Reliance on PSA May Lead to Overtreatment

VITALS

Major Finding: Common PSA triggers would have led to overtreatment of prostate cancer in 14%-84% of men on active surveillance.

Data Source: Prospective study of 315 men with localized prostate cancer and PSA levels less than 15 ng/mL at enrollment in monitoring program.

Disclosures: Dr. Loblaw reported having no conflicts of interest related to the study.

BY SUSAN LONDON

SAN FRANCISCO — Men with prostate cancer who are on active surveillance may be overtreated if their clinicians rely strictly on certain commonly used prostate-specific antigen triggers for starting treatment, Dr. Andrew Loblaw told attendees of a symposium on genitourinary cancers.

In a cohort of 315 such men who had no evidence of disease progression, the percentage in whom treatment would have been falsely triggered ranged widely—from 14% to 84%—depending on which of nine PSA measures was used for monitoring. The lowest value seen was with a PSA threshold of 20 ng/mL.

Dr. Loblaw said that research shows that active surveillance can achieve good outcomes in men with low-risk prostate cancer. This surveillance typically entails some type of PSA monitoring, with the decision to initiate treatment often based on a PSA trigger, said the radiation oncologist at the Sunnybrook Health Sciences Centre in Toronto.

The investigators therefore tested the performance of various PSA triggers in 315 men with localized prostate cancer who declined radical treatment, were enrolled in an active surveillance program, and did not have any evidence of progression after a median of 6.8 years (7.2 years for survivors).

At enrollment, the patients' PSA levels were all less than 15 ng/mL. Their monitoring had consisted of periodic physical examination, digital rectal examination, blood work, transrectal ultrasound, bone scans, and repeated prostate biopsies.

"All of the triggers or definitions that we looked at had a false or high trigger for treatment," Dr. Loblaw reported at the symposium, which was sponsored by the American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Urologic Oncology.

The false trigger rate was lowest for a PSA threshold of 20 ng/mL (according to which 14% of the men would have been treated) and highest for a successive PSA velocity of greater than 2 ng/mL (84%).

The rate was intermediate for a PSA threshold of 10 ng/mL (38%); first-last PSA doubling times of less than 2 and less than 3 years (39% and 50%); linear regression PSA doubling times of less than 2 and less than 3 years (37% and 48%); overall PSA velocity of greater than 2 ng/mL per year (42%); and a 1-year PSA velocity of greater than 2 ng/mL (51%).

The findings suggest that only a 20-ng/mL threshold has a low false-trigger rate and that men on active surveillance may be overtreated when clinicians rely on the other PSA triggers, he said. ■

MY TAKE

Active Surveillance May Not Catch On

Active surveillance is a hot topic. More and more men with low-risk disease are being diagnosed with prostate cancer in the United States and around the world. Many of these men would be candidates for active surveillance. In real-world practice, however, many questions remain about offering active surveillance to men with localized prostate cancer, including these:

► Is it prudent to offer active surveillance to young, healthy men who have a very long life expectancy?

► Does a patient on active surveillance need repeat prostate biopsies every year or two, or can we rely on PSA?

► As Dr. Loblaw and his colleagues asked, what is the best PSA change determinant to suggest a switch from active surveillance to active treatment for a patient with localized prostate cancer?

In their study of 315 men, the researchers found that a PSA threshold of 20 ng/mL had the lowest false-trigger rate for men on active surveillance. In other words, by allowing the PSA to go above 20 before offering active treatment, the authors suggested that this PSA threshold may be the most appropriate marker for switching from active surveillance to active treatment.

Although I applaud the researchers for doing this work, many patients would be very uncomfortable allowing their PSA to go as high as 20 before considering a repeat biopsy or treatment. In the D'Amico risk stratification scheme in localized prostate cancer, men with a PSA rated at 20 have high-risk disease. Therefore, if we allow a PSA to go above 20 in men on active surveillance before we recommend active treatment, we will be treating only high-risk patients who have progressed on active surveillance. This may be unacceptable to many clinicians and patients alike.

The key is that we need more prospective, randomized, controlled trials—such as the multicenter START—that address active surveillance. Again, I congratulate the researchers on excellent work, and look forward to further studies of active surveillance and new information about this hot topic.

JUDD W. MOUL, M.D., *is professor and chief of the Division of Urologic Surgery, and director of the Duke Prostate Center at Duke University, Durham, N.C. He had no relevant conflicts of interest.*

Novel Urinary Assay Improves Prostate Cancer Detection

BY SUSAN LONDON

SAN FRANCISCO — A new urinary assay for a common gene rearrangement in prostate cancer improves the detection of this disease and the differentiation of its more aggressive forms, according to two cohort studies reported at a symposium on genitourinary cancers.

The studies, conducted among men who were scheduled for prostate biopsy or prostatectomy, found that the assay supplemented conventional risk factors for accurately identifying those having prostate cancer. In addition, higher assay scores correlated with the presence of adverse tumor features.

Dr. John T. Wei presented results of the first study on behalf of Sheila M.J. Aubin, Ph.D., of Gen-Probe Inc., the company that is developing the assay.

Prostate-specific antigen (PSA) level and digital rectal examination both have poor specificity for detecting prostate cancer. Moreover, these tests are unable to differentiate indolent from aggressive cancer, said the professor of urology at the University of Michigan in Ann Arbor.

About half of prostate cancers exhibit fusion of the androgen-regulated TMPRSS2 gene and the ERG oncogene. Cancers that harbor this fusion gene (abbreviated T2:ERG) have increased cell growth, invasion, and metastasis, and decreased apoptosis, Dr. Wei said at the symposium, which was sponsored by the American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Urologic Oncology.

In the first study, the investigators assessed the performance of the novel assay, which measures levels of T2:ERG messenger RNA in urine, using urine specimens collected after digital rectal examination and before either prostate biopsy (623 men) or prostatectomy (142 men).

Analyses of biopsy-based indicators showed that the T2:ERG score was correlated with the number of cores that were positive, the percentage of cores that were positive, and the greatest percentage involvement of any core by cancer, according to Dr. Wei. Also, the median score was higher among patients with biopsy-significant cancer as defined by Epstein criteria.

Analyses of prostatectomy-based indicators showed that the T2:ERG score was correlated with the maximum tumor dimension. In addition, the median score was higher among patients who had an upgrade of the Gleason score between biopsy and prostatectomy, a prostatectomy Gleason score of greater than 6, and prostatectomy-significant cancer as defined from tumor characteristics.

Compared with the PCPT (Prostate Cancer Prevention Trial) risk score alone, the combination of this score with the T2:ERG score more accurately identified men who had prostate cancer (area under the curve, 0.75 vs. 0.65).

Dr. Wei noted that at cutoff scores of 100 and 200, the T2:ERG assay had high specificity for distinguishing between patients with and without cancer (88%-93%), with biopsy-significant and -insignificant cancer (85%-95%), and with prostatectomy-significant and -insignificant cancer (95%-100%).

Independent trials of the assay are needed, Dr. Wei acknowledged.

In the second study, investigators tested the same T2:ERG assay using urine specimens that were collected after digital rectal examination from 471 men who were scheduled for prostate cancer biopsy at community clinics, according to Dr. James B. Amberson.

Some 44% of patients had positive biopsies, he reported. The median age was 66 years in the patients with cancer and 63 years in the patients without it. The median serum PSA level was 5.0 and 4.3 ng/mL, respectively.

When used alone, the T2:ERG score had a high specificity (87%) for detection of biopsy-proven cancer, reported Dr. Amberson, divisional medical director of Dianon Systems Inc., the manufacturer of another test that was also used in the study. Sensitivity was 39%.

The median T2:ERG score was higher in patients who had a Gleason score of 7 or greater, involvement of more than 50% of positive cores by cancer, and three or more positive cores.

"The T2:ERG assay significantly improved the diagnostic accuracy of a logistic regression model" for prostate cancer detection, said Dr. Amberson.

Dr. Wei and Dr. Amberson reported receiving research funding from Gen-Probe Inc. Some coauthors of both studies disclosed employment or leadership roles and stock ownership in Gen-Probe. ■