Prostate Cancer Screening, Treatment Revisited

BY JEFF EVANS
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ORLANDO, FLA. — Emerging insights into the clinical significance of prostate-specific antigen levels are leading to new approaches to screening, treatment, and patient counseling, speakers said at a symposium on prostate cancer sponsored by the American Society of Clinical Oncology.

PSA testing has led to the detection of indolent, slow-growing prostate cancers in many men. Overdetection of these biologically inconsequential cancers should prompt doctors to question their screening practices and the way they approach managing such patients, the speakers suggested.

The word "cancer" promotes aggressive treatment, which is often disproportionate to the natural history of minimal-volume, low-grade, "good risk" prostate cancer, said Laurence Klotz, M.D., professor of surgery at the University of Toronto

Interpreting PSA Levels

Accumulating evidence suggests that a normal PSA level—commonly thought of as below 4.0 ng/mL—is losing its clinical relevance for detecting prostate cancer.

The Prostate Cancer Prevention Trial (PCPT), the largest prostate cancer screening study to date, randomized 18,882 patients to the 5-α-reductase inhibitor finasteride or placebo. The trial is the only major study to date to obtain prostate biopsies when clinically indicated or when PSA levels rose above 4.0 ng/mL and at the end of the study, regardless of PSA level or treatment.

Among 2,950 men in the placebo arm of the PCPT who never had a PSA level higher than 4.0 ng/mL or an abnormal digital rectal examination, 15% had a biopsy positive for prostate cancer at the end of the 7-year study. About 27% of those with a PSA level of 3.1-4.0 ng/mL had a positive biopsy, and even 6.6% of men with a PSA level of up to 0.5 ng/mL had a positive biopsy (N. Engl. J. Med. 2004;350:2239-46).

"There is no level of PSA at which you have no risk of prostate cancer," said Ian Thompson, M.D., lead investigator of the PCPT.

Despite the large percentage of placebo patients who had prostate cancer with PSA levels below 4.0 ng/mL, only 2.3% of them had high-grade cancer with a Gleason score of 7 or higher, and only 0.24% had high-grade cancer with a Gleason score of 8 or 9 (and none had a score of 10), noted Howard L. Parnes, M.D., chief of the prostate and urologic cancers research group in the division of cancer prevention at the National Cancer Institute.

That prostate cancer can occur at all PSA levels indicates "PSA is just a marker, like cholesterol. It is not dichotomous," said Dr. Thompson, urology department chair at the University of Texas, San Antonio.

Physicians will need to individualize the decision to biopsy in light of these results, rather than just biopsy patients with PSA levels above 4.0 ng/mL, Dr. Parnes advised.

The Case for Watchful Waiting

In men older than 55 years with an initial PSA level of 3.0 ng/mL or less, systematic use of PSA testing and subsequent biopsying of men who had a PSA level of more than 4.0 ng/mL or an abnormal digital rectal examination resulted in a prostate cancer detection rate of about 24% during a 7-year period, according to the results of the PCPT (N. Engl. J. Med. 2003;349:215-24).

But screening has been shown to increase the incidence-to-mortality ratio for prostate cancer from 2.5:1 to 15:1, Dr. Klotz said at a separate session at the symposium, which was cosponsored by the Society of Urologic Oncology and the American Society for Therapeutic Radiology and Oncology.

Prostate cancer progresses slowly in most patients, with long windows of curability. About 85%-90% of prostate cancer patients with a Gleason score of 6 or less have "insignificant" prostate cancer, which is not destined to cause morbidity or mortality during a patient's lifetime. Only 4%-8% of cancers with a Gleason score of 6 or less will progress to high-grade cancer after 8 years, he said. And even then, only some patients will die of the cancer.

Dr. Klotz suggested that doctors should consider "watchful waiting" more often in good-risk prostate cancer patients—those with a Gleason score of 6 or less, PSA level of 10.0 or less, and T1c-T2a tumor grade.

He and his associates followed 299 patients with clinically localized prostate cancer (Gleason score of 7 or less, stage T1b-T2b, and PSA level of 15.0 ng/mL or less). The patients were seen every 3 months for 2 years and then every 6 months thereafter, waiting for either an increase in PSA level, clinical progression, or histologic upgrade on repeat biopsy before implementing appropriate treatment.

The median PSA doubling time in the cohort was 7 years. About 22% had a doubling time of less than 3 years, and 42% had a doubling time of more than 10 years. Only two patients died from prostate cancer, each at 5 years after diagnosis, which "implies that both had incurable disease at diagnosis," he said. Overall, two-thirds of the patients remain free from progression.

Rapid PSA progression has generally been defined as a doubling time of less than 3 years. Some researchers have found that a PSA velocity of more than 2.0 ng/mL per year corresponds to disease progression (N. Engl. J. Med. 2004;351:125-35).

The intervention criteria on a program of watchful waiting or "active surveillance" should include PSA doubling time or grade progression, Dr. Klotz advised. (See box.)

Criteria for Intervention

In patients with "good risk" prostate cancer (Gleason score of 6 or less, PSA level of 10.0 ng/mL or less, and clinically localized stage T1c-T2a), physicians may want to use either of the following strategies to determine when to intervene and begin appropriate treatment:

Rapid PSA Doubling Time

► Measure PSA level every 3 months for 2 years and then every 6 months thereafter.

► If the PSA doubling time is less than 3 years, it may be time to intervene.

Gleason Grade Progression on Repeat Biopsy

► Biopsy between 1 and 2 years, then every 3 years, stopping at age 80 years.

► Treat if there is progression to a predominant Gleason pattern 4 or worse.

Source: Dr. Klotz

A 50-year-old man with good-risk prostate cancer could potentially face the psychological burden of living with prostate cancer for around 30 years, Dr. Klotz noted. But even patients who have been treated for prostate cancer still worry. At an office visit, the first thing that comes to the mind of a patient treated for prostate cancer is his PSA level.

To determine the validity of a watchful waiting approach, the START trial (Standard Treatment Against Restricted Treatment) will randomize 1,200-2,000 good-risk prostate cancer patients to active surveillance with selective delayed treatment or definitive therapy (radical prostatectomy, brachytherapy, or external beam radiation therapy).

Selective Use of PSA Testing

Instead of routinely testing PSA levels in all men, physicians could provide information on prostate cancer screening, suggested Timothy J. Wilt, M.D., an internist at the Minneapolis Veterans Affairs Center for Chronic Disease Outcomes Research.

This information could include the difference between prostate cancer and other prostate problems, descriptions of what PSA testing and digital rectal examinations can and cannot tell them, the consequences that may result from having a PSA test, and the risks and benefits of treatment options available for prostate cancer.

Physicians should target testing or treatment to men most likely to benefit from them but should also reassure those who are unlikely to benefit that not testing PSA or undergoing watchful waiting "is compassionate care that is likely to provide superior health outcomes," Dr. Wilt recommended during another session at the symposium. ■