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Outcomes With "Watchful Waiting" in Prostate Cancer in US Now So Good, Active Treatment May Not Be Better

Zosia Chustecka

September 16, 2009 — Outcomes have greatly improved in recent years for men diagnosed with localized prostate cancer who opt for "watchful waiting" or "active surveillance," and are now so good that this option of conservative management should be considered as a reasonable alternative to immediate treatment.

This is the conclusion from the largest study to be conducted in the United States since the advent of prostate-specific antigen (PSA) screening. The results appear in the September 16 issue of the *Journal of the American Medical Association*.

The study followed 14,516 men diagnosed between 1992 and 2002 for a median of 8.3 years. The results show a 10-year overall survival of 94%.

"This has never been seen before," lead author Grace Lu-Yao MPH, PhD, from the Cancer Institute of New Jersey in New Brunswick, told *Medscape Oncology*.

The researchers suggest that now that the survival rate with conservative management is so high, there may be little room for improvement from active treatment.

This is an important paper.

"This is an important paper," said Timothy J. Wilt, MD, MPH, professor of medicine and core investigator at the Minneapolis VA Center for Chronic Disease Outcomes Research and the University of Minnesota School of Medicine, who was approached by *Medscape Oncology* for comment.

This study "reinforces accumulating evidence that the vast majority of men with prostate cancer detected by PSA testing have a very good prognosis and are unlikely to die of their cancer or suffer serious medical consequences from disease spread at 10 or more years, even if not treated with surgery, radiation, or hormone therapy," he said.

"This study also supports the view that many men are detected and treated who are unlikely to benefit, and thus may undergo harms that exceed benefits," he added.

"This is a pertinent and timely paper," said Brantley Thrasher, MD, professor of urology at the University of Kansas Medical Center in Kansas City, and a spokesperson for the American Urological Association. "There is no question that there is a place for watchful waiting, rather more appropriately called active surveillance," he told *Medscape Oncology* in an interview. But he emphasized that the message from this paper should not be generalized, and to say globally that active surveillance might be a good option is both "erroneous and inaccurate."

Dr. Thrasher pointed out that the median age of patients in the *JAMA* paper was 78 years. He agrees that active surveillance is a reasonable option for patients who are older than 75 years who have low-grade tumors that are clinically localized with low PSA levels, and/or who have other health problems, "but this is a minority of the patients who are seen in clinical practice," he pointed out. The situation is quite different if the patient has a high- or intermediate-grade tumor, and/or if the patient is younger and is otherwise in good health, with a life expectancy of 30 or so years, he said. In that situation, a radical prostatectomy or other active treatment could be more appropriate.

"There is no standard treatment," Dr. Thrasher emphasized, which is why there are so many "provocative discussions" about which approach is best, and why the various approaches are still being studied in randomized trials.

"Once you know there is a cancer, you have to be very careful," Dr. Thrasher noted. If the patient opts for active surveillance but then is noncompliant with regular follow-up tests, and a metastatic prostate cancer is discovered after a few years, then there is danger — especially in the litigious environment of the United States — of a claim of medical negligence, because there might have been a window of opportunity for curative treatment that was missed, he explained.

Survival Rates Better Than Any Seen Before

Dr. Lu-Yao and colleagues report a 10-year survival of 94%. Studies conducted in the pre-PSA testing era have shown 10-year survival rates of around 77% to 85%, she said in an interview, so these latest data suggest that there has been a reduction in mortality of around 60% to 70%.

The latest results are better than the 90% survival rate in a similar population of men treated with radical prostatectomy in the widely cited Scandinavian study (*N Engl J Med.* 2005;352:1977-1984), she noted. That study found a better survival after prostatectomy than watchful waiting, but it was conducted in a setting in which there is little PSA testing. Now that survival with conservative management is so high, it may be difficult — in the post-PSA era — to show an absolute benefit from surgery such as was seen in the Scandinavian study, the researchers write.

Survival rates have improved because PSA testing detects prostate cancer at a much earlier stage, Dr. Lu-Yao explained, but there have also been changes in the way that prostate cancer is classified, and this reclassification has also contributed.

"Survival is getting better all the time," Dr. Lu-Yao said in an interview, adding that "doctors should share these new data with their patients."

"Ultimately, the decision of what to do lies with the patient," she acknowledged, but she added that "patients often overestimate the potential benefit from treatment and they believe that surgery or radiation can save their life." They also often underestimate the potential risk for harm that can result from these treatments.

This has made it difficult to enroll patients into clinical trials in which patients are randomized to either active treatment or watchful waiting, she added. "Patients usually already have a strong opinion about wanting treatment," she said, adding that it can be difficult to explain to a patient just diagnosed with cancer that what appears to be "doing nothing" might actually be a good option.

These latest data "add weight" to this side of the equation, she explained. They show patients that if they do not opt for immediate treatment, their chance of dying from prostate cancer over the next 10 years is only 6%.

"Considering the favorable 10-year outcomes following conservative management, men with a life expectancy of less than 10 years may wish to consider an active-surveillance or watchful-waiting protocol as an alternative to immediate attempted curative therapy," the researchers conclude.

Difficult Now to Show Benefit From Active Treatment

Dr. Wilt agreed with the researchers that now that survival rates with conservative management have been shown to be 94% at 10 years, it might be difficult to show any improvement from active treatment in the post-PSA era.

"Early intervention with surgery, radiation, or androgen-suppression therapy (hormones) might not have a large absolute impact on disease-specific survival," he said

This issue is being addressed in ongoing randomized clinical trials — PIVOT in the United States and PROTECT in the United Kingdom. These trials are evaluating overall and disease-specific survival and quality of life after early treatment and after conservative management in men with localized prostate cancer primarily detected with PSA testing, Dr. Wilt explained. The results should be available within the next few years.

In the meantime, however, the data from Dr. Lu-Yao's group and others "strongly suggest that many men with PSA-detected prostate cancer may be treated unnecessarily with early interventions and face the risk of adverse effects, such as erectile, bowel, and urinary dysfunction, that can result in early and long-term negative impact on quality of life," he noted.

"It is very likely that men diagnosed currently and treated conservatively will have even better 10-year results," Dr. Wilt said, because PSA is now more widespread and picks up even smaller cancers. PSA testing (like all screening tests) is more likely to detect slower-growing tumors, and these screened cancers have a better long-term natural history than cancers detected in the absence of screening, even if no treatment is provided.

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The men in this latest study were diagnosed between 1992 and 2002, which is considered to be "early-mid PSA era," he said, when PSA testing was just becoming widespread.

"PSA testing has now been widespread for many years. The threshold for calling a test abnormal and obtaining biopsy is currently at lower levels than previously. Many men now have had multiple PSA tests and even multiple biopsies prior to their cancer being detected. Additionally, the percent of men with cancer detected by PSA testing (rather than felt on a digital rectal exam) today is much higher (80%+), and the PSA levels in men detected today are likely much lower and the size of tumors smaller than those reported by Lu-Yao," he explained.

Medscape Oncology also approached for comment Lars Holmberg, PhD, MD, from the Division of Cancer Studies at King's College Medical School in London, United Kingdom, and one of the authors of the Scandinavian study. He said that the study reported by Dr. Lu-Yao and colleagues "is basically sound and the results seem valid. The improved survival for those managed with surveillance over time can probably be explained by earlier diagnosis and the fact that the clinicians are getting better at choosing which men safely can be managed by initial surveillance."

"The authors are right, I think, to say that the room for improvement in survival by therapy is now smaller than when the Scandinavian study was done," Dr. Holmberg added. However, he pointed out that "observational data such as these are inherently very difficult to interpret," and that randomized trials are needed to more exactly quantify the benefits of different treatments and compare them to one another. "This is especially true for prostate cancer, where we are looking at very complex patterns of selection for screening, different trigger points for biopsy, different selection mechanisms to choose who gets which treatment, adherence to treatment protocol, instigation of secondary therapies, etc," he added.

The study was supported by grants from the US Army Medical Research Acquisition Activity, the Department of Defense, the Ohl Foundation, and the National Cancer Institute. Dr. Lu-Yao reports having received clinical research funding from the Ohl Foundation, the New Jersey Commission on Cancer Research, and the Agency for Healthcare Research and Quality, and is employed by HealthStat. Details of the financial relationships of her coauthors are listed in the paper.

JAMA. 2009;302:1202-1209.

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