EARLY DETECTION OF PROSTATE CANCER

Adapted from:
Prostate cancer early detection: a clinical perspective.
ABSTRACT

Prostate cancer is the most commonly diagnosed malignancy and second leading cause of cancer-related death for men in the United States. The introduction and routine use of serum prostate-specific antigen (PSA) testing in men at risk for the disease has led to significant changes in prostate cancer incidence, presentation and treatment. It is believed that these changes will eventually translate into decreased disease-specific morbidity and mortality. The purpose of the current article is to provide a clinical perspective on prostate cancer early detection by addressing the magnitude of the problem and discussing the various screening tests available. In addition, variations on PSA testing designed to enhance its performance will be considered.
INTRODUCTION AND MAGNITUDE OF THE PROBLEM

Prostate cancer is a significant public health concern in the United States due to its high incidence and mortality, the costs associated with its detection and treatment, and the fact that no consensus exists as to what constitutes the best form of treatment for any stage of disease. Excluding skin cancers, prostate cancer is the most commonly diagnosed malignancy in American men. It has been estimated that 189,000 new cases will be diagnosed in the United States in 2003, leading to 30,200 prostate cancer-related deaths.

With the introduction of prostate specific antigen (PSA) as an effective screening test in the mid 1980’s, a dramatic increase in the incidence of new prostate cancer cases occurred. The introduction of the PSA test led to detection of earlier stage disease in more patients (i.e. stage migration). Approximately 75% of prostate cancers currently diagnosed are detected when the disease is clinically confined to the prostate. This is in contrast to a 25% rate of organ-confined disease prior to the introduction of PSA screening. The routine use of serum PSA testing in men beginning at age 50 has also led to a marked decrease in the age at diagnosis of patients with prostate cancer. Perhaps reflecting this earlier disease stage at presentation, as well as more effective treatment for localized disease, 5-year cancer-specific survival rates have increased from approximately 70% in the early 1980s to over 90% a decade later. However, as yet, there are no conclusive data to confirm that early detection will decrease disease-specific morbidity and mortality. Until properly conducted trials of screening are completed, the benefits and risks of prostate cancer early detection and the accompanying treatment methods should be thoroughly discussed with patients.

METHODS OF PROSTATE CANCER DETECTION

Digital Rectal Examination

Prostate cancer screening or early detection has been accomplished using digital-rectal examination (DRE), measurement of serum PSA (and its various forms), transrectal ultrasound (TRUS), and combinations of these tests. The vast majority of prostatic
carcinomas arise in the peripheral zone of the prostate, which comprises the posterior surface of the gland including the apical, lateral, posterolateral and anterolateral portions of the prostate. It is this part of the gland that is accessible by DRE. Prostate cancer may present as a firm nodule that is palpable on the periphery of the gland; however, subtle findings such as asymmetry between prostate lobes may also be suggestive of the presence of prostate cancer. Although DRE can detect prostate cancer, it has limited sensitivity and, overall, detects fewer cancers than PSA. Unfortunately, many cancers detected using DRE are either locally or regionally advanced. Despite these limitations, DRE should not be abandoned as 20% of prostate cancers may be associated with a normal serum PSA and may be detected by DRE.

Serum PSA

PSA is a substance produced by benign and malignant prostate tissue and secreted into the blood stream. Although it is produced in small amounts in other tissues, it should be considered to be prostate specific clinically. PSA circulates in the serum in both free (unbound) and complexed (bound) forms. The majority of PSA is bound to alpha-2 macroglobulin and not measurable in most assays. Of the measurable bound PSA, the majority is bound to alpha-1-antichymotrypsin.

Serum PSA may be transiently elevated in cases of prostatic inflammation (prostatitis) and after endoscopic urethral manipulation, prostatic biopsy and possibly ejaculation. Routine DRE usually has little effect on serum PSA concentration, but many physicians defer PSA testing after such an examination. The half-life of serum PSA is 2.2 to 3.2 days. Therefore, one should wait approximately 4 to 8 weeks after significant prostate manipulation and inflammation (cystoscopy, prostate biopsy, and prostatitis) before obtaining serum PSA. The most common cause for an elevated serum PSA is benign prostatic hyperplasia (BPH), the incidence of which increases with age similar to prostate cancer.

Serum PSA concentrations can be decreased by treatments that lower serum testosterone levels such as orchiectomy (removal of the testes), leutinizing hormone releasing
hormone (LHRH) agonists and antagonists, anti-androgens such as flutamide and bicalutamide, and the 5-α reductase inhibitor, finasteride, which is used for the management of benign prostatic hyperplasia and male pattern baldness.

Use of Total Serum PSA and DRE for Prostate Cancer Early Detection

The risk of prostate cancer is associated with serum PSA concentration and DRE findings. The positive predictive value (PPV, or likelihood of having prostate cancer) of a serum PSA level between 4.0 ng/ml and 10 ng/ml for prostate cancer is approximately 20% to 30%. For levels in excess of 10 ng/ml, the PPV increases to 42% to 71.4%. The use of DRE complements serum PSA testing (Table 1).

More than 80% of prostate cancers detected by serum PSA are clinically significant based on cancer grade and volume. In contrast to the use of DRE alone for early prostate cancer detection, the majority of PSA-detected cancers are clinically confined to the prostate.

Variations on PSA Testing: Enhancing Performance

A number of different strategies have been developed to enhance PSA performance, by increasing sensitivity in certain populations and/or increasing specificity in others. These include use of PSA density, PSA transition zone density, age-specific reference ranges, PSA velocity and use of the molecular forms of PSA (free or complexed PSA).

PSA density is a measurement that attempts to correct for elevated PSA levels due to the presence of BPH. PSA density (PSAD) is defined as the total serum PSA level divided by the prostate gland volume (in cc) measured by TRUS. As prostate gland volume increases due to BPH, PSA usually rises as well. However, prostate cancer releases more PSA into the serum than does BPH. Some have suggested that a PSA density cut-point of 0.15 or greater may better discriminate between patients with an elevated serum PSA due to BPH from those with an elevated PSA due to prostate cancer. The use of PSA density is associated with several limitations including the need to perform TRUS in all patients, variations in the accuracy of TRUS with respect to measurement of prostate...
volume and the fact that PSA levels due to BPH are influenced by the ratio of stromal to epithelial components of BPH which vary from patient to patient. As many as 50% of prostate cancers may be missed if a PSA density cutoff of 0.15 is used to determine the need for prostate biopsy.

Some have attempted to compensate for the limitations of PSA density by correlating PSA with transition zone volume (PSA-TZ). The transition zone is the portion of the prostate where BPH typically arises. In referral based populations of men with serum PSA levels between 4.0 and 10.0 ng/ml, total serum PSA, PSA-TZ, and PSAD are significantly higher in men with prostate cancer. PSA-TZ has limitations as it requires the use of TRUS and adds little to the use of percent fPSA in most cases. Therefore, it may be best used in combination with percent fPSA in determining which patients with abnormal PSA levels and a previous negative TRUS-guided biopsy require a second biopsy.

Age specific PSA reference ranges were developed to compensate for the fact that the standard PSA reference range of 0.0 to 4.0 ng/ml does not reflect age-related volume changes in the prostate due to BPH. A single cut-point may, therefore, be inappropriate for all ages. Many have proposed age-related reference ranges to improve test sensitivity in younger men (who have less BPH and, therefore, would be expected to have lower levels of PSA) and to improve test specificity in older men (who are more likely to have BPH and higher PSA values which accompany it). Race may also have an impact on PSA levels. Using age-specific reference ranges, cancer detection rates will increase 8% to 18% in men < 60 years of age and decrease 4% to 22% in older men. Use of age-specific reference ranges will decrease the overall biopsy rate in men undergoing screening, especially in older men in whom the biopsy rate has been shown to decrease approximately 21%. However, the overall cancer detection rate will also decrease as fewer elderly men, the group most likely to have prostate cancer, will undergo prostate biopsy.
PSA velocity refers to the rate of change in serum PSA over time. PSA velocity is calculated using the equation, $1/2 \left( \frac{(PSA2-PSA1/\text{time 1 in years}) + (PSA3 – PSA2/\text{time 2 in years})}{\text{time}} \right)$, where PSA1 is the first, PSA2 the second and PSA3 the third PSA measurement. Time represents the interval (in years) between PSA measurements. At least 3 PSA measurements obtained over 24 months are required for optimal accuracy. A PSA velocity exceeding 0.75 ng/ml/year is highly predictive of prostate cancer using one assay (sensitivity 72% and specificity 95%). The use of PSA velocity is limited by the fact that multiple measurements using the same assay over a relatively long period of time are necessary for accuracy. In addition, there is substantial biological and laboratory variability in serum PSA testing which may limit the accurate interpretation of PSA velocity.

Perhaps the greatest enhancement of PSA testing has been based on the knowledge that PSA exists in the serum in both free (unbound) and complexed forms (bound to serum proteins). The free form of serum PSA (fPSA) is higher in men without prostate cancer than in those with the disease. Calculating the free-to-total PSA ratio, when compared to total PSA alone, can enhance the specificity of PSA testing for the detection of prostate cancer. Using a free PSA cutoff of 20% to provide approximately 95% sensitivity, 20%-29% of unnecessary biopsies may be eliminated (20% specificity). Measurement of percent free PSA enhances the specificity of PSA testing in African American men as well as Caucasians using similar cutpoints (i.e. 25%).

Clinicians should be aware of several issues when deciding how to use percent fPSA and in interpreting results of the assay. Age, prostate volume and method of serum storage before processing may influence PSA ratios. Assays performed by different methods may yield different results. The percent free PSA cutpoint advised by manufacturers of these assays varies. Therefore clinicians need to be well acquainted with the methods used for free PSA testing before interpreting the results. Lastly, it needs to emphasized that because use of percent fPSA improves specificity of detection, some cancers will be missed. Both physicians and patients need to be aware of this, as some will find any decrement in sensitivity unacceptable. Percent free PSA testing may be used best when
determining the need for a second prostate biopsy in patients with a normal DRE, a total serum PSA between 4.0 and 10 ng/ml and a previously negative biopsy.

*Human kallikrein 2 (hK2)* is a serum protease which bears considerable homology to PSA. It is thought that hK2 might activate the precursor form (proenzyme) of PSA. HK2 levels and hK2/fPSA ratios are higher in men with prostate cancer compared to those with benign disease.

Similar to use of percent fPSA, investigators have assessed the measurement of complexed PSA (PSA bound to alpha-1-antichymotrypsin) for the detection of prostate cancer. How best to use hK2 and complexed PSA for prostate cancer detection is currently under study.

**Transrectal Ultrasound (TRUS) Guided Prostate Biopsy**

TRUS has become an important tool in the routine evaluation of patients suspected of having prostate cancer.

Prostate cancer may be identified on TRUS as a hypoechoic lesion. However, only 60% of prostate cancers appear hypoechoic on ultrasound while most of the remaining cancers appear isoechoic (similar) with respect to the surrounding parenchyma. Because other disease processes, such as BPH and prostatitis may have a similar appearance to prostate cancer, it is impossible to reliably differentiate these lesions from prostate cancer based on sonographic characteristics alone. Consequently, TRUS should not be used as a first-line screening study as it lacks acceptable specificity, is relatively expensive when compared with DRE and PSA testing, and adds little information to that already gained by the use of serum PSA and DRE. The most important role for TRUS in prostate cancer detection comes from its usefulness in guiding prostate biopsy in those patients who have an elevated serum PSA, an abnormal DRE, or both.

Prostate biopsy is best performed under TRUS guidance using a spring-loaded biopsy device coupled to the transrectal probe. The transrectal approach facilitates accurate
needle placement and tissue sampling. Rather than just sampling an area abnormal on the basis of DRE or TRUS imaging, systematic biopsy strategies have been developed which improve cancer detection and risk assessment.

Traditionally, six (sextant) biopsies have been taken along a parasagittal line between the lateral edge and the midline of the prostate at the apex, mid-gland and base bilaterally. Increasing the number of biopsies as well as sampling specific portions/zones of the prostate improves detection, however more laterally-directed biopsies of the peripheral zone will increase detection rates by 14% to 20% over the more traditional sextant technique. Most physicians have found that routine transition zone biopsies add little unique information to that gained from routine peripheral zone biopsy schemes. Therefore, transition zone biopsy should be considered only in those patients with a high suspicion of prostate cancer based on serum PSA who have undergone previous peripheral zone biopsies without cancer detection. Patients should be advised that a negative prostate biopsy does not completely exclude cancer, as 13-31% of patients with an initially negative biopsy will be found to have cancer on subsequent biopsy.

Although the primary goal of prostate biopsy is cancer detection, information gained from the results, if positive, can be of considerable value in initial risk assessment. The number of cores with cancer, as well as the cancer grade determined by biopsy, correlate with the risk of extracapsular disease extension and cancer progression.

Although transrectal ultrasound guided prostate biopsy is usually very well tolerated, approximately 24% of those undergoing the procedure will find it very painful. Hematospermia (blood in the semen) and hematuria (blood in the urine) are common occurring in 40% to 50% of patients. High fever is rare occurring in 2.9% to 4.2% of patients. Antibiotic prophylaxis is commonly given. Recent use of aspirin or non-steroidal anti-inflammatory agents is not a contraindication for this procedure.

**Early Detection – One Approach**
On the basis of information gained to date, early detection of prostate cancer should be performed in all symptomatic men and those at high risk for the disease. It should also be considered in all asymptomatic, healthy men with a reasonable life expectancy. First line early detection efforts should focus on the use of DRE and serum PSA. Although use of free/total serum PSA, hK2, and PSA-TZ adds specificity to PSA testing, these latter tests should be used, for the most part, in determining which patients need repeat biopsy until additional information on their utility is available.

The frequency of PSA testing remains a matter of some debate. In men with a normal DRE and a PSA > 2.5 ng/ml, PSA testing should be performed yearly. PSA testing may be performed biannually in those with a normal DRE and serum PSA < 2.5 ng/ml. Although annual PSA testing beginning at age 50 is recommended by many, PSA testing at ages 40 and 45 years followed by biannual testing at age 50 may be more efficient.

**SUMMARY**

**To Detect or Not To Detect?**

The case for prostate cancer early detection is supported by several arguments: the disease is burdensome; PSA improves detection of clinically important tumors without increasing the detection of “insignificant” tumors; most PSA-detected tumors are curable using current techniques; and there is no cure for metastatic disease. In addition, some studies have suggested a reduction in cause-specific mortality with early detection. In the United States, the age-adjusted mortality rate for Caucasian men has decreased 16.1% since 1991, and the annual rate of decline has accelerated over time. The age-adjusted mortality rate for African American men has declined 10.9% since 1993. However, it must be emphasized that the causal relationship between screening and decreased mortality remains to be proven in clinical trials that are currently underway both in the United States and Europe.

Economic issues must also be considered when discussing prostate cancer early detection. The cost of early detection is not limited to the screening tests alone but also
includes the cost of prostate biopsy in men with an abnormal screening test, treatment for prostate cancer in asymptomatic men with the disease and managing the complications associated with prostate cancer therapy. Indeed, it has been estimated that treatment accounts for more than 60% of the total cost of prostate cancer screening.

In summary, patients must be informed of the risks and benefits of prostate cancer screening before it is carried out. If screening (and eventual treatment) are to be offered to asymptomatic patients, it should be offered to those in whom age and health status are such that they may benefit from early detection of a disease which may have a protracted natural history. In addition, men found to have prostate cancer must be advised, in detail, of all treatment options including surveillance alone.

SELECTED REFERENCES

Publications


Web Support
Table 1 - Probability of Prostate Cancer Based on Serum PSA and DRE (11)

<table>
<thead>
<tr>
<th>Author</th>
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Table 2 - Age-adjusted PSA References Ranges (11) (89-91)

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* ng/ml