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Five-year Nationwide Follow-up Study of Active Surveillance for Prostate Cancer

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Abstract

Background: Active surveillance (AS) is an important yet underutilized strategy to reduce prostate cancer (PCa) overtreatment.
Objective: To examine the 5-yr outcomes of AS in a population-based setting.
Design, setting, and participants: From the National Prostate Cancer Register of Sweden, we identified 11 726 men ≤70 yr diagnosed with very low-risk to intermediate-risk PCa from 2003 to 2007 who completed 5 yr of follow-up. Of these men, 1729 (15%) chose AS for the primary management strategy.
Outcome measurements and statistical analysis: We calculated the probability of discontinuation of AS over time, and Cox proportional hazards models were used to determine factors associated with discontinuation. Reasons for discontinuation were assessed by data extraction from medical charts.
Results and limitations: By 5 yr, 64% of the men remained on AS. Predictors of discontinuation were younger age, fewer comorbidities, more education, higher prostate-specific antigen (PSA), and clinical stage T2 disease; marital status did not predict discontinuation. In a subset with data on the reason for discontinuation (86%), 20% of men discontinued because of patient preference, 52% because of PSA progression, 24% because of biopsy progression, and 3% for other reasons.
Conclusions: In a population-based setting, the majority of men remained on AS at 5 yr. However, one-fifth of the men who discontinued AS did so for nonbiologic reasons. Thus, there is a need for support and counseling for men to continue AS in the absence of signs of progression to improve adherence to AS and decrease overtreatment.
Patient summary: Active surveillance (AS) is an important option to delay or avoid treatment for men with favorable prostate cancer features. This study shows that at 5 yr, 64% of men across an entire population remained on AS. We concluded that AS is a durable option and that counseling may be useful to promote adherence for men without progression.

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1. Introduction

Active surveillance (AS) is an important management strategy to reduce prostate cancer (PCa) overtreatment [1]. While this strategy is supported in numerous guideline statements, adoption of AS demonstrates wide regional variability. AS is underutilized in the United States [2], whereas the majority of men with very low-risk PCa in Sweden currently select AS for their primary management strategy [3,4]. Little is known about long-term adherence to AS and the outcomes with this strategy. A more thorough understanding of these issues might help in encouraging broader adoption of AS.

A recent consensus statement from the National Institutes of Health emphasized the need for future research into the factors affecting adherence to AS [1]. A systematic review of seven major AS programs from around the world reported that one-third of patients received curative treatment after a median period of only 2.5 yr on AS [5]. However, these data may be difficult to generalize since they are based on a limited number of established AS programs, all with strict inclusion criteria and defined triggers for intervention. It is unclear to what extent the high rates of discontinuation are appropriate (ie, discontinuation for biologic reasons such as disease progression) or are secondary to patient fear, misinformation, or lack of emotional support. The latter reasons may present a potential target for interventions such as patient support and counseling.

Despite its great importance to the reduction of PCa overtreatment, relatively little is known about adherence to AS at the population level. Thus, the goal of our study was to examine real-world 5-yr adherence to AS using data from the entire nation of Sweden. We hypothesized that adherence rates would be lower across the entire Swedish population outside the confines of a predefined AS protocol. We obtained data on the reasons for AS discontinuation over time, which could have important implications for the successful implementation of this strategy around the world.

2. Patients and methods

The National Prostate Cancer Register (NPCR) of Sweden contains data on 98% of all PCa cases nationwide since 1998; in contrast, reporting to the Swedish Cancer Register is mandatory [4,6]. As previously described, clinical stage, prostate-specific antigen (PSA), biopsy Gleason score, ratio of positive biopsy cores, and primary therapy are recorded. Using the unique national identification number, cross-linkage was performed in Prostate Cancer Data Base (PCBaSe) between NPCR and several nationwide population-based health care registers and demographic databases, including the National Patient Register and the longitudinal integration database for health insurance and the labor market (LISA is its Swedish acronym), with data including marital status and educational level. The Charlson comorbidity index (CCI) was calculated based on discharge diagnoses in the patient register $\leq$10 yr prior to the date of PCa diagnosis and/or cancer diagnosis other than PCa in the NPCR [7].

In 2003, the NPCR began a follow-up study of all men $\leq$70 yr diagnosed with localized PCa (clinical stage T1/T2 with PSA $<$20 ng/ml). To examine 5-yr outcomes of AS, we identified 11 726 men from the follow-up study diagnosed with low- and intermediate-risk PCa from 2003 to 2007 with complete follow-up through December 31, 2013. As shown in Supplemental Figure 1, the primary treatment was radical prostatectomy for 57% of the men, radiation therapy in 18%, watchful waiting in 5%, hormonal therapy in 2%, and other forms of primary treatment in 2%. The remaining 1729 men (15%) were initially managed with AS and formed the current study population.

In these men, we examined adherence using Kaplan-Meier analysis to estimate the probability of discontinuation during follow-up. Multivariable Cox proportional hazards models were used to examine predictors of time to discontinuation of AS overall and for men in specific risk categories. In these models, the reference groups were year of diagnosis 2003, aged $<$60 yr, clinical stage T1c, Gleason score $\leq$6, very low-risk category, single, and low education; PSA and CCI were coded as continuous variables. A separate model was done with age as a continuous variable. Subset analysis was also performed in 1034 of the men on AS (60%) with data on the number of total and positive biopsy cores. To examine discontinuation by reason, we also calculated the cumulative incidence of discontinuation in a competing risks setting.

The follow-up extraction form included the following options for reasons for discontinuing AS: PSA progression, biopsy progression (upgrading or a larger extent of cancer on biopsy), patient preference, and other reasons. Demographics and tumor features were then compared between men who discontinued AS because of biologic reasons (PSA or biopsy progression) versus because of preference. R v.3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses. The study was approved by the research ethics board at Umeå University Hospital.

3. Results

Of 11 726 men aged $\leq$70 yr diagnosed with very low-risk to intermediate-risk PCa in Sweden nationwide from 2003 to 2007, 1729 men (15%) chose AS as initial management (Supplemental Fig. 1). Of these men, 644 (37%) were very low risk, 757 (44%) were low risk, and 328 (19%) were intermediate risk. Table 1 shows the demographics of the study population. During follow-up, 614 of 1729 men (36%) converted to active treatment.

At 1 yr, 2 yr, 3 yr, 4 yr, and 5 yr, the probability of discontinuing AS was 4%, 15%, 23%, 30%, and 36%, respectively (Fig. 1). In the very low-risk group, the probability of discontinuing AS was 3%, 15%, 23%, 30%, and 35% at 1 yr, 2 yr, 3 yr, 4 yr, and 5 yr, respectively. In the low-risk group, the probability of discontinuing AS was 4%, 13%, 21%, 27%, and 33% at 1 yr, 2 yr, 3 yr, 4 yr, and 5 yr, respectively. In the intermediate-risk group, the probability of discontinuing AS was 6%, 18%, 29%, 37%, and 41% at 1 yr, 2 yr, 3 yr, 4 yr, and 5 yr, respectively. The median PSA at the time of discontinuing AS was 8.2 ng/ml, and the median absolute change from baseline to discontinuation was 3.0 (range: 0–32).

On multivariable analysis (Table 2), clinical stage T2 (hazard ratio [HR]: 1.63; 95% confidence interval [CI], 1.32–2.02; $p < 0.001$ compared with nonpalpable disease), serum PSA (HR: 1.01; 95% CI, 1.00–1.01; $p < 0.001$), and high education (HR: 1.45; 95% CI, 1.17–1.80; $p < 0.001$) were significantly associated with greater risk of discontinuing AS. By contrast, men aged 65–70 yr (HR: 0.69; 95% CI, 0.55–0.85; $p < 0.001$) and men with high CCI (HR: 0.86; 95% CI, 0.75–0.98; $p = 0.02$) had significantly lower risk of