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PROGRAM TOP3 • RELEASE DATE: JUNE 15, 2010 • EXPIRATION DATE: JUNE 15, 2011

ESTIMATED TIME TO COMPLETE: 1.0 HOUR

# Active Surveillance as a Management Strategy for Low-risk Prostate Cancer

By Scott E. Eggener, MD  
Assistant Professor of Surgery/Urology, University of Chicago Medical Center, Chicago, Illinois

## STATEMENT OF NEED

With the introduction and widespread use of prostate-specific antigen screening, the number of men being diagnosed with prostate cancer has increased. Almost 50% of these cancers, however, have biological characteristics associated with a low risk of cancer progression. As a result, clinicians are interested in management strategies that offer the possibility of delaying, obviating, or minimizing the impact of treatment to avoid having patients undergo unnecessary treatment. Oncology nurses and pharmacists should be aware of the most recent data regarding one such strategy, active surveillance with selective delayed intervention, so that they may discuss it with patients diagnosed with various types of prostate cancer.

## TARGET AUDIENCE

Registered pharmacists and other interested healthcare professionals, especially those caring for cancer patients

## LEARNING OBJECTIVES

After completing this activity, the reader should be better able to:

- Discuss active surveillance with selective delayed intervention with patients diagnosed with prostate cancer
- Appropriately select candidates for active surveillance based on disease characteristics at diagnosis
- Evaluate patient progress to determine if, and, when treatment may be warranted

The number of American men dying of prostate cancer has decreased 30% over the past 25 years, but it remains the second leading cause of cancer death. In 2009, an estimated 192,280 new cases of prostate cancer were diagnosed and 27,360 men died of the disease.<sup>1</sup> There is no universally accepted strategy for screening, diagnosis, and treatment of prostate cancer.<sup>2</sup> The introduction and widespread use of prostate-

specific antigen (PSA) screening, however, has led to an increasing number of men being diagnosed with prostate cancer each year. Almost 50% of these cancers have biological characteristics associated with a low risk of cancer progression.<sup>3</sup> The challenge facing patients and physicians is accurately determining which men have cancers with a significant risk of progression or metastases whom would benefit from treatment, compared with those unlikely to be impacted by the cancer during their natural lifespan.

Although radical prostatectomy (RP) and radiation therapy are effective treatments, they can result in serious long-term side effects such as urinary problems and erectile dysfunction. As a result, clinicians are interested in management strategies that offer the possibility of delaying, obviating, or minimizing the impact of treatment to avoid having patients undergo unnecessary treatment.<sup>3</sup> One strategy is active surveillance (AS) with selective delayed intervention.<sup>3</sup> AS involves characterizing the cancer using all available tools, determining whether the patient is a good candidate for AS, and frequently evaluating the cancer and overall health of the patient to determine if, and, when treatment may be warranted.<sup>2</sup>

## Current clinical practice guidelines

Because many prostate cancers detected through PSA screening may not require immediate treatment, the American Urological Association and National Comprehensive Cancer Network (NCCN) recommend that during discussion of treatment approaches for cancer clinicians include AS as an option for men with low-risk prostate cancer who have a life expectancy of less than 10 years.<sup>4,5</sup> In addition, a new “very low risk” category has been added to the

updated NCCN guidelines using a modification of the Epstein criteria for clinically insignificant prostate cancer (Table). AS is offered and recommended for men in this category when life expectancy is less than 20 years.<sup>5</sup>

## Multicenter study examines active surveillance

Studies have assessed the safety and efficacy of AS for low-risk localized prostate cancer.<sup>2,3,6</sup> One multicenter, retrospective study evaluated the actuarial rates and predictors of remaining on AS, the incidence of disease progression, and the pathologic findings of delayed RP.<sup>3</sup>

## Patient criteria

Each man in a cohort of 262 men from four institutions was offered multiple options but ultimately chose AS. All patients met the following criteria for eligibility<sup>3</sup>:

- 75 years of age or younger
- PSA 10 ng/mL or less
- Clinical stage T1 to T2a
- Biopsy Gleason sum 6 or less
- Three or fewer positive cores at diagnostic biopsy
- No single core with >50% cancer
- Repeat biopsy before AS (restaging)
- No treatment for 6 months following the repeat biopsy.

## Patient assessment

AS was defined as starting on the date of the second biopsy. Evaluation of patient progress included office visits, review of general health and urinary symptoms, digital rectal examinations, and PSA screenings every 6 to 12 months. Biopsies were routinely recommended within 18 months of starting AS and subsequently every 1 to 3

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- Scott E. Eggener, MD, has nothing to disclose.
- David Frame, PharmD, has nothing to disclose.

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years or prompted by a change in clinical status, a sign of possible disease progression. Magnetic resonance imaging (MRI) of the prostate was selectively used at diagnosis and every 1 to 3 years after starting AS. In isolated cases, MRI findings warranted biopsy earlier than was scheduled.

#### Study results

Forty-three (16%) patients elected

active treatment, with a median follow-up of 29 months. The 2- and 5-year probabilities of remaining on AS were 91% and 75%, respectively. Of the 43 patients undergoing delayed treatment, 41 (95%) were without disease progression at a median of 23 months following treatment. The most commonly reported reasons for stopping AS included upgrading (35%) or higher volume of cancer (16%) on surveillance biopsy or a change in

patient preference (14%). The active treatment choices among the cohort were RP for 26 (61%) patients, radiation therapy for 13 (30%), cryotherapy for one (2%), and androgen deprivation for three (7%).

Patients with cancer on the second biopsy (hazard ratio [HR], 2.23; 95% confidence interval [CI], 1.23-4.06,  $P = .007$ ) and a greater number of cancerous cores from the two biopsies combined ( $P =$

.002) were more likely to undergo treatment. Bone metastases developed in one patient 38 months after starting AS. Age, PSA, clinical stage, prostate volume, and the number of total biopsy cores were not predictive of outcome.

#### Clinical implications of AS

This study demonstrates that for select patients with low-risk prostate

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## COMMENTARY

# Active Surveillance as a Management Strategy for Low-risk Prostate Cancer: A Pharmacist's Perspective

David Frame, PharmD

*Clinical Hematology/Oncology/BMT Specialist and Assistant Professor of Pharmacy, University of Michigan, Ann Arbor*

Egger discussed the role of active surveillance (AS) in the treatment of prostate cancer, addressing an important option that is often overlooked. We must remember that the Hippocratic oath is to do no harm. The potential of causing harm by performing a radical prostatectomy is very real and can even result in mortality. A Canadian study exploring complications occurring within 30 days after radical prostatectomy among 11,010 men who underwent this surgery between 1990 and 1999 showed a low, but clinically significant, 0.5% mortality rate with another 20.4% having one or more complications within these 30 days.<sup>1</sup> Other risks associated with this procedure are deep vein thrombosis and herniation, and the most common side effects are impotence and incontinence, which may be long-term and significantly affect quality of life. Because of these risks of radical prostatectomy, it is essential to consider AS if these side effects could be spared without increasing the risk of mortality from the cancer in individuals diagnosed with low- or very-low-risk prostate cancer.

Prostate cancer is the second leading cause of cancer death in men, effecting 192,280 men and accounting for approximately 25% of all new cancer diagnoses in men in 2009. Given these numbers, even low percentages of unnecessary procedures could result in a significant increase in the percentage of unnecessary complications. To this end, the American Cancer Society (ACS) revised its recommendations on prostate cancer screening in March of this year.<sup>2</sup> The revised recommendations are partially based on two large trials that sought to determine whether prostate cancer screening with prostate-specific

antigen (PSA) levels and digital rectal examination (DRE) saves lives.<sup>3,4</sup> In the American study, more than 76,000 men were randomized to receive "usual care" or to have annual PSA tests for 6 years, and DREs every year for 4 years. Overall, no significant difference in prostate cancer death rates was demonstrated between the two groups after 7 to 10 years of follow-up.<sup>3</sup> In the European trial, 182,000 men were stratified to either a control group or a screening group.<sup>4</sup> Men in the screening group had PSA tests every 4 years and, on average, two DREs during that period. Interestingly, after approximately a 9-year follow-up, the researchers found that screening did reduce the rate of prostate cancer death by 20% but also was associated with a high risk of overdiagnoses. It is important to realize that much longer maturity is required before these studies can be fully analyzed. The reason for these studies, as pointed out by Egger, is to help further determine whether finding prostate cancer early truly leads to decreased mortality. Some prostate cancers grow slowly and may never cause any problems, whereas others are more aggressive. This distinction, however, cannot necessarily be determined by the standard PSA and DRE screening tools.

Based on all of the current information, the ACS recommends that men without high risk who have no symptoms at 50 years of age and are in relatively good health with a life expectancy of 10 years or more, use decision-making tools to help them make an informed choice about testing. Men with no symptoms who are not expected to live more than 10 years (because of age or poor health) should not be offered prostate cancer screening at

all.<sup>2</sup> So for those readers unsure of the appropriateness of the revised American Urological Association and National Comprehensive Cancer Network (NCCN) recommendations to include AS in discussions of treatment approaches for men with low-risk prostate cancer who have a life expectancy of less than 10 years or 20 years in the very-low-risk category, they seem to pale in comparison with the new ACS screening guidelines.

It should also be noted that in the revised NCCN guidelines the recommendation for AS for the very-low-risk group with less than 20 years expected survival is a category 2B recommendation, which means the recommendation is based on lower level evidence and there is not a uniform consensus among committee members.<sup>5</sup> I believe that a significant question that needs to be further explored is the potential risk of AS, that is, the risk of developing advanced cancer due to inadequate diagnosis, classification, or follow-up of these patients. A Scandinavian trial comparing AS with radical prostatectomy in localized prostate cancer demonstrated a relative risk of 0.65 for both 12-year disease-specific mortality ( $P = .03$ ) and distant metastasis ( $P = .006$ ).<sup>6</sup> The Epstein criteria for predicting pathologically insignificant prostate cancer have been shown to misdiagnose in as many as 8% of cases of nonorgan-confined disease upon postsurgical findings.<sup>7</sup>

Finally, it is very important that if patients agree to AS, they must commit to regularly scheduled examinations, including repeat biopsies. Cancer progression is suggested when more core biopsies are positive, when no single core has less than 50% can-

cer by volume, when the Gleason score increases to 4 or 5, or when PSA doubling time is less than 3 years. Although "trigger" points for intervention are suggested, these have also not been validated with good clinical trials. Because it is likely that many patients will be on AS, pharmacists must fully understand the potential benefits as well as the unanswered questions with this approach. In the near future, AS will likely be revisited, because many ongoing studies are evaluating genetic components as they relate to disease-risk classification.

#### References

1. Alibhai SM, Leach M, Tomlinson G, et al. 30-day mortality and major complications after radical prostatectomy: influence of age and comorbidity. *Natl Cancer Inst.* 2005;97:1525-1532.
2. American Cancer Society. Prostate cancer: early detection. 2010. [www.cancer.org/docroot/CRI/content/CRI\\_2\\_6x\\_Prostate\\_Cancer\\_Early\\_Detection.asp?sitearea=&level=](http://www.cancer.org/docroot/CRI/content/CRI_2_6x_Prostate_Cancer_Early_Detection.asp?sitearea=&level=). Accessed April 15, 2010.
3. Andriole GL, Grubb RL, Buys SS, et al; for the PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med.* 2009;360:1310-1319.
4. Schroder FH, Hugosson J, Roobol MJ, et al; for the ERSPC Investigators. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med.* 2009;360:1320-1328.
5. National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology: Prostate Cancer*. V.1.2010. [www.nccn.org/professionals/physician\\_gls/PDF/prostate.pdf](http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf). Accessed April 15, 2010.
6. Bill-Axelsson A, Holmberg L, Filen F, et al; for the Scandinavian Prostate Cancer Group Study Number 4. Radical prostatectomy versus watchful waiting in localized prostate cancer: The Scandinavian Prostate Cancer Group-4 randomized trial. *J Natl Cancer Inst.* 2008; 100:1144-1154.
7. Jeldes C, Suardi N, Waltz J, et al. Validation of the contemporary Epstein criteria for insignificant prostate cancer in European men. *Eur Urol.* 2008;54:1306-1313.

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## CASE STUDY

A 66-year-old man who had been undergoing annual prostate-specific antigen (PSA)-based prostate cancer screening had a normal digital rectal examination (DRE) but a PSA level of 6.4 ng/mL. PSA testing was repeated 1 month later and found to be 6.2 ng/mL. Prostate biopsy revealed two of 12 cores with Gleason 6 prostate cancer, encompassing 20% of each core. He had excellent sexual and urinary function. His medical history showed moderate obesity and medication-controlled hypertension. After meeting with multiple specialists and considering his options, he elected to proceed with active surveillance (AS) and, therefore, underwent a restaging 12-core biopsy. No cancer was identified and he formally entered AS. For 6 years, he underwent evaluations every 6 months without a significant change in health status, DRE, or PSA (range, 4.3 ng/mL-7.1 ng/mL). Surveillance biopsies performed every 12 to 18 months did not show a higher-grade or higher-volume cancer and ranged from zero to two cores with cancer. Seven years following the initiation of AS, the patient experienced a myocardial infarction, underwent the placement of two coronary stents, and was started on clopidogrel and aspirin. He continues routine surveillance of his prostate cancer with annual evaluations.

**Table. Modified Epstein Criteria for Clinically Insignificant Prostate Cancer**

• Clinical stage T1c
• Biopsy Gleason score $\leq 6$
• Presence of disease in fewer than three biopsy cores
• $\leq 50\%$ prostate cancer involvement in any core
• Prostate-specific antigen density $< 0.15$ ng/mL/g

Source: Reference 5.

cancer, AS with judicious monitoring appears to be safe, durable, and associated with a low risk of systemic progression within the first 5 years. My colleagues and I strongly recommend a second biopsy before considering AS, because cancer detected at restaging biopsy and a higher number of cores with cancer are linked with a lower likelihood of remaining on AS.<sup>3</sup>

The success of any AS program relies on accurate disease characterization at diagnosis. Because this study specified strict clinical and pathologic inclusion criteria and required a second biopsy before starting AS, we were able to identify a cohort of men with a low risk of

cancer progression. The rate of discontinuing AS was about 5% per year, lower than that of similar studies, largely due to the strict inclusion criteria. Furthermore, it is crucial that all men participating in an AS program be counseled on the low but real risk of potentially life-threatening cancer progression.<sup>3</sup> Early to intermediate-term data for appropriately selected AS patients suggest metastasis rates are consistently less than 1%, with follow-ups ranging from 2 to 8 years.<sup>2</sup> To minimize the risk, we strongly recommend a restaging biopsy. This proactive approach excludes up to 30% of patients considered for AS based on the initial diagnostic biopsy, mini-

mizes the risk of Gleason grade sampling error, and predicts the likelihood of continuing on AS.<sup>3</sup>

Studies indicate that AS is used as a treatment strategy in only 10% of patients with newly diagnosed prostate cancer.<sup>2,3</sup> Our findings as well as those from other researchers show that AS should be discussed and considered for appropriately selected patients.<sup>2,3,6</sup>

Multiple limitations of this study, however, warrant consideration. Based on the short-term follow-up of this study (median, 29 months) and of other studies (median, 22-64 months), caution should be exercised in extrapolating these findings to justify AS as a long-term management strategy. Extended follow-up is mandatory to address this concern.<sup>3</sup> The data in this study provide an observational experience, which will continue to provide insights into the natural history of low-risk prostate cancer, generalized rates of delayed treatment given the variable practice patterns, overall cancer-specific success rates, and causes of death.<sup>3</sup>

Whereas a strength of this study is the multi-institutional cohort, this has also led to variations in the intensity of follow-up, diagnostic and restaging strat-

egies, occurrence of surveillance biopsies, pathologic assessment, and indications for treatment.<sup>3</sup> Therefore, generalizing of the findings to include other populations should be done with caution. The most common reason for stopping AS in this study was the outcome of a surveillance biopsy; in other AS studies it was patient preference or increasing PSA alone, underscoring the variable nature of currently available series and need for pre-specified study methodology.<sup>3</sup>

My view on AS is to appropriately select patients, discuss initial observation as an option, monitor frequently (based on serial prostate biopsies), and, if necessary, implement active therapy while the disease is still at a highly curable stage. Most men will not require an intervention, and those who do can benefit from a period when quality of life and cancer-related outcomes do not appear to be compromised. ●

## References

1. American Cancer Society. What are the key statistics about prostate cancer? March 3, 2010. [www.cancer.org/docroot/CRI/content/CRI\\_2\\_4\\_1\\_X\\_What\\_are\\_the\\_key\\_statistics\\_for\\_prostate\\_cancer\\_36.asp?sitearea=](http://www.cancer.org/docroot/CRI/content/CRI_2_4_1_X_What_are_the_key_statistics_for_prostate_cancer_36.asp?sitearea=). Accessed March 12, 2010.
2. Large MC, Eggener SE. Active surveillance for low-risk localized prostate cancer. *Oncology (Williston Park)*. 2009;23:974-979.
3. Eggener SE, Mueller A, Berglund RK, et al. A multi-institutional evaluation of active surveillance for low risk prostate cancer. *J Urol*. 2009;181:1635-1641.
4. American Urological Association. *Prostate-Specific Antigen: Best Practice Statement: 2009 Update*. Linthicum, MD: American Urological Association Education and Research Inc; 2009.
5. National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology: Prostate Cancer*. V.1.2010. [www.nccn.org/professionals/physician\\_gls/PDF/prostate.pdf](http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf). Accessed March 12, 2010.
6. Klotz L, Zhang L, Lam A, et al. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol*. 2010;28:126-131.

Eileen Koutnik-Fotopoulos contributed to the preparation of this manuscript.