Prostate Specific Antigen: The Past, Present and Future

Harcharan Gill Jonathan Wu

Department of Urology, Stanford University School of Medicine, Stanford, Calif., USA

Key Words

Prostate cancer • Prostate-specific antigen • Screening

Abstract

Aim: To review current data available on use of prostate specific antigen for screening healthy men for prostate cancer.

Methods: Literature was reviewed and the guidelines from, American cancer Society, American Urologic Association was reviewed. **Results:** Current screening protocols lead to over diagnosis of prostate cancer. This often results in unnecessary biopsy procedures and treatments. **Conclusion:** We must consider the benefit of screening and treatment with the harms of over diagnosis and over treatment. Newer imaging modalities like magnetic resonance imaging have to be evaluated further.

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age groups”. This recommendation was made for all men that do not have clinical symptoms suspicious for prostate cancer regardless of age, race, or family history. Based on their review of the literature and current evidence, they issued a grade D recommendation which states that “there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.”

This recommendation is in stark contrast to clinical guidelines issued by other national healthcare organizations such as the American Cancer Society (ACS). Currently, the ACS still recommends that patients have a discussion with their doctor about the risks and potential benefits of prostate cancer screening. This discussion should take place at age 50 for men who are at average risk of prostate cancer and have at least a 10-year life expectancy [2]. The organization further states that this discussion should start at age 45 for those at high risk of developing prostate cancer (i.e. African American men or men who have a first degree relative diagnosed prior to age 65) and at age 40 for those at even higher risk (i.e. men with more than one first degree relative diagnosed prior to the age of 65).

As the main professional organization for urologists both in the United States and worldwide, the American Urological Association (AUA) recommends that all men have a baseline PSA test performed at the age of 40 if they have an anticipated life expectancy of at least 10 years and then return for regular PSA and digital rectal examination (DRE) [3]. They further add that the decision to proceed with a prostate biopsy should not be based on a single threshold value of PSA. Rather, the decision to biopsy should also be based on other factors such as free and total PSA, PSA velocity, PSA density, patient age, family history, ethnicity, prior biopsy history and co-morbidities in addition to PSA and DRE results.

Current Guidelines

In October 2011, the United States Preventative Services Task Force (USPSTF) sparked major headlines when the organization released a draft of its new prostate cancer screening guidelines [1]. In a major shift from current practice, the USPSTF “now recommends against PSA-based screening for prostate cancer in all

Current Controversies

Most of the controversy surrounding the utility of PSA screening surrounds the fact that it is unclear what the true benefit really is. There have been several trials looking at PSA screening but they are of varying quality and not all patients are screened or treated in the same manner so it can be difficult to draw meaningful conclusions. The PSA screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial project randomized 76,693 men to either annual PSA screening or usual care from 1993 until 2001 [4]. These men were between the ages of 55 to 74 years old and the study used a PSA threshold of 4.0 ng/ml to refer men for prostate biopsy. After 7 years of follow-up, the incidence of prostate cancer per 10,000 person-years was 116 in the screening group and 95 in the control group (rate ratio of 1.22, 95% confidence interval 1.16 to 1.29). Further, they found that the incidence of death per 10,000 person-years was 2.0 in the screening group and 1.7 in the control group (rate ratio 1.13, 95% confidence interval 0.75 to 1.70). Based on these data, the group concluded that there was no real difference in prostate cancer death rates between the screening arm and control arm of the study. Many experts criticize this study due to its high rate of contamination as about half of the men in the control arm actually received PSA screening. Furthermore, about 40% of the subjects received PSA testing in the 3 years prior to enrollment. This statistic suggests that this study was performed in a highly pre-screened population, which could substantially affect the power of this study to find mortality differences between the 2 groups.

The other recently publicized trial was the European Randomized Study of Screening for Prostate Cancer (ERSPC). This study involved 182,000 men between the ages of 50 and 74 years in 7 European countries [5]. Men were randomized to a screening group that was offered PSA testing or to a control group that was not screened. The study demonstrated an 8.2% incidence of prostate cancer in the screening group compared to 4.8% in the control group after a median follow-up period of 9 years. In terms of prostate cancer specific death, this trial showed a rate ratio of 0.80 (95% confidence interval 0.65–0.98) for the screening group compared to the control group when looking at men between the ages of 55 to 69 years. Based on the absolute risk reduction, the investigators concluded that 1,410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated in order to prevent one death from prostate cancer. Critics of this study cite that vari-

ous PSA thresholds were used by different centers (ranging 2.5–4.0 ng/ml) and screening intervals ranged from every 2 to 7 years. Others point out that subjects in the screened group were more likely to be treated in a university setting compared to the controls. Furthermore, some experts state that due to the slow growing nature of most prostate cancers, the mortality benefit of PSA screening may not be seen until more extended follow-up is performed. One group has modeled expected mortality benefits with longer follow-up based on the data from the ERSPC trial and demonstrated that the number needed to screen and number needed to treat in order to prevent one death from prostate cancer would decrease to 503 and 18, respectively, with 12 years of follow-up [6].

The main downside of current screening protocols is that it leads to over diagnosis and overtreatment of prostate cancer. This leads to unnecessary biopsy procedures and treatments. Urologists do not have a good way to differentiate aggressive forms of prostate cancer that should be treated from more indolent forms that would never be diagnosed in a patient's lifetime without PSA screening. Major efforts are currently being made to assess the utility of active surveillance protocols where men with low risk prostate cancers are closely followed and only offered definitive treatment if they show signs of disease progression [7]. These men are re-evaluated with PSA, DRE, and prostate biopsy at regular pre-determined intervals. The goal of these protocols is to minimize unnecessary treatment without adversely affecting survival from prostate cancer by under treating more aggressive cancers. Entry criteria for these active surveillance protocols are designed to select for patients with low risk cancers but these criteria can vary somewhat between institutions. Most of these criteria rely on Gleason grade, clinical stage, PSA, and tumor volume while some protocols use PSA density as well. The definition of disease progression in these trials is variable as well but most define progression in terms of Gleason grade, tumor volume, and/or PSA kinetics. Across the major active surveillance protocols, rates of progression to treatment range from 14 to 41% depending on the length of follow-up. Interestingly, a small percentage (ranging 2–18%) of men in these protocols will opt for definitive treatment without meeting criteria for disease progression. Although this phenomenon has not been well studied, some experts attribute the anxiety of living with cancer as a factor while others think that these men may actually be having small rises in PSA during surveillance without meeting strict criteria for progression. This latter fact highlights the fact that PSA is not specific for pros-

tate cancer and can be elevated for a variety of reasons from infection or inflammation to benign enlargement of the prostate gland. In general, depending on the threshold used, false-positive PSA tests can be quite common. Analysis of the PLCO trial data cited a 12.9% risk of having at least one false-positive result and no prostate cancer diagnosis after 3 years [1]. These false positive tests lead to unnecessary biopsy related morbidity and anxiety. In addition, some experts are advocating the use of new terminology to avoid the stigma associated with the word cancer; the designation of these low risk tumors as indolent lesions of epithelial origin or indolent lesions of epithelial origin tumors has been proposed [9].

Ultimately, one must consider the benefit of screening and treatment with the harms of over diagnosis and over-treatment. The risks of prostate biopsy include hematospermia, hematuria, fever, urinary retention, prostatitis, urosepsis in addition to pain and discomfort. Compared to watchful waiting strategies in which patients are only treated once they are clinically diagnosed, radical prostatectomy is associated with a significantly increased risk of urinary incontinence and erectile dysfunction. Radiation treatment for prostate cancer is also associated with a substantially increased risk of impotence and bowel dysfunction [10, 11].

Future Directions

Future directions in the field of diagnosis are aimed at addressing the 2 main shortcomings of current PSA screening strategies. Mainly, urologists need to do a better job at detecting prostate cancer and discriminate between aggressive forms of prostate cancer that should be treated from more indolent forms. Research efforts are currently underway to discover and translate new biomarkers and imaging modalities for prostate cancer. Biomarkers such as prostate cancer antigen 3, prostatic acid phosphatase, six transmembrane epithelial antigen of the prostate, prostate specific membrane antigen, prostatic stem cell antigen are some of the promising molecular targets being studied currently for their use with high throughput screening technologies and specific molecular imaging techniques. Prostate cancer antigen 3 is a promising urine based biomarker of non-coding mRNA that is currently being studied for its utility in diagnosing prostate cancer as well as differentiating high grade and high volume disease from more indolent cancers [12–15].

The field of prostate imaging shows incredible promise for its clinical applications. For instance, new imag-

ing techniques may help reduce the number of biopsy cores taken and improve the overall yield of biopsies, and may even obviate the need for repeat biopsies in the active surveillance setting. Another role for imaging may be its use for tracking tumor relapse or recurrence after focal therapy with cyroablation or high intensity focused ultrasound [16].

In terms of imaging modalities, magnetic resonance imaging (MRI) and ultrasound technologies are the main techniques being studied. Advances in development of various MRI sequences (i.e. diffusion weighted imaging, magnetic resonance spectroscopic imaging, and dynamic contrast enhanced imaging), improved endorectal coil technology, and the evolution of more powerful magnetic coils have greatly improved ability of MRI to detect prostate cancer [17, 18]. Traditional MRI relies on the finding that prostate cancer has lower signal intensity compared to surrounding benign tissue in T2 weighted images. Dynamic contrast enhanced MRI relies on differential contrast enhancement properties between tumor and benign tissue that is attributed to differences in microvasculature. Magnetic resonance spectroscopic imaging leverages the fact that prostate cancer typically has increased choline and decreased citrate content compared to benign prostate tissue [19]. Newer methods are using magnetic resonance spectroscopic imaging to detect differences in metabolites such as lactate and pyruvate to discriminate prostate cancer from benign tissue [17, 20, 21]. Diffusion weighted imaging detects differences in the apparent diffusion coefficient between malignant and benign prostate tissue. The sensitivity of this sequence can be improved with greater diffusion weighting, but this also results in a reduced signal-to-noise ratio [22, 23].

Contrast enhanced ultrasound is another promising modality that is being developed. Prostate cancer tissue is associated with increased microvessel density and this modality utilizes microbubbles which improve the acoustic signal [24]. These contrast agents are able to dwell within the intravascular space for several minutes and are small enough to pass through the pulmonary capillary bed. Studies have demonstrated that with contrast enhanced targeted biopsy, a larger number of prostate cancers may be detected with fewer biopsy cores compared to routine systematic core biopsies [25, 26]. Newer microbubble contrast agents are being outfitted with specific moieties to target prostate specific biomarkers such as prostate specific membrane antigen [27].

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