Studies Find Little Risk in 'Watchful Waiting'

BY ROBERT FINN

FROM THE ANNUAL MEETING OF THE AMERICAN UROLOGICAL ASSOCIATION

SAN FRANCISCO — Men who were diagnosed with low-grade prostate cancer have little to fear from a strategy of "watchful waiting," also called "active surveillance," according to two longitudinal studies

In one study, Dr. Laurence Klotz, chief of urology at the University of Toronto, followed a prospective cohort of 452 men for 10 years. During that time there were only five deaths from prostate cancer. The men in the study were 18.6 times more likely to die from other causes than from prostate cancer.

Among the original cohort, 315 men (70%) had stable disease. "In this group none have metastasized, none have been upgraded, and none have been treated," Dr. Klotz said during a press briefing.

"So we took these 315 patients and [asked], 'If we apply various PSA [prostate-specific antigen] triggers to this stable cohort, how does it perform?' " Dr. Klotz said. "And the remarkable thing is that these patients very frequently have a trigger for intervention."

This suggests that none of these triggers for intervention based on PSA values is very reliable. For example, 84% of the men with stable disease had two or more successive PSA tests during the study indicating a PSA velocity greater than 2 ng/mL per year.

Other commonly used measures of PSA kinetics also yielded false-positive signals in these men with stable disease. Among those unreliable measures were PSA linear regression, differences between first and last PSA, and PSA threshold greater than 10 ng/mL.

'What we are doing now is using the PSA not as a trigger for intervention,' but as a trigger for diagnostic tests.

DR. KLOTZ

"The bottom line is, these commonly used PSA triggers give what we consider to be a false signal for intervention very, very frequently," Dr. Klotz said. "You have to interpret these values with caution."

In the other study, Dr. Jared Whitson of the University of California, San Francisco, followed 532 men with low-grade prostate cancer for a mean of 55 months. The overall survival was 97%, and not a single man died from prostate cancer.

The men received prostate biopsies every 12-18 months, and 69% were still in active surveillance at the end of the study.

Of the 83 men who opted for radical prostatectomy, only 26 (31%) reached stage pT3, and only 22 (27%) had an extracapsular extension.

"Even among men who had not been upgraded, about 20% over 5 years will decide to be treated despite no change," Dr. Whitson said at the press briefing.

"What we are doing now is using the PSA not as a trigger for intervention, but as a trigger for further diagnostic tests," Dr. Klotz said. ■

VITALS

Major Finding: One study found that men on active surveillance after a prostate cancer diagnosis are almost 19 times as likely to die from other causes as from prostate cancer over 10 years. Another study found that over 5 years, not a single man diagnosed with prostate cancer died of the disease while under active surveillance, and only 3% died of other causes.

Data Source: Two prospective cohort studies of men with low-grade prostate cancer, one with 452 men followed for 10 years, and the other with 532 men followed for 5 years.

Disclosures: Both investigators said that they had no conflicts of interest. Dr. Whitson's study was supported by the University of California, San Francisco; Dr. Klotz's study was supported by the Prostate Cancer Research Foundation of Canada.

MY TAKE

Active Surveillance Not Yet Standard

The studies by Dr. Klotz and Dr. Whitson both suggest that active surveillance is a reasonable strategy in men with low-grade prostate cancer. But I think it's still too soon to say that this strategy is the standard of care. In all fairness, I think we need to be a bit careful in saying that this is something we ought to be offering everyone. We just don't know enough about it yet.

What we really need from studies of active surveillance is longer-term follow-up. We need to know how many of these men we might have saved by active treatment vs. how many went on to never have to worry about prostate cancer. There are many adjuvant therapies that we can offer if they fail: radiation therapy, hormonal therapy, chemotherapy, and now immunotherapy. So I think the critical question is, what do we give up with active surveillance? We don't know that yet.

Most of these active surveillance protocols have a significant amount of fallout, some of it due to the treating physicians and some of it driven by the patients. One of the problems is that most of our patients concentrate on the PSA level. But a PSA level obtained today and one obtained tomorrow may be very different. Often patients get very anxious about active surveillance. PSA could stand for "patient-stimulated anxiety."

J. BRANTLEY THRASHER, M.D., *is a professor and the William L. Valk chair of urology at the University of Kansas Medical Center, Kansas City. The text is an edited version of remarks Dr. Thrasher made at a press briefing announcing the two studies at the AUA meeting.*

Data Back Surveillance for Men at Low Prostate Cancer Risk

BY RICHARD HYER

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY

CHICAGO — A prospective cohort study comparing immediate radical prostatectomy with delayed surgery in 1,120 men who qualified for active surveillance suggests waiting is a viable option for most patients deemed to be at low risk of developing prostate cancer.

Men in the delayed-surgery group were twice as likely to have a Gleason score of 7 or higher, reported Bruce J. Trock, Ph.D., and his coinvestigators from Johns Hopkins University, Baltimore. The delayed-surgery group also had more tumors that were not organ confined.

VITALS

Major Finding: Gleason scores of 7 or higher were twice as common, 44% vs. 22%, in low-risk men who delayed radical prostatectomy compared with men who passed up active surveillance for immediate surgery, but many of the delayed surgeries were ordered after Gleason score reached 7 or higher on surveillance biopsies.

Data Source: 1,120 men who were eligible for active surveillance: 772 who chose the monitoring strategy and 348 who opted for immediate radical prostatectomy.

Disclosures: The investigators and discussant disclosed no conflicts of interest.

This appeared to be the result of selection bias, however. Many of the delayed surgeries were ordered after a surveillance biopsy showed the patient had a Gleason score of 7 or higher, explained Dr. Trock, director of the division of epidemiology at the university's Brady Urological Institute. When these men were excluded, surgical pathology was similar in the remaining men who delayed radical prostatectomy and those who opted for immediate surgery.

"So it appears that a missed high-grade tumor at [the initial] biopsy is the predominant risk in the active-surveillance cohort," Dr. Trock said, suggesting that higher risk was confined to men who had been undergraded in their initial biopsies. The median time to delayed surgery was 23 months, he noted.

The study began in 1995 and compared 772 men in an active-surveillance cohort with 348 men who were eligible for active surveillance but instead elected to have immediate radical prostatectomy.

Eligibility for active surveillance included a prostate-specific antigen density less than 0.15 ng/mL per cc, biopsy Gleason score of 6 or less, two or fewer positive cores, and 50 % or less of any biopsy core involved with tumor.

Progression was considered to occur if the pathology of a follow-up biopsy exceeded these eligibility criteria and triggered a recommendation for treatment. Of the 772 men enrolled in the active-surveillance program, 116 (15%) have since undergone radical prostatectomy: 25 had "no trigger" indicating higher-risk disease but chose surgery anyway, 43 had a biopsy upgrade (Gleason score 7 or higher), and 48 had more than two positive cores or more than 50% of a core involved with tumor.

These 116 patients were frequency matched 1:3 with 348 men who met eligibility for active surveillance but decided on immediate radical prostatectomy.

Looking just at the men who underwent surgery, the study found that 44% of the delayed-surgery group had Gleason 7 or greater at surgery vs. 22 % of the immediate-surgery group. Non–organ confined tumors occurred in 27% of the delayed surgeries vs. 16% of the immediate surgeries.

These differences were even more pronounced when the men upgraded at a surveillance biopsy were compared with the immediate-surgery group: 76% vs. 22%, respectively, for Gleason score of 7 or higher and 34% vs. 16% for non–organ confined disease. Among 67 men who were not upgraded before delayed surgery, 25% had Gleason scores of 7 or higher and 23% had non–organ confined disease. Neither measure was significantly different from the pathology in the immediate-prostatectomy group.

The clinical translation of these findings is that about 15% of men under active surveillance undergo radical prostatectomy within 2-3 years, according to Dr. Trock. Overall, the risk of adverse pathology at radical prostatectomy is low: The chance of a high-grade Gleason score greater than or equal to 7 is 4.5 per 100 person-years, while the risk of non–organ confined pathology is 1.2 per 100 person-years. ■