The Role of Active Surveillance in the Management of Prostate Cancer

Simon D. Fung-Kee-Fung, MD[a]; Sima P. Porten, MD, MPH[b]; Maxwell V. Meng, MD[b]; and Michael Kuettel, MD, PhD, MBA[a]

Abstract

In 2010, NCCN incorporated active surveillance (AS) into the NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, and the 2012 update serves as an excellent resource with the most current evidence regarding treatment options for men with all stages of disease. However, the lack of clinical trials that directly compare various treatment modalities or identify the best management, especially for men with low-risk prostate cancer, makes the decision-making process difficult for both patients and physicians. Although general agreement exists on definitions of candidates for AS—men with low-volume and low-grade disease thought to be at low risk for rapid progression—several key issues remain in establishing and supporting the role of AS in the management of prostate cancer, such as optimal timing and appropriate triggers for active treatment. The decision to initially pursue AS rather than active treatment after prostate cancer diagnosis is complex and involves myriad factors, including estimation of life expectancy, consideration of quality of life, and assessment of ultimate oncologic outcome. (*JNCCN* 2013;11:183–187)

The recent controversy and debate regarding the use of prostate-specific antigen (PSA) testing to screen for prostate cancer has highlighted critical aspects of prostate cancer management and stimulated reconsideration of how to care for men with the disease. Although uncertainty remains with respect to the optimal screening strategy and magnitude of benefit, earlier detection of disease clearly reduces cancer-related morbidity and mortality in some men and has contributed to the reduction in deaths from prostate cancer over the past 20 years. Nevertheless, the primary limitation of prostate cancer screening is the high rate of treatment in men diagnosed with disease, with a significant risk of overtreatment particularly in those with low-risk disease. Active surveillance (AS) provides a management strategy in this group that may help identify men who truly need treatment and avoid treatment-related side effects in those who do not require intervention.[1] In 2010, NCCN incorporated AS into the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), and the updated 2012 version provides an excellent resource with the most current evidence regarding treatment options for men with low-risk disease (to view the most recent version of these guidelines, visit NCCN.org).[2] However, the lack of clinical trials that directly compare various treatment modalities or identify the best management, especially for men with low-risk prostate cancer, makes the decision-making process difficult for both patients and physicians. This article examines the role of AS in the contemporary management of prostate cancer, focusing on key issues that influence decision-making, including competing risks of mortality and health-related quality of life (HRQOL).

AS for prostate cancer involves close monitoring of the disease course, with intervention if progression is identified. A protocol of periodic PSA tests combined with digital rectal examinations (DRE) and repeat biopsies is gaining acceptance as an alternative management strategy for men with low-risk prostate cancer. This was reflected by the inclusion of AS in the 2010 NCCN Guidelines for Prostate Cancer algorithm, in addition to a new "very low-risk" category that incorporated strict criteria for clinically insignificant disease.[2] Benefits of AS include maintaining current levels of quality of life and routine activity, avoiding side effects associated

From the [a]Department of Radiation Oncology, Roswell Park Cancer Institute, Buffalo, New York, and [b]Department of Urology, UCSF Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, California.

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Correspondence: Michael Kuettel, MD, PhD, MBA, Department of Radiation Medicine, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263. E-mail: Michael.Kuettel@roswellpark.org

with all forms of definitive treatment, and decreased health care costs until treatment is required. Drawbacks to AS are potential progression of the disease, leading to a loss of local control, large volume of disease requiring treatment with a greater risk of side effects, and reduced ability to cure disease. In addition, the increased anxiety experienced by patients living with an untreated cancer and the emotional toll of each surveillance visit must be considered,[3] not to mention the need for frequent blood work, examinations, and prostate biopsies.

The candidates best suited for AS have yet to be uniformly defined. This is demonstrated in the largest prospective cohorts, in which inclusion criteria show slight variations (Table 1). Despite their differences, all of the studies included patients with the same basic theme: low-volume, low-grade disease on prostate biopsy and low PSA. The current version of the NCCN Guidelines[2] favors AS in patients with "very low-risk" disease and a life expectancy of less than 20 years (to view the most recent version of these guidelines, visit NCCN.org). Very low-risk disease is defined as stage T1c, Gleason 6, PSA less than 10 ng/mL, with fewer than 3 positive biopsy cores and less than 50% of any core involved with disease, and PSA density less than 0.15 ng/mL/g. The NCCN Guidelines also favor AS in elderly patients with low-risk disease (stage T1c–2a, Gleason ≤6, PSA ≤10 ng/mL) and less than 10 years of life expectancy.[3] AS is also an option for patients with low-risk disease but greater than 10 years of life expectancy, along with some form of treatment, such as surgery or radiation therapy.

Two large randomized trials, the Prostate Testing for Cancer and Treatment (ProtecT; ClinicalTrials.gov identifier: NCT00632983) trial in the United Kingdom and the Surveillance Therapy Against Radical Treatment (START; ClinicalTrials.gov identifier: NCT00499174) trial in North America, are currently comparing AS versus treatment with radiation or surgery. Although the data from these trials will take years to mature, they are expected to further identify important aspects regarding the efficacy of AS in these men. Until then, the recommendation for AS should be based on individualized assessment and counseling, weighing a man's life expectancy, disease characteristics, potential for side effects of treatment, and preferences for treatment. Current NCCN Guidelines recommend that an AS program include the following: PSA measurements as often as every 3 months but at least every 6 months, DRE performed as often as every 6 months but at least every 12 months, and a needle biopsy may be repeated within 6 months of diagnosis if the initial biopsy included fewer than 10 cores.

The 2 prospective AS studies with the longest follow-up are those from the University of Toronto and The Johns Hopkins University. In the University of Toronto experience,[4] with a median 6.8 years of follow-up, 30% of patients were offered definitive therapy based on reclassification to higher-risk disease. Actuarial 10-year overall survival was 68%, but 10-year cause-specific survival was 97%. In the Johns Hopkins experience,[5] with a median follow-up of 2.7 years, 33% of patients underwent curative intervention; 67 men underwent treatment without reclassification, whereas 38 men who were reclassified as high risk by volume only deferred curative intervention and elected to remain on surveillance. At 2.7 years, overall survival was 98% and cause-specific survival was 100%, with no deaths attributed to prostate cancer. Recently, Cooperberg et al[6] published an update of the AS program at the University of California San Francisco (UCSF), comparing outcomes of AS in men with both low- and intermediate-risk disease. Thirty-percent of low-risk and 35% of intermediate-risk men underwent treatment within 4 years of diagnosis. Progression-free survival did not differ by clinical risk group: 54% of low-risk and 61% of intermediate-risk men were progression-free at 4 years (ie, remained on AS).

Another key aspect of AS that remains unsettled is the cutoff for reclassifying disease from low risk to higher risk, which triggers a recommendation to the patient to undergo some form of active treatment. The Toronto group reclassified patients as higher risk based on 3 criteria: PSA doubling time (PSADT) of less than 3 years; Gleason score upgrade on repeat prostate biopsy; and clinical progression, defined as development of an unequivocal palpable nodule.[4] The Johns Hopkins group defined reclassification according to the results of a surveillance biopsy reflecting that enrollment criteria were no longer met (upgrade to Gleason score >6, or >2 cores with cancer, or >50% cancer involvement of any core).[5] Notably, serum PSA concentration and PSA kinetics were not used as triggers for treatment intervention in this study. The UCSF group defined progression as any Gleason pattern of 4 or greater on repeat biopsy for those with

Table 1 Inclusion Criteria of Recently Published Prospective Active Surveillance Trials

Institution	Most Recent Report	Total No.	Strict No.	Median Age (y)	Inclusion Criteria			
					Gleason	PSA (ng/mL)	cT Stage	Volume
Royal Marsden	van As et al,[21] 2008	326	326	67	≤3+4	≤15	≤2a	≤50% of cores positive
Johns Hopkins	Tosoian et al,[5] 2011	769	633	66	≤3+3	PSA density ≤0.15 ng/mL/mL	1c	≤2 cores positive; ≤50% of any core positive
University of California San Francisco	Cooperberg et al,[6] 2011	640	376	62	≤3+3	≤10	≤2	≤33% of cores positive; ≤50% of any core positive
University of Toronto	Klotz et al,[4] 2010	453	453	70	≤6[a]	≤10[a]	1b–2b	—
Memorial Sloan-Kettering	Adamy et al,[22] 2011	238	238	64	≤3+3	≤10	≤2a	≤3 cores positive; ≤50% of any core positive

Abbreviation: PSA, prostate-specific antigen.
[a]Until January 2000, study was offered to men >70 years with Gleason ≤3+4 or PSA ≤15 ng/mL.

original biopsy Gleason scores of 6 or less, or Gleason score 4+3 or greater for those with Gleason score 3+4 at diagnosis; PSADT of 3 years or less; or active treatment (ie, surgery, radiation, and/or androgen deprivation therapy).[6] Whether reclassification should be determined based solely on a histopathologic definition, Gleason upgrade, and/or increased volume of disease versus including some form of criteria for reclassification based on PSA level or kinetics remains unclear and is an opportunity for future study.

A critical element in the decision-making process of selecting treatment for men with prostate cancer is the estimation of life expectancy. Multiple studies have shown that physicians are poor at predicting life expectancy.[7–9] However, limited tools are available to help physicians accurately determine the number of remaining years for an individual man, and the use of age alone as the primary factor is clearly insufficient. The complex balance between tumor characteristics, patient life expectancy, and the influence of various treatments on cancer-specific survival factors into the appropriate counseling of men with all stages of prostate cancer, especially those with very low-risk and low-risk disease.

Daskivich et al[10] examined this issue in a retrospective study of 1482 men with nonmetastatic prostate cancer. Survival outcomes were assessed using Kaplan-Meier survival curves for Charlson comorbidity groups and competing risks regression analysis. Ten years after diagnosis, men with Charlson scores 0, 1, 2, and 3+ had non–prostate cancer mortality rates of 17%, 34%, 52%, and 74%, respectively. Each point increase in Charlson score was associated with a 2-fold increase in hazard of non–prostate cancer mortality. Even after stratification by risk groups, non–prostate cancer mortality was significantly higher among men with higher Charlson scores, and prostate cancer mortality was rare in low- and intermediate-risk groups (0.4% and 3.0%, respectively).

A similar analysis was performed using the SEER-Medicare database in 19,639 men older than 65 years diagnosed with localized prostate cancer not receiving initial definitive treatment (within 6 months of diagnosis).[11] The 10-year overall and prostate cancer–specific mortality in low-risk patients (cT1c and Gleason 5–7) aged 66 to 74 years with comorbidity scores of 0, 1, and 2+ were 29% and 4.8%, 51% and 2%, and 83% and 5.3%, respectively. Even in patients with stage T2 disease with Gleason 5 to 7, the 10-year prostate cancer–specific mortality rates were low in this age group (1.0%–11.9%). This study further suggests that few men older than 65 years with

localized prostate cancer die as a result of prostate cancer within 10 years of diagnosis, particularly those with moderately differentiated disease (Gleason 5–7), and that men with 2 or more comorbidities have a substantial risk of dying from a competing risk.

Abdollah et al[12] used SEER data in a competing-risk analysis to examine cancer-specific morality after accounting for other-cause mortality in men treated with either radical prostatectomy (RP) or observation, and developed novel nomograms to calculate cancer-specific and other-cause mortality based on age at diagnosis, race, Charlson comorbidity index, tumor stage, Gleason score, and treatment (ie, RP or observation). The 10-year cancer-specific mortality was 2.8% for RP versus 5.8% for observation ($P<.001$), although in multivariable analyses the cancer-specific mortality hazard ratio (HR) for RP was 0.48 relative to observation.

The same group also compared radiotherapy and observation in similar analyses based on patients within the SEER database. Radiotherapy was beneficial with respect to 10-year cancer-specific mortality in elderly patients (age 75–80 years) compared with observation (5.6% vs. 7.3%; HR, 0.7) and in those with no comorbidities (HR, 0.81), one comorbidity (HR, 0.87), and more than one comorbidity (HR, 0.79). However, a benefit of radiotherapy was not seen in men with low-/intermediate-risk disease (Gleason <8 and stage <T2c) at 10 years (3.7% vs. 4.1%; HR, 0.91; $P=0.2$). The greatest benefit of radiotherapy was observed in men with high-risk disease, with an HR of cancer-specific mortality of 0.59 relative to observation.[13]

A large part of the appeal of AS is not only to minimize overtreatment but also to maximize and maintain quality of life. Unfortunately, current treatment options all have drawbacks with respect to some combination of urinary, bowel, and sexual side effects that negatively impact quality of life. HRQOL among treatment options is difficult to compare because of confounders such as age, comorbidity, and psychosocial issues. High-quality studies using validated instruments are rare, and because AS is a relatively new management strategy, long-term data are lacking.

The largest prospective study comparing HRQOL outcomes after active prostate cancer treatment (not including AS) was published by Sanda et al[14] and examined 1201 patients treated with RP, brachytherapy, or external-beam radiation therapy (EBRT). In patients who underwent RP, urinary incontinence was worse at 2 months after surgery and improved in most men by 2 years. Those who underwent EBRT experienced worsening of irritative/obstructive voiding symptoms 1 year after treatment that improved by 2 years; however, men undergoing brachytherapy experienced persistence of symptoms after 1 year. Both forms of radiotherapy were associated with a reduced quality of life in terms of bowel symptoms that persisted over 1 year. All 3 modalities had significant impact on sexual function that was mitigated by nerve-sparing procedures in the RP group. Interestingly, worsening quality of life in terms of sexual function was reflected by a patient's partners, with the highest distress seen with regard to men undergoing RP. Factors that affected overall patient-reported outcomes were large prostate size, obesity, older age, black race, and a high pretreatment PSA. Adjuvant androgen deprivation in the radiation treatment groups exacerbated adverse outcomes and HRQOL in all domains. Two other large prospective studies (Spanish Multicentric Study of Clinically Localize Prostate Cancer and CaPSURE) showed similar results: active treatment of any type adversely affects HRQOL, with a greater impact on disease-specific parameters rather than general HRQOL. RP resulted in potential urinary incontinence and sexual dysfunction but improved irritative/obstructive symptoms, whereas radiotherapy caused irritative/obstructive symptoms and bowel side effects with some sexual dysfunction. Differences between treatment adverse effects and HRQOL for all domains declined over time, with little change seen beyond 3 years.[15,16]

A recent prospective study reported HRQOL in patients managed with AS within a cohort of 124 patients enrolled in the Finnish arm of the Prostate Cancer Research International: Active Surveillance (PRIAS) study who were followed up for at least 1 year.[17] No changes were seen in urinary function, sexual function, or HRQOL in the short follow-up period and no patient changed treatment because of anxiety. In contrast to these findings, a study of approximately 150 men on AS who underwent a mean of 2.3 serial biopsies showed a decrease in erectile function but not urinary function over a period of approximately 3 years.[18] Repeat biopsy is an integral part of all AS protocols, and the long-term adverse outcomes and impact on HRQOL are unknown. This study highlights the fact that more research is needed on the side effects of an AS protocol in order to help patients decide what management strategy to pursue.

Decision models have been used to compare effectiveness of treatment choices in men with low-risk

prostate cancer, incorporating important information regarding quality of life. These tools may help guide patients in making management decisions. Two recent studies have incorporated AS into decision analysis.[16,19] Hayes et al[20] reported that AS as an initial management strategy is associated with the longest quality-adjusted life expectancy compared with brachytherapy, intensity-modulated radiation therapy, or RP in a 65-year-old man with low-risk prostate cancer. It is important to note, however, that these findings are based on a "base case" and may not be applicable to men of different ages. In addition, potential bias exists in assigning utilities and estimating quality-adjusted life expectancy among treatments.[20] Liu et al[19] expanded on these results and compared RP with AS in men with low-risk prostate cancer in a wider age range (50–75 years old) and incorporated comorbidities as assessed by overall health status (excellent, average, or poor). They found that older men in worse health had better quality-adjusted life expectancy with AS. Calculated outcomes were strongly dependent on patient preferences, such as the ability to "live" without anxiety while on AS or with asymptomatic PSA recurrence, and perception of side effects.

AS seems to be associated with a favorable quality-adjusted life expectancy compared with other treatment options in properly selected individuals. The decision by patients to choose AS as the initial management strategy is dependent on individual preferences and plays an important role in shared decision-making. Further research and longer follow-up are needed to determine true HRQOL in men on AS.

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