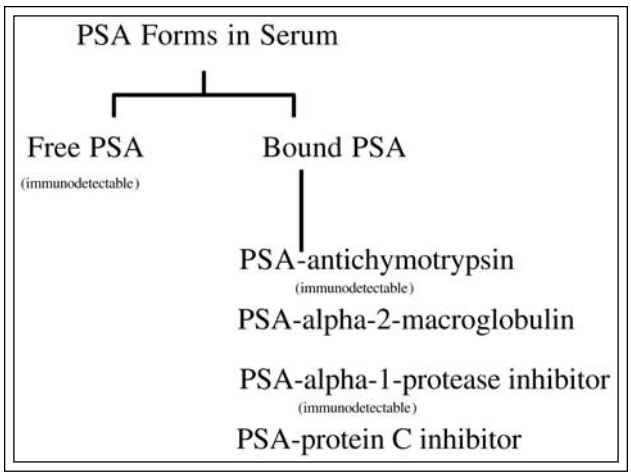

Figure 1. PSA forms in serum. Free PSA and PSA bound to antichymotrypsin and alpha-1-protease inhibitors are the only currently immunodetectable forms of PSA.

variable in this test. The authors suggest that serum samples should be stored frozen if not analyzed immediately or acidified to pH 5.5 to prevent the artificial reduction of fPSA levels.[75] Hence, %fPSA measurements may be difficult in remote centers that do not have the ability to perform the test themselves or do not have the ability to freeze and send samples appropriately.

Bayer has a commercially available assay for cPSA which has the advantages of being a single measurement, being less sensitive to DRE and prostatic manipulation compared to free and total PSA, and better stability in storage.[76,77] On the other hand, cPSA seems to have the highest intraindividual variability (25.4%) compared to other PSA tests.[78]

So, although the molecular basis for the differences in ACT binding between cancer and BPH remains undefined, all observations to date suggest that use of free-to-total PSA ratios may increase the specificity and positive predictive value of PSA in the early detection of prostate cancer especially at PSA levels between 4 and 10 ug/L.

hK2

Human glandular kallikrein belongs to the same serine protease family, has 80% homology to PSA, is specific to the prostate[79] and is androgen-regulated.[80] This enzyme cleaves PSA from its zymogen form (proPSA) to convert PSA into its active form.[81] Recently, many studies have investigated the use of hK2 as a new marker for prostate cancer. Kwaiatkowski et al examined hK2/%fPSA ratios in 90 men with PSA between 4 and 10 ug/L.[82] They showed that this ratio was more sensitive and more specific than %fPSA/total PSA ratios in detecting prostate cancer. Partin et al had the same finding of the improvement of the detection of prostate cancer while limiting the number of biopsies in men with a PSA in the range of 2-4 ug/L.[83]

Furthermore, hK2 expression correlates closely to pathological stage of prostate cancers. In a study by Haese et al[84] of 68 men who underwent radical prostatectomy, hK2 expression was significantly better than PSA in predicting organ-confined disease.[84] Also of interest is the fact that poorly differentiated tumors (i.e. high grade tumors) continue to produce hK2, whereas, PSA levels drop. Hence, hK2 may have a role in late stage and poorly differentiated tumors as well as in predicting organ confined disease prior to radical prostatectomy or radiation treatment.[85,86] In summary, hK2 may be a useful tool not only to detect prostate cancer, but also to predict tumor grade and stage.

Pro-PSA and bPSA

The understanding of the different components of free-PSA offers an opportunity for clinical application. Free-PSA is composed of proenzyme or precursor PSA (proPSA), BPSA, and another form of inactive PSA that has similar homology to the native active PSA Figure 2 and Figure 3. Precursor PSA has been shown to be associated with prostate cancer,[87] and is cleaved by hK2 to be converted into enzymatic active form of PSA.[81] The expression of proPSA remains high even in poorly differentiated cancers. BPSA has been associated with BPH[88] in that it is more highly concentrated in benign tissue than cancerous tissues and may be used in the assessment of BPH treatment strategies.[89] The use of these two free-PSA components

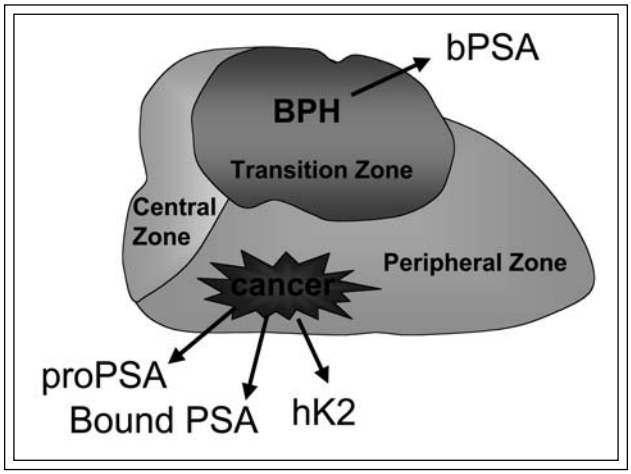

Figure 2. Disease associated PSA Forms in prostate tissue. Benign prostatic hyperplasia increases the relative amount of bPSA levels. Prostate cancer produces increased relative amounts of proPSA, bound PSA, and human kallikrein 2 (hK2).

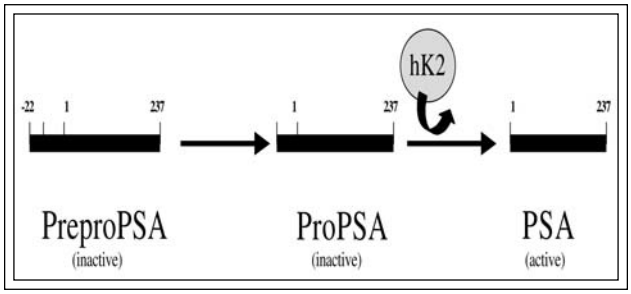

Figure 3. PSA formation pathway. PSA is a 237 amino acid sequence that is synthesized from proPSA after cleavage by human kallikrein 2 (hK2). The precursor molecule, preproPSA, is synthesized with a 17- amino acid leader sequence that is cleaved to generate an inactive 244-amino acid precursor protein, proPSA. When in serum, PSA is inactivated by serine proteases.

further requires more research to define their role in screening and management in prostate cancer.

Recent data from Khan and Partin[90] have revealed that when proPSA is considered with serum PSA and %fPSA, overall specificity can be improved. They examined serum samples from 93 men with total PSA levels between 4-10 ug/L who underwent 12-core biopsies. When proPSA was added, specificity was improved from 23% to 44%.[90] These authors suggest that the use of proPSA may reduce the number of unnecessary biopsies. However, the cost-effectiveness of adding the proPSA test is still unknown and these assays remain investigational for now.

PSA in the clinical staging of prostate cancer

Several studies have demonstrated that serum PSA correlates well with tumor volume and advancing clinical and pathological stage,[25,26,91-93] but there is too much overlap between stages for accurate preoperative staging. However, preoperative PSA levels can help stratify men into low or high risk groups. When preoperative PSA levels are below 4 ug/L, up to 80% of men have organ-confined tumors; approximately 60% of tumors are organ-confined when serum PSA is between 4 and 10 ug/L and over 50% of men with PSA levels above 10 ug/L have extra-prostatic extension.[25,26,92-94] Although PSA is not accurate enough as a staging tool when used alone, the staging accuracy of PSA may be improved by combining it with DRE findings and the tumor grade on needle biopsy.[93]

Serum PSA levels tend to be higher in men with lymph node metastases. Most men with PSA levels above 50 ug/L have positive pelvic lymph nodes and a low serum PSA is a good negative predictor of the presence of pelvic lymph node disease. If PSA levels are below 10 ug/L or if the PSA is less than 20 ug/L with low grade cancer (Gleason score < 7) the risk of finding positive nodal metastasis is negligible and it is possible to avoid pelvic lymphadenectomy.[94,95] Furthermore, if PSA is less than 25 ug/L CT scans are unable to detect lymphadenopathy and should not be used as a staging tool unless PSA exceeds 25 ug/L.[96,97]

Serum PSA levels are also useful in identifying patients with a low probability of having osseous metastases. Chybowski et al[98] found that only 1 of 306 patients with a PSA level less than 20 ug/L had a positive bone scan. They calculated the negative predictive value of a serum PSA less than 20 ug/L to be 99.7%. Gleave et al[99] retrospectively reviewed 490 evaluable patients with prostate cancer at Vancouver Hospital and identified 4.5% (22/490) with a positive bone scan on initial evaluation. They found that 0 of 290 patients with PSA levels below 10 ug/L, 3 (4%) of 85 patients with PSA 10-20 ug/L, and 19 (17%) of 115 patients with PSA > 20 ug/L had positive bone scans at presentation. In summary, bone scans may not be necessary in men with PSA < 20 ug/L unless there is history of skeletal pain, high-grade disease or clinically advanced local involvement. Cher et al has showed that in patients who have had a radical prostatectomy, the probability of obtaining a positive finding on bone scan is < 5% until the PSA is between 45 –50 ug/L.[100]

PSA following treatment of prostate cancer

PSA has become a powerful tool in the follow-up assessment of patients after radical prostatectomy, radiotherapy, or hormonal ablation. The pattern of PSA change after treatment often determines the need for further adjuvant or salvage treatment. For example, a detectable and rising PSA following radical prostatectomy suggests the presence of residual carcinoma, and possible need for adjuvant therapy. After radiation therapy, PSA is expected to reach its nadir over 17-32 months.[101-103] An interesting "bounce" phenomenon may occur following brachytherapy, external beam, and three-dimensional conformal therapy with an initial rising PSA followed by a fall to nadir.[104-106] Men who have an initial rising a nadir of < 0.5 ug/L or who do not fail by American Society for Therapeutic Radiology and Oncology (ASTRO) definition of three rises of PSA above nadir values post treatment have excellent 5-year recurrence-free rates.[107,108] A detailed discussion of the benefits and timing of adjuvant and salvage therapies are beyond the scope of this manuscript, but suffice to say that PSA monitoring post-treatment allows for the initiation of these treatments at an early point in the biological history of the cancer.

Post-treatment PSA monitoring can also be useful in differentiating between local and distant disease recurrence. Pound et al showed that post-radical prostatectomy, patients whose PSA levels did not drop to undetectable levels, whose PSA doubling time was > 6 months, or whose PSA rises within 12 months of treatment were more likely to have distant recurrence and metastasis.[109]

Medical or surgical castration results in the down-regulation of PSA gene expression, with a rapid and dramatic lowering of serum levels. Serum PSA nadir following androgen ablation therapy can stratify patients into good and poor prognostic groups. Bruchovsky et al[110] observed that at least 32 weeks of

treatment are necessary in order to bring the serum PSA into the normal range in 70% of men with advanced prostate cancer. In the remaining 30%, serum PSA will decrease temporarily and then increase; if a plateau is reached it will be short-lived or stabilize outside of the normal range. This is usually a sign of early progression to androgen independence and is associated with a poor prognosis. In this series, if the serum PSA remains above 4 ug/L between 24 - 32 weeks of treatment, the median survival time is only 18 months. On the other hand, if the serum PSA is below 4 ug/L between 24 and 32 weeks of therapy, the median survival time at 40 months is more than twice as long. Other studies have also shown that those with an undetectable PSA or a PSA decreases of 90% or more at 3 and 6 months have a longer disease-free surviva.l[111,112] On the contrary, a PSA increase precedes clinical evidence of progression with a mean lead-time of 6 to 12 months, in almost all cases.[111,112]

Serial PSA measurements are also important in monitoring men with prostate cancer treated expectantly. Klotz et al have suggested that a PSA doubling time of < 2 years be used to identify patients with a high likelihood of local progression in lieu of otherwise favorable prognostic factors.[113] In their prospective study of men with prostate cancer treated expectantly, 28 (14%) of 200 men had PSA doubling times of < 2 years. Within this group, nine eventually had a radical prostatectomy, and all nine patients had stage progression. Because of the aggressive nature of tumor in those with short doubling times, the authors suggest that a threshold of intervention is a doubling time of "around 3 years". Although PSA is an indicator of disease progression and tumor aggressiveness, more studies will be needed to define the optimal timing of PSA measurements, PSA thresholds to trigger intervention, and also to determine the survival benefits of early intervention in those initially managed by watchful waiting.

Conclusion

The discovery of PSA has brought us into a new era in the diagnosis, treatment and monitoring of prostate cancer. Though we still have much to learn about the use of PSA, it has become an established tool of the urologist/oncologist. With the further refinement of PSA derivatives, we will improve our ability to detect the clinically significant cancers at an early, curable stage, while at the same time identifying, but not actively treating, the clinically indolent tumors that are so prevalent in the ageing male. Our patients are increasingly aware of PSA and they want to take a more active part in their therapy. PSA allows us to both reassure the patient with clinically stable disease and prognosticate for the patient with recurrent or progressive cancer. □

References

1. Canadian Cancer Statistics, 2003.
2. Oesterling JE. Prostate specific antigen: A critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. *J Urol* 1991;145:907-923.
3. Partin AW, Oesterling JE. The clinical usefulness of prostate specific antigen: Update 1994. *J Urol* 1994;152:1358.
4. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for the detection of prostate cancer. *JAMA* 1995;273:289-294.
5. Hara M, Koyanogi Y, Inoue T, Fukutara T. Some physico-chemical characteristics of "gamma-seminoprotein," an antigenic component specific for human seminal plasma. Forensic immunologic study of body fluids and secretion. *Jap J Legal Med* 1971;25:322.
6. Graves HCB, Sensabaugh GF, Blake RT. Postcoital detection of male-specific semen protein. Application to the investigation of rape. *New Engl J Med* 1985;312:338.
7. Wang MC, Valenzuela LA, Murphy GP, Chu TM: Purification of a human prostate specific antigen. *Invest Urol* 1979;17:159-163.
8. Papsidero, LD, Kuriyama, M, Wang, M, Horoszewicz, JS, Leong, SS, Valenzuela, L, Murphy, GP, Chu, TM. Prostate antigen: a marker for human prostate epithelial cells. *J Natl Cancer Inst* 1981;66:37-42.
9. Lilja H. Structure and function of prostatic- and seminal vesicle-secreted proteins involved in the gelation and liquefaction of human semen. *Scand J Clin Lab Invest* Suppl 1988;191:13-20.
10. Nadji M, Tabei SZ, Castro A, Chu, TM, Murphy GP, Wang MC, Morales AR. Prostate-specific antigen: an immunohistologic marker for prostatic neoplasms. *Cancer* 1981;48:1229.
11. Lechevallier E, Eghazarian C, Ortega JC, Roux F, Coulange C. Effect of digital rectal examination on serum complexed and free prostate-specific antigen and percentage of free prostate-specific antigen. *Urology* 1999;54(5):857-861.
12. Ornstein DK, Rao GS, Smith DS, Ratliff TL, Basler JW, Catalona WJ. Effect of digital rectal examination and needle biopsy on serum total and percentage of free prostate specific antigen levels. *Urology* 1999;54(5):857-861.
13. Yuan JJ, Coplen DE, Petros JA, Figenshau RS, Ratliff TL, Smith DS, Catalona WJ. Effects of rectal examination, prostatic massage, ultrasonography and needle biopsy on serum prostate specific antigen levels. *J Urol* 1992;147(3 Pt 2):810-814.
14. Tchetgen MB, Song JT, Strawderman M et al. Ejaculation increases the serum PSA concentration. *Urology* 1996;47:511.
15. Yan Y. Measurments and Implications For Early Detection of Prostate Carcinoma. *Cancer* 2001;92:776–780.
16. Eastham JA, Riedel E, Scardino PT, et al. Variation of Serum Prostate-Specific Antigen Levels: an evaluation of year-to-year fluctuations. *JAMA* 2000;289(20):2695-2700.
17. Guess HA, Gormley GJ, Stoner E, Oesterling JE. The effect of finasteride on prostate specific antigen: review of available data. *J Urol* 1996;155(1):3-9.
18. Pannek J, Marks LS, Pearson JD, Rittenhouse HG, Chan DW, Shery ED, Gormley GJ, Subong EN, Kelley CA, Stoner E, Partin A. Influence of finasteride on free and total serum prostate specific antigen levels in men with benign prostatic hyperplasia. *J Urol* 1998;159(2):449-453.

19. Ramsey EW. Early detection of prostate cancer. Recommendations from the Canadian Urological Association. *Can J Oncol* 1994;Suppl 1:82-85.
20. Smith RA, Cokkinides V, von Eschenbach AC, et al. American Cancer Society guidelines for the early detection of cancer. *CA Cancer J Clin* 2002;52(1):8-22.
21. Prostate-specific antigen (PSA) best practice policy. American Urological Association (AUA). *Oncology (Huntingt)* 2000;14(2):267-280.
22. Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys* 1997;37(5):1035-1041.
23. Scardino PT. Early detection of prostate cancer. *Urol Clin North Am* 1990;16;635-655.
24. Cooner WH, Mosely BR, Rutherford CL et al. Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. *J Urol* 1990;143:1146-1154.
25. Catalona WJ, Smith .S, Ratliff TL et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *N Engl J Med* 1991;324:1156-1161.
26. Brawer MK, Chetner MP, Beatie J et al. Screening for prostatic carcinoma with prostate-specific antigen. *J Urol* 1992;147:841-845.
27. Mettlin C, Murphy GP, Babaian RJ, Chesley A, Kane RA, Littrup PJ, Mostofi FK, Ray PS, Shanberg AM, Toi A. The results of a five-year early prostate cancer detection intervention. Investigators of the American Cancer Society National Prostate Cancer Detection Project. *Cancer* 1996;77(1):150-159.
28. Jacobsen SJ, Bergstralh EJ, Guess HA, Katusic SK, Klee GG, Oesterling JE, Lieber MM. Predictive properties of serum-prostate-specific antigen testing in a community-based setting. *Arch Intern Med* 1996;156(21):2462-2468.
29. Punglia RS, D'Amico AV, Catalona WJ, Roehl KA, Kuntz KM. Effect of verification bias on screening for prostate cancer by measurement of prostate-specific antigen. *N Engl J Med* 2003;349(4):335-342.
30. Oesterling JE, Jacobson SJ, Chute CG, Guess HA, Girman CJ, Panser LA, Lieber MM. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. *JAMA* 1993;270:860.
31. Fang J, Metter EJ, Landis P, Chan DW, Morrell CH, Carter HB. Low levels of prostate-specific antigen predict long-term risk of prostate cancer: results from the Baltimore Longitudinal Study of Aging. *Urology* 2001;58(3):411-416.
32. Andriole GL, Catalona WJ. Using PSA to screen for prostate cancer. The Washington University experience. *Urol Clin N Amer* 1993;20:647.
33. Stone NN, DeAntoni EP, Crawford ED and the Prostatic Education Council: Screening for prostate cancer: rectal examination and prostate specific antigen. Results of Prostate Cancer Awareness Week. *Urology* 1995:44:180.
34. Mettlin C, Lee F, Drago J et al. The American Cancer Society National Prostate Cancer Detection Project. Findings on the detection of early prostate cancer in 2425 men. *Cancer* 1991;67:2949-2958.
35. Kerlikowski K, Grady D, Barclay J, Sickles EA, Eaton A, Ernster V. Positive predictive value of screening mammography by age and family history of breast cancer. *JAMA* 1993;270:2444-2450.
36. Benoit RM, Naslund MJ. An economic rationale for prostate cancer screening. *Urology* 1994;44:795-802.
37. Catalona WJ, Richie JP, Ahmann FR et al. Comparison of digital rectal examination and prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol* 1994;151:1283-1290.
38. Brawer MK. Prostate specific antigen: Critical issues. *Urology* 1994;44:917.
39. Labrie F, Candas B, Dupont A, Cusan L, Gomez JL, Suburu RE, Diamond P, Levesque J, Belanger A. Screening decreases prostate cancer death: first analysis of the 1988 Quebec prospective randomized controlled trial. *Prostate* 1999;38(2):83-91.
40. Roberts RO, Bergstralh EJ, Katusic SK, Lieber MM, Jacobsen SJ. Decline in prostate cancer mortality from 1980 to 1997, and an update on incidence trends in Olmsted County, Minnesota. *J Urol* 1999;161:529-533.
41. Meyer F, Moore L, Bairati I, Fradet Y. Downward trend in prostate cancer mortality in Quebec and Canada. *J Urol* 1999;161:1189-1191.
42. Mettlin CJ, Murphy GP. Why is the prostate cancer death rate declining in the United States? *Cancer* 1998;82:249-251.
43. Blumenfeld AJ, Fleshner N, Casselman B, Trachtenberg J. Nutritional aspects of prostate cancer: a review. *Can J Urol* 2000;7:927-935.
44. Schulman CC, Ekane S, Zlotta AR. Nutrition and prostate cancer; evidence or suspicion? *Urology* 2001;58:318-334.
45. Feuer EJ, Merrill RM, Hankey BF. Cancer surveillance series: interpret in trends in prostate cancer — part II: cause of death misclassification and the recent rise and fall in prostate cancer mortality. *J Natl Cancer Inst* 1999;91(12):1025-1032.
46. Bartsch G, Horninger W, Klocker H, Reissigl A, Oberaigner W, Schonitzer D et al. Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, Austria. *Urology* 2001;58:417-424.
47. Holmberg L, Bill-Axelson A, Helgesen F, Salo JO, Folmerz P, Haggman M, Andersson SO, Spangberg A, Busch C, Nordling S, Palmgren J, Adami HO, Johansson JE, Norlen BJ. Scandinavian Prostatic Cancer Group Study Number 4. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *N Engl J Med* 2002;347(11):781-789.
48. Stamey TA, Freiha FS, McNeal JE, Redwine EA, Whittemore AS, Schmid HP. Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer. *Cancer* 1993;71(3 Suppl):933-938.
49. Catalona, WJ, Smith DS, Ratliff TL, Basler JW. Detection of organ-confined prostate cancer is increased through prostate-specific antigen screening. *JAMA* 1993;270:948.
50. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA* 1994;271:368-374.
51. Oesterling JE, Suman VJ, Zincke H, Bostwick DG. PSA-detected (clinical stage T1c or B0) prostate cancer. Pathologically significant tumors. *Urol Clin N Amer* 1993;20:687.
52. Dugan JA, Bostwick DG, Myers RP, Qian J, Bergstralh EJ, Oesterling JE. The definition and preoperative prediction of clinically insignificant prostate cancer. *JAMA* 1996;275(4):288-294.
53. Stamey TA, Johnstone IM, McNeal JE, Lu AY, Yemoto CM. Preoperative serum prostate specific antigen levels between 2 and 22 ng./ml. correlate poorly with post-radical prostatectomy cancer morphology: prostate specific antigen cure rates appear constant between 2 and 9 ng./ml. *J Urol* 2002;167(1):103-111.
54. Stamey TA. Preoperative serum prostate-specific antigen (PSA) below 10 microg/l predicts neither the presence of prostate cancer nor the rate of postoperative PSA failure. *Clin Chem* 2001;47(4):631-634.
55. Stamey TA. More information on prostate specific antigen and prostate cancer. *J Urol* 2003;170(2 Pt 1):457-458.
56. Salomon et al. Prognostic Significance of Tumor Volume After Radical Prostatectomy: A Multivariate Analysis of Pathological Prognostic Factors. *European Urology* 2003;43:39-44.

57. Epstein et al. Is Tumor Volume An Independent Predictor of Progression Following Radical Prostatectomy? *J Urol* 1993;149:1478-1481.
58. Oesterling JE, Jacobson SJ, Chute CG, Guess HA, Girman CJ, Panser LA, Lieber MM. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. *JAMA* 1993;270:860.
59. Dalkin BL, Ahmann FR, Kopp JB. Prostate specific antigen levels in men older than 50 years without clinical evidence of prostatic carcinoma. *J Urol* 1993;150:1837-1839.
60. Carter HB, Pearson JD, Metter EJ et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA* 1992;267:2215-2220.
61. Benson MC, Whang IS, Olsson C A et al. The use of prostate-specific antigen density to enhance the predictive value of intermediate levels of serum prostate-specific antigen. *J Urol* 1992;147:817-821.
62. Feneley MR, Webb JA, McLean A, Kirby RS. Post-operative serial prostate-specific antigen and transrectal ultrasound for staging incidental carcinoma of the prostate. *Br J Urol* 1995;75(1):14-20.
63. Presti JC, Hovey R, Carrol PR, Shinohara K. Prospective evaluation of prostate specific antigen and PSA density in the detection of nonpalpable and stage T1C carcinoma of the prostate. *J Urol* 1996;156:1685-1690.
64. Djavan B, Zlotta AR, Byttebier G, Shariat S, Omar M, Schulman CC, Marberger M. Prostate specific antigen density of the transition zone for early detection of prostate cancer. *J Urol* 1998;160(2):411-418.
65. Lilja H, Christensson A, Dahlen U, Matikainen M-J, Nilsson O, Pettersson K, Lovgen T. Prostate-specific antigen in serum occurs predominantly in complex with a-1 antichymotrypsin. *Clin Chem* 1991;37:1618.
66. Stenman UH, Leinonen J, Alfthan H, Rannikko S, Tuhkanen K, Alfthan O. A complex between prostate-specific antigen and a-1-antichymotrypsin is the major form of prostate-specific antigen in serum of patients with prostate cancer: assay of the complex improves clinical sensitivity for cancer. *Cancer Res* 1991;51:222.
67. Lilja H. Significance of different molecular forms of serum PSA. The free, noncomplexed form of PSA vs that complexed to a-1-antichymotrypsin. *Urol Clin N Amer* 1993;20:681.
68. Christensson A, Bjork T, Nilsson O et al. Serum prostate-specific antigen complexed to a-1-antichymotrypsin as an indicator of prostate cancer. *J Urol* 1993;150:100.
69. Bjork T, Bjartell A, Abrahamsson P-A, Hulkko S, Sant'Agnese A, Lilja H. Alpha-1-antichymotrypsin production in PSA-producing cells is common in prostate cancer but rare in benign prostatic hyperplasia. *Urology* 1994;43:427-434.
70. Catalona WJ, Partin AW, Slawin KM et al. A multicenter clinical trial evaluation of free PSA in the differentiation of prostate cancer from benign disease. *J Urol* 1997;157(4):434A.
71. Chen YT, Thiel RP, Soriano TF, Luderer AA. Free PSA proportions and the probability of CaP. *J Urol* 1996;155:423A.
72. Veltri R. Miller MC. Free/total PSA ratio improves differentiation of benign and malignant disease of the prostate: critical analysis of two different test populations. *Urology* 1999;53:736.
73. Catalona WJ, Southwick PC et al. Comparison of percent free PSA, PSA density, and age-specific PSA cutoffs for prostate cancer detection and staging. *Urology* 2000;56:255.
74. Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements. *JAMA* 1997;277(18):1452-1455.
75. Paus E, Nilsson O, Bormer OP, Fossa SD, Otnes B, Skovlund E. Stability of free and total prostate specific antigen in serum from patients with prostate carcinoma and benign hyperplasia. *J Urol* 1998;159(5):1599-1605.
76. Lechevallier E, Eghazarian C, Ortega JC, Roux F, Coulange C. Effect of digital rectal examination on serum complexed and free prostate-specific antigen and percentage of free prostate-specific antigen. *Urology* 1999;54(5):857-861.
77. Jung K, Lein M, Brux B, Sinha P, Schnorr D, Loening SA. Different stability of free and complexed prostate-specific antigen in serum in relation to specimen handling and storage conditions. *Clin Chem Lab Med* 2000;38(12):1271-1275.
78. Bunting PS, DeBoer G, Choo R, Danjoux C, Klotz L, Fleshner N. Intraindividual variation of PSA, free PSA and complexed PSA in a cohort of patients with prostate cancer managed with watchful observation. *Clin Biochem* 2002;35(6):471-475.
79. Chapdelaine P, Paradis G, Tremblay. High Level of Expression in the Prostate of a Human Glandular Kallikrein mRNA related to Prostate Specific Antigen. *FEBS Letters* 1988;236:205.
80. Murtha, Tindall. Androgen Induction of a human prostate-specific kallikrein, hKLK2: characterization of an androgen response element in the 5'promoter region of the gene. *Biochemistry* 1993;32:6459.
81. Lovgren J. Activation of the zymogen form pf prostate-specific antigen by human glandular kallikrein 2. *Biochem Biophys Res Commun* 1997;238:549.
82. Kwiatkowski Recker F, Piironen T, Pettersson K, Otto T, Wernli M, Tscholl R. In prostatism patients the ratio of human glandular kallikrein to free PSA improves the discrimination between prostate cancer and benign hyperplasia within the diagnostic "gray zone" of total PSA 4 to 10 ng/mL. *Urology* 1998;52:360-365.
83. Partin AW, Catalona WJ, Finlay JA, Darte C, Tindall DJ, Young CY, Klee GG, Chan DW, Rittenhouse HG, Wolfert RL, Woodrum DL. Use of human glandular kallikrein 2 for the detection of prostate cancer: preliminary analysis. *Urology* 1999;54(5):839-845.
84. Haese A, Becker C, Noldus J, Graefen M, Huland E, Huland H, Lilja H. Human glandular kallikrein 2: a potential serum marker for predicting the organ confined versus non-organ confined growth of prostate cancer. *J Urol* 2000;163(5):1491-1497.
85. Recker F, Kwiatkowski MK, Piironen T, Pettersson K, Huber A, Lummen G, Tscholl R. Human glandular kallikrein as a tool to improve discrimination of poorly differentiated and non-organ-confined prostate cancer compared with prostate-specific antigen. *Urology* 2000;55(4):481-485.
86. Darson MF, Pacelli A, Roche P, Rittenhouse HG, Wolfert RL, Young CY, Klee GG, Tindall DJ, Bostwick DG. Human glandular kallikrein 2 (hK2) expression in prostatic intraepithelial neoplasia and adenocarcinoma: a novel prostate cancer marker. *Urology* 1997;49(6):857-862.
87. Mikolajczyk SD, Millar LS, Wang TJ, Rittenhouse HG, Marks LS, Song W, Wheeler TM, Slawin KM. A precursor form of prostate-specific antigen is more highly elevated in prostate cancer compared with benign transition zone prostate tissue. *Cancer Res* 2000;60(3):756-759.
88. Mikolajczyk SD, Millar LS, Wang TJ, Rittenhouse HG, Wolfert RL, Marks LS, Song W, Wheeler TM, Slawin KM. "BPSA," a specific molecular form of free prostate-specific antigen, is found predominantly in the transition zone of patients with nodular benign prostatic hyperplasia. *Urology* 2000;55(1):41-45.
89. Mikolajczyk SD, Marks LS, Partin AW, Rittenhouse HG. Free prostate-specific antigen in serum is becoming more complex. *Urology* 2002 Jun;59(6):797-802.
90. Khan, Partin et al. Evaluation of Proprostate Specific Antigen For Early Detection of Prostate Cancer in Men With a Total Prostate Specific Antigen Range of 5-10 ng/ml. *J Urol* 2003;170(3):723-726.

91. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS Redwine E. Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 1987;317:909-916.
92. Lange PH, Ercole CJ, Lightner DJ, Fraley EE, Vessella R. The value of serum prostate specific antigen determinations before and after radical prostatectomy. *J Urol* 1989;141:873-879.
93. Partin AW, Subong ENP, Walsh PC et al. Combination of PSA, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer: A multi-institutional update. *JAMA* 1997;277:1445-1451.
94. Oesterling JE, Chan DW, Epstein JI et al. Prostate specific antigen in the preoperative and postoperative evaluation of localized prostatic cancer treated with radical prostatectomy. *J Urol* 1988;139:766.
95. Sullivan LD, Rabbani F. Should we reconsider the indications for ileo-obturator node dissection with localized prostate cancer? *Br J Urol* 1995;75:33-37.
96. Tiguert R, Gheiler EL, Tefilli MV, Oskanian P, Banerjee M, Grignon DJ, Sakr W, Pontes JE, Wood DP Jr. Lymph node size does not correlate with the presence of prostate cancer metastasis. *Urology* 1999;53(2):367-371.
97. Flanigan RC, McKay TC, Olson M, Shankey TV, Pyle J, Waters WB. Limited efficacy of preoperative computed tomographic scanning for the evaluation of lymph node metastasis in patients before radical prostatectomy. *Urology* 1996;48(3):428-432.
98. Chybowski FM, Larson Keller JJ, Bergstralh EJ, Oesterling JE. Predicting radionuclide bone scan findings in patients with newly diagnosed prostate cancer: prostate specific antigen is superior to all other clinical parameters. *J Urol* 1991;145:313-318.
99. Gleave ME, Coupland D, Drachenberg D, Cohen L, Kwong S, Goldenberg SL, Sullivan LD. Ability of serum prostate-specific antigen levels to predict normal bone scans in patients with newly diagnosed prostate cancer. *Urology* 1996;47(5):708-712.
100. Cher M et al. Limited Role of Radionuclide Bone Scintigraphy in Patients with Prostate Specific Antigen Elevations After Radical Prostatectomy. *J Urol* 1998;60:1387-1391
101. Aref I, Eapen L, Agboola O, Cross P. The relationship between biochemical failure and time to nadir in patients treated with external beam therapy for T1-T3 prostate carcinoma. *Radiother Oncol* 1998;48:203–207
102. Hanlon AL, Diratzouian H, Hanks GE. Posttreatment prostate-specific antigen nadir highly predictive of distant failure and death from prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;53:297–303
103. Kestin LL, Vicini FA, Ziaja EL, Stromberg JS, Frazier RC, Martinez AA. Defining biochemical cure for prostate carcinoma patients treated with external beam radiation therapy. *Cancer* 1999;86:1557–1566
104. Critz FA, Williams WH, Benton JB, Levinson AK, Holladay CT, Holladay DA. Prostate specific antigen bounce after radioactive seed implantation followed by external beam radiation for prostate cancer. *J Urol* 2000;163:1085–1089.
105. Rosser CJ, Kuban DA, Levy LB, Chichakli R, Pollack A, Lee AK et al. The prostate specific antigen bounce phenomenon after external beam radiation for clinically localized prostate cancer. *J Urol* 2002;168:2001–2005.
106. Hanlon AL, Pinover WH, Horwitz EM, Hanks GE. Patterns and fate of PSA bouncing following 3D-CRT. *Int J Radiat Oncol Biol Phys* 2001;50:845–849.
107. Shipley WU, Thames HD, Sandler HM, Hanks GE, Zietman AL, Perez CA, Kuban DA, Hancock SL, Smith CD. Radiation therapy for clinically localized prostate cancer: a multi-institutional pooled analysis. *JAMA* 1999;281(17):1598-1604.
108. Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys* 1997;37(5):1035-1041.
109. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281(17):1591-1597.
110. Bruchovsky N, Goldenberg SL, Akakura K, Rennie PS. LHRH agonists in prostate cancer: elimination of flare reaction by pretreatment with cyproterone acetate and low-dose diethylstilbestrol. *Cancer* 1993;72:1685.
111. Miller JI, Ahmann FR, Drach GW, Emerson SS. Bottaccini MR. The clinical usefulness of serum prostate specific antigen after hormonal therapy of metastatic prostate cancer. *J Urol* 1992;147:956-961.
112. Killian CS, Yang N, Enrich LJ, Vargas FP, Kuriyama M, Wang MC, Slack NH, Papsidero LD, Murph, GP, Chu TM and Investigators of the National Prostatic Cancer Project. Prognostic importance of prostate-specific antigen for monitoring patients with stage B2 to D1 prostate cancer. *Cancer Res* 1985;45:886-891.
113. Klotz L. Expectant management with selective delayed intervention for favorable risk prostate cancer. *Urol Oncol* 2002;7(5):175-179.