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DANCE ROUND

WE DANCE ROUND IN A RING AND SUPPOSE,
BUT THE SECRET SITS IN THE MIDDLE AND KNOWS.
ROBERT FROST

THE PROS AND CONS OF PROSTATE-SPECIFIC ANTIGEN TESTING

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After its isolation in 1979, the prostate-specific antigen focused the interest of the urologists and soon became one of the most popular serum tumor markers. A large body of evidence, accumulated throughout the last two decades, convincingly proves that prostate-specific antigen is not only useful for marking the progress of prostatic carcinoma, but additionally has a potential role for the screening and diagnosis of this disease. This Dance Round *briefly summarizes the various aspects of the clinical utility of prostate-specific antigen testing, the existing controversy due to its numerous limitations, and the current refinements in prostate-specific antigen levels, aiding to improve the specificity of the test. When all the pros and cons of prostate-specific antigen testing are evaluated, it becomes evident that the benefits of the test significantly outweigh its drawbacks.*
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INTRODUCTION

Being one of the leading causes of male mortality, with the highest incidence of newly diagnosed cases, prostate cancer currently represents a major health problem worldwide. Constant attempts are being made to detect the disease as early as possible, to avoid local tumor invasion and the distant spread of metastasis, and to achieve optimal results from the curative therapy that might be applied. The diagnosis of prostate cancer generally relies on three main diagnostic tools: physical examination by digital rectal examination (DRE), transrectal ultrasound (TRUS), and blood testing of the prostate-specific antigen (PSA). In case of abnormal finding by any of these three tests, ultrasound-guided needle biopsies are recommended to verify the clinical diagnosis.

Recently, in many countries of the world, there has been a growing tendency patients with prostate cancer to be diagnosed at an earlier age and at an earlier stage of the disease, even before the initial symptoms had occurred. No doubt that this is mainly due to the advent and the wide clinical application of one of the most popular serum tumor markers, namely PSA.

PSA was identified as a result of the attempts to find a unique substance in the seminal fluid that would aid in the investigation of rape victims. It was first isolated in 1971 by Hara *et al* (1) from human seminal plasma, and therefore named initially gamma seminoprotein. Later on, this protein was isolated from the prostate, as well, and thus received its present name, prostate-specific antigen (2). It is a 34-kD single chain glycoprotein neutral serine protease (3). Its primary structure shares about 80% homology with the proteases of the kallikrein family, although this proteolytic enzyme is unlikely to be present in the serum in active form. PSA splits the seminal vesicle proteins seminogelin I and II, resulting in liquefaction of the seminal coagulum. PSA is secreted by the prostatic epithelial cells, and is normally present in the seminal fluid,

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serum and the urine. All normal, hyperplastic and neoplastic epithelial cells produce PSA, but the PSA produced by cancer cells is 10 times higher per gram of tissue than that produced by normal or hyperplastic tissue. In the circulation, PSA forms complexes with other serum proteins. Free or unbound PSA accounts for only a small amount of PSA in the circulation, although it is the major form found in the ejaculate. The majority of serum PSA is bound to a variety of protease inhibitors, including α-1-antichymotrypsin, α-2-macroglobulin and protein C inhibitor. The realization that the proportions of free PSA and complexed PSA may differ in the presence of prostatic carcinoma, as opposed to benign conditions, has led to attempts to use this phenomenon to optimize diagnostic performance.

The first serologic test allowing PSA to be measured in the serum has been developed in 1980 (4). In 1985, Graves *et al* published a report on the postcoital investigation of rape victims using the presence of this new protein. The first results of the use of PSA as a diagnostic tool in prostate cancer were published in 1987 by Stamey *et al* (5). This report was followed by numerous clinical studies carried out world-wide, which continue to prove the diagnostic utility of PSA testing. Although still rising some controversies, in the last decade, PSA became the most widely used tumor marker in urooncological laboratory diagnostics. It revolutionized the clinical approach to prostate cancer and fundamentally changed the management and follow up of the disease.

This *Dance Round* is an attempt to summarize the various aspects of the clinical utility of PSA testing, the existing controversy due to its numerous limitations, and the current refinements in prostate-specific antigen levels, aiding to improve the specificity of the test.

PSA TESTING IN EARLY DIAGNOSIS AND SCREENING OF PROSTATE CANCER

Before the advent of PSA, the DRE was the main method, used by the urologists to detect prostate cancer. Other biochemical tumor markers, used at this time, like prostate acid phosphatase and alkaline phosphatase lacked the sensitivity and specificity required, and thus did not contribute much to the final diagnosis. The combination of DRE and PSA significantly increased the percentage of positive results (6). It was established that when the PSA level in men with prostate cancer was within the normal range (0-4 ng/ml), positive DRE findings could be found in 10-20% only, but when the PSA level was above 4 ng/mL, positive DRE results might be present in 42-72% of the patients. Due to PSA testing the urologists can detect nowadays one third of the newly diagnosed cases of prostate cancer early, even before the tumor can be palpated in the prostate. In more than 90% of the patients, prostate cancer can be diagnosed before the first symptoms occur (6).

The level of PSA correlates with the detection rate of prostate cancer. When PSA level is between 2.5-4.0 ng/mL, the incidence of prostate cancer proved by prostatic biopsy in a screening population of men is about 25%, with 68% clinically significant cancers among them. However, 95% of men with PSA levels of 4.0 ng/mL or less have a potentially curative disease. Men older than 50 years have a 20-30% possibility of having prostate cancer if their PSA level is greater than 4.0 ng/mL. For PSA levels greater than 10 ng/mL, the possibility of positive biopsy findings increases to 42-64%.

The introduction of PSA into clinical practice led to a dramatic change in the percentage of localized, organ confined disease, which can be found now in approximately 50% of all cancers detected because of an elevated PSA level. On the other hand, the percentage of men who already had clinically metastatic disease at the time of initial diagnosis was significantly reduced - from 75% to 5% only.

The PSA levels significantly correlate with the stage of the disease. Partin *et al* (7) found that nearly 50% of the patients with prostate cancer and PSA levels of 4-10 ng/mL treated with radical prostatectomy had extraprostatic extension. When the PSA level was greater than 10 ng/mL, the risk of extraprostatic cancer was significantly increased. Nearly 80% of men with PSA levels greater than 20 ng/mL had extraprostatic disease. The PSA levels also correlate with the grade of cancer: the higher the grade, the higher the serum PSA level (7).

Identification of early prostatic carcinoma is vital, because such localized disease could be completely cured by radical prostatectomy or radiotherapy. Patients in this stage initially present with only mild or vague prostatic symptoms, and often only elevated values of PSA aid in the differentiation of malignant from benign disease, and allow selection of high risk individuals for prostatic biopsy. However, the use of standard total PSA in this regard is far from perfect. Due to the low specificity of PSA test a substantial proportion of patients might be overdiagnosed and subjected to unnecessary prostatic biopsies, while in the mean time some cancers might be missed, because of normal PSA values.

Besides, in many cases, like the low-grade tumors for example, the disease does not progress for years, with patients remaining asymptomatic for long periods of time. The so called "watchful waiting" strategy remains an attractive option, especially in elderly patients. Therefore, with the true natural history of prostatic carcinoma remaining obscure, it remains rather controversial whether prostatic carcinoma should in fact be screened for in the general asymptomatic male population, given the attendant morbidity and mortality associated with subsequent investigation and treatment of the disease. Large scale screening campaigns had been recently conducted in the Scandinavian countries, USA, etc, while others, England for example, remain more conservative with regard to

screening.

Due to the widespread PSA screening for early detection of prostate cancer, its incidence increased dramatically in the late 1980s and early 1990s. Since 1992, however, there has been a steady decrease in the incidence rate of prostate cancer. Today, in many countries of the world, the prostate is still the leading cancer site. In USA, for example, prostate cancer accounts for 29% of new male cases. One in 5 American men is expected to be diagnosed with this disease (8).

There still exists a great deal of controversy regarding the role of prostate-specific antigen in prostate cancer screening. While large PSA screening studies have demonstrated an appreciable increase in the detection of organ confined, potentially curable prostate cancers, no study to date has yet demonstrated that the increased detection rate will decrease the prostate cancer-specific mortality rate. Yet more importantly, no study to date has demonstrated that early diagnosis using PSA will not decrease the prostate cancer specific mortality rate and, as Partin and Oesterling (9) point out, until such data exist, PSA should be used to aid in early diagnosis and treatment planning for men with prostate cancer.

PSA IN MONITORING THE RESULTS OF THERAPY

Serial PSA measurements currently provide the most effective means to monitor the results of therapy. All this became possible with the latest ultrasensitive PSA assays, which can measure now PSA levels as low as 0.001 ng/mL. They have a 10-fold increased sensitivity, compared with the conventional first- and second-generation PSA assays.

Following radical prostatectomy, most men have a rapid decline in their PSA levels, which are expected to be undetectable within a month. Failure to achieve this level is indicative of residual cancer. In patients, who had been treated by radiotherapy, PSA levels decline more slowly, and a nadir may not be reached for a median of 17 months. An elevation of PSA level following a period of undetectability connotes the presence of prostate cells somewhere in the body. This may be from residual normal glandular elements remaining in the bladder wall or at the apex of the prostate, but generally, a detectable and rising PSA level indicates the presence of cancer cells.

Many studies focus on PSA kinetics as an aid for predicting tumor aggressiveness. Rapid PSA doubling time is associated with metastatic disease, whereas slow doubling time is associated with local recurrence (10). When PSA becomes detectable after prostatectomy, the main patient concern is what this elevated PSA means, whether prostate cancer has recurred and, if so, how life expectancy is affected (10).

Although detectable PSA after prostatectomy predicts recurrent cancer, it cannot predict when metastasis may develop or when death may occur. The low rate of and long interval to metastatic disease as well as the variability of disease progression raise questions on the significance of PSA recurrence. Within 10 years after prostatectomy 15% to 35% of men have detectable serum PSA (10-12). However, a significant number of these patients do not die of prostate cancer. In fact, there is an 8-year mean actuarial interval from biochemical recurrence to progression to metastasis and a 5-year mean actuarial interval from metastasis to death (13). In addition, the rate of disease progression varies widely (14). Therefore, the challenge is to identify patients who may eventually have metastatic disease and, thus, may benefit from early hormonal therapy.

PSA doubling time is the only marker now available that represents a timed reference for the growth rate of cancer recurrence (13). The pattern of PSA rise after local therapy has been used to predict the period between PSA recurrence and metastasis, and distinguish local recurrence from systemic disease (12).

Patients with rapidly progressive PSA have short doubling times and are more likely to have metastatic disease. Distant disease can be predicted if the PSA does not become undetectable after a radical prostatectomy, starts to rise within the first 12 months, or has a doubling time of 6 months. The same characteristics might be applied to radiation therapy and cryotherapy, although the time to nadir in these cases is usually prolonged. In contrast, local recurrence can be predicted if PSA level becomes detectable 24 months or more after radical prostatectomy. Patients with PSA doubling times of 12 months or more following surgery, radiation therapy, or cryotherapy are also most likely to have local recurrence. All these judgements are important in determining which patients might benefit from local radiation therapy following prostatectomy, or adjuvant hormonal therapy that might prolong survival in case of metastatic spread.

Recently, a variety of nomograms have been published as an attempt to assist the clinicians in predicting PSA recurrence after radical prostatectomy or after definite radiotherapy (15,16). These nomograms use different pretreatment or postoperative variables, such as Gleason score, pathological stage, tumor volume, DNA ploidy, extraprostatic extension, seminal vesicle and/or lymph node involvement, preoperative PSA, patient age and margin status. There are also nomograms using increased PSA to predict disease recurrence or metastasis.

LIMITATIONS OF PSA TESTING

The main limitation for PSA is that it is considered to be prostate organ specific but not prostate cancer specific. PSA levels can be altered by pharmacologic therapies, prostatic diseases other than cancer, and various urologic manipulations. The serum PSA level can be significantly (by 50%) reduced by finasteride, which is commonly prescribed for the treatment

of benign prostatic hyperplasia (BPH) (17). All medications that alter testosterone levels can also affect the serum PSA: luteinizing hormone-releasing hormone (LHRH) agonists, antiandrogens, estrogens, etc. PSA levels have shown to be elevated in case of benign diseases, such as BPH, acute prostatitis, subclinical or chronic prostatitis, and urinary retention (18). A temporary increase in PSA levels has been reported following ejaculation, vigorous prostate massage, cystoscopy, or prostatic biopsy (19-21). The elevated PSA levels usually return to normal within 48 hours, but in some cases, as a persistent infection for example, this process may take weeks or even months.

Another limitation of PSA testing is that PSA levels are age and race dependent. PSA levels are higher in black men compared to white men, even when controlled for age, clinical stage, and Gleason grade. PSA levels normally tend to increase with age. This is probably due to the increase of the prostate volume, which is an age related phenomenon. Therefore, some investigators (22) proposed cutoff values, based on age to be used in order to define the normal range for a specific age. For example, in men younger than 50 years, the PSA level normally should not exceed 2.5 ng/mL, while in those older than 70 years, the normal range of PSA levels can reach 6.5 ng/mL. Nowadays, most clinicians continue to use the standard value of 4.0 ng/mL as the cutoff for cancer detection regardless of age, but when younger patients are addressed, for cancer detection and for screening purposes, then a lower cutoff of 2.5 or 3.0 ng/mL seems to be appropriate.

Assay variability represents another limitation of PSA testing today (23). Because of the existing differences between the numerous commercial PSA immunoassays currently available on the medical market, and because of the significant interlaboratory variations of the results achieved by each of them, reaching 20-30%, or even 55% (24) in some cases, the results between the various investigators are often difficult to be compared and interpreted. The reported variability between the PSA assays is mainly due to differences in assay calibration, assay kinetics, or different detection standardization of PSA in the serum. The proper handling, processing and storage of the blood samples is also very important for the final result. Assay variability is especially important when PSA is in the so called "intermediate", or "grey zone", between 4 and 10 ng/mL. At these PSA levels, the clinician is attempting to make a decision about the need for a biopsy, to differentiate prostate cancer from other common nonmalignant diseases that can also cause rising of the PSA levels, like BPH and prostatitis. The same variability for an initial PSA is less relevant when the PSA level is high (>10 ng/mL) because a biopsy is performed regardless.

REFINEMENTS IN PSA LEVELS

Although it currently remains the major indicator for the diagnosis and management of prostate cancer, PSA lacks specificity, especially within the range of 4-10 ng/mL. In this range, 25% of men actually have prostate cancer. Several possibilities further to improve the specificity of PSA testing have been recently explored.

Besides combining PSA with other urologic procedures, like DRE and TRUS, the ability of some PSA-based parameters to enhance the specificity of PSA testing has been profoundly studied (25). These novel PSA refinements include the selective determination of free (fPSA), complexed (cPSA), and total PSA (tPSA) in the same sample, the determination of the PSA/prostate volume ratio, that is, PSA density (PSAD), the change in the PSA concentration over time, that is, PSA velocity (PSAV), and finally, age-specific reference ranges for PSA. It is important to emphasize that all the attempts to improve the specificity of PSA testing have been with limited success.

Free PSA, free-to-total PSA and complexed PSA

It has been reported that men with prostate cancer had more cPSA than fPSA, in contrast to men with BPH. Therefore, the fPSA expressed as a ratio with the tPSA has been used as a surrogate marker for the changes occurring in the development of malignancy. The free-to-total PSA (f/tPSA) is lower in men with prostate cancer. A number of studies showed that in the PSA range of 4-10 ng/ml, in the so called "gray zone" of tPSA, the f/tPSA is more discriminatory for prostate cancer than tPSA (26-28).

A novel approach to the measurement of cPSA has recently emerged that involves the measurement of the immunologically detectable cPSA after the antibody "knockout" of fPSA (29). This assay uses the same polyclonal sandwich approach as that in the Bayer tPSA method but with the additional step of immunological inactivation of fPSA with a third antibody. A few studies (30,31) recently revealed that the overall diagnostic performance of Bayer cPSA appears to be better than the other PSA tests and ratios studied. The use of cPSA as a ratio with tPSA (32), and more importantly as a single standalone test (33,34) follows more closely the development and progression of prostatic carcinoma and may thus lead to a reduction in the number of men undergoing unnecessary prostatic biopsy. A possible explanation for this result may lie in the observation that prostate cancer cells seem to produce α-1-antichymotrypsin, whereas benign prostatic cells do not (35). This means that any excess secretion of PSA into the extracellular matrix may be bound to α-1-antichymotrypsin before entering circulation, which explains the higher proportion of cPSA found in prostatic carcinoma. In addition, the absence of a "PSA gap" using the Bayer cPSA assay would suggest that the relevant cPSA forms are being measured.

PSA density

PSA density is defined as the total serum PSA is divided by

prostate volume, as determined by transrectal ultrasound measurement (36). However, the value of PSAD alone is limited: firstly, because of the individual variations in performing the prostate volume measurements, and secondly, because of the existing variations between individuals regarding their epithelial-to-stromal ratios (37,38). As PSA is produced only by the epithelial cells, the BPH volume does not always correlate with serum PSA values.

To increase the specificity of PSAD, two other refinements of the original PSAD had been recently made: the PSA transition zone density (PSA-TZ), and the peripheral zone fraction of PSA (PSA-PZ) (39). They were predicated on the assumption that the US measuring of TZ volume is more accurate than measuring the entire prostate volume. Most of the PSA, measured in the serum, arises from the TZ. Prostate cancer usually originates from the peripheral zone, which contributes to a less extent to the total production of PSA in the human body, but cancer cells are considered to produce10-fold more PSA than normal or hyperplastic prostate tissue.

PSA velocity

PSAV monitors the change in PSA over time using longitudinal measurements (40-42). It is calculated by a special formula, using at least three PSA measurements performed during a 2-year period or at least 12-18 months apart to obtain maximal benefit from the results. When these specimen collection criteria are met, more than 95% of men without prostate cancer will have a PSAV less than 0.75 ng/ml/year, whereas approximately 70% of men with prostate cancer will have a PSAV above this threshold. PSAV value is thus more specific than routine PSA testing for the presence of prostate cancer, because few men (< 5%) without prostate cancer have a PSAV sufficient to trigger performance of a prostate biopsy. A rising PSA level of more than 20% per year or an increase of 0.75 ng/ml or greater in a year is strongly suggestive of cancer and should be taken into consideration, regardless of the absolute PSA value, when the need for initial or repetitive biopsy is discussed.

Age-specific reference ranges

The standard PSA reference range of 0.0-4.0 ng/ml does not take into consideration changes in the volume of the prostate due to the development of BPH with increased age. Some investigators (22) believe that age-specific reference ranges would improve cancer detection rates in younger men and would increase the specificity of PSA testing in older men. Using reference ranges of 0-2.5 for men aged 40-49 years, 0-3.5 for men aged 50-59 years, 0-4.5 for men aged 60-69 years, and 0-6.5 for men aged 70-79 years, the specificity of the test might be increased up to 95%.

However, controversy exists regarding the advantage of age-specific PSA reference ranges compared to the standard PSA cutoff of 4.0 ng/ml. Some authors believe that the standard reference range still remains the most effective and least costly means for screening (43,44). A lower PSA cutoff in younger men could result in additional unnecessary biopsies and greater health care costs; whereas raising the cutoff level for older men could result in fewer cancers being detected.

CURRENT RECOMMENDATIONS

According to guidelines established by the American Urological Association and the American Cancer Society PSA screening is recommended annually for all men aged 50 years and older who have an anticipated lifespan of 10 years or more. In some cases, however, as for men with a family history of prostate cancer, PSA testing should begin at a lower age and be repeated at 6-month intervals.

All patients with abnormal PSA levels should be referred to an urologist for evaluation and a determination of the need for a biopsy. The decision of performing a prostatic biopsy in any individual case requires proper clinical judgment and should be taken after a profound examination of the patient, including DRE and TRUS. In suspicious cases, some of the aforementioned refinements in the PSA values should also be taken into consideration.

Confusion still exists regarding what value should be taken as a normal PSA level. The standard reference range has been considered to be 0-4 ng/ml, but this may be too high for men in their 40s and 50s and too low for men older than 75 years. Certainly, rapidly rising PSA levels should be investigated carefully. Prostatic biopsies should be performed on all those patients whose PSA levels rise more than 20-25% or 0.75 ng/ml in a year.

CONCLUSION

The advent of PSA testing has revolutionized the diagnosis of prostate cancer and has provided a powerful tool to assess the effects of therapy. PSA cannot totally replace other diagnostic procedures, like DRE and TRUS, used routinely in the diagnosis of prostate cancer, but definitely it can enhance the diagnostic sensitivity and can improve the efficiency of the prostatic biopsy that is both expensive and distressing for the patient. Therefore, we can conclude that the benefits of PSA testing significantly outweigh its drawbacks.

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