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# Active Surveillance Versus Watchful Waiting for Localized Prostate Cancer: A Model to Inform Decisions

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**Abstract**

***Background:*** An increasing proportion of prostate cancer is being managed conservatively. However, there are no randomized trials or consensus regarding the optimal follow-up strategy.
***Objective:*** To compare life expectancy and quality of life between watchful waiting (WW) versus different strategies of active surveillance (AS).
***Design, setting, and participants:*** A Markov model was created for US men starting at age 50, diagnosed with localized prostate cancer who chose conservative management by WW or AS using different testing protocols (prostate-specific antigen every 3–6 mo, biopsy every 1–5 yr, or magnetic resonance imaging based). Transition probabilities and utilities were obtained from the literature.
***Outcome measurements and statistical analysis:*** Primary outcomes were life years and quality-adjusted life years (QALYs). Secondary outcomes include radical treatment, metastasis, and prostate cancer death.
***Results and limitations:*** All AS strategies yielded more life years compared with WW. Lifetime risks of prostate cancer death and metastasis were, respectively, 5.42% and 6.40% with AS versus 8.72% and 10.30% with WW. AS yielded more QALYs than WW except in cohorts age >65 yr at diagnosis, or when treatment-related complications were long term. The preferred follow-up strategy was also sensitive to whether people value short-term over long-term benefits (time preference). Depending on the AS protocol, 30–41% underwent radical treatment within 10 yr. Extending the surveillance biopsy interval from 1 to 5 yr reduced life years slightly, with a 0.26 difference in QALYs.
***Conclusions:*** AS extends life more than WW, particularly for men with higher-risk features, but this is partly offset by the decrement in quality of life since many men eventually receive treatment.
***Patient summary:*** More intensive active surveillance protocols extend life more than watchful waiting, but this is partly offset by decrements in quality of life from subsequent treatment.


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## 1. Introduction

Prostate cancer (PCa) screening reduces advanced disease and PCa-specific death [1,2], but also leads to "overdiagnosis" and overtreatment of indolent tumors [3,4]. Conservative management is increasingly utilized for favorable-risk PCa to delay or avoid aggressive treatment and potential side effects [5]. Prior comparative-effectiveness models have confirmed that this is a valid strategy for certain patients [6–8], with improved quality of life (QOL) and reduced initial resource utilization [9].

Despite agreement on the importance of conservative management to preserve screening benefits and reduce overtreatment [10], there is no consensus what to do next [11,12]. Conservative management encompasses two very different strategies: "watchful waiting" (WW) without curative intent and "active surveillance" (AS) with serial testing for "disease progression" to offer selective delayed treatment with curative intent. No randomized trials have compared benefits and harms between WW and contemporary AS. Furthermore, for patients choosing AS, there is no consensus on the type, frequency, or sequence of follow-up tests to monitor for disease progression [11]. Thus, the objective of this clinical decision analysis is to compare life expectancy and quality-adjusted life expectancy between WW and different AS protocols for US men ≥50 yr.

## 2. Patients and methods

We developed a state-transition Markov model to compare different strategies of conservative management for a cohort of US men diagnosed with clinically localized PCa who chose conservative management. Markov models represent a hypothetical cohort moving among predefined health states that are mutually exclusive and collectively exhaustive [13]. Our model starts when the patient is diagnosed with PCa and begins conservative management. We used this model to evaluate two different outcomes: life years (LYs) and quality-adjusted life years (QALYs), which put quality and quantity of life into the same metric by multiplying the predicted duration of each health state by the utility (QOL weight) for living in that state. The model was analyzed and reported according to ISPOR/SMDM international recommendations [13].

The base case analyses compare WW (follow without further testing until the development of advanced PCa or death from other causes) with AS with prostate-specific antigen (PSA) every 6 mo and yearly biopsy (based on the Johns Hopkins AS protocol [14]). We also examined an AS strategy with more frequent PSAs (quarterly) with biopsies at years 1, 3, 7, and 10, and then every 5 yr, similar to Prostate Cancer Research International Active Surveillance (PRIAS) [15], and an exploratory strategy including PSA every 6 mo and magnetic resonance imaging (MRI) yearly where biopsy is performed only if MRI is abnormal. Finally, we evaluated an exploratory strategy with PSA every 6 mo and biopsy every 5 yr. For all strategies, biopsies were discontinued at age 75 yr in the main analysis, as in the Johns Hopkins program [14].

We used a state-transition cohort model to obtain estimates for specific populations of interest determined a priori, based on clinical features. For the main analysis, the cohort started at age 50 yr, and the model was rerun for cohorts starting at age 40, 65, 70, and 75 yr. Figure 1 shows a schematic of the model. At the start, men have been diagnosed with PCa and they have chosen conservative management. Some were classified accurately with Gleason 6 (grade group 1), while others were misclassified and have undetected higher-grade disease. During each model cycle, individuals can remain on conservative management, undergo treatment for reclassification (then into a post-treatment state), develop metastases, or die. We used a cycle length of 1 mo and a lifelong time horizon due to the long natural history of PCa. Depending on the approach to conservative management, some cycles may include rebiopsy. Overall mortality data were obtained from US life tables, with a priori adjustment by a multiplier of 0.45 to account for the highly selected healthier population affected by localized PCa [14]. Our model considered the following potential harms: biopsy complications, short- and long-term complications of PCa treatment (aggregate measure including sexual, urinary, and bowel dysfunction), and development of metastasis. Since our objective was to examine efficacy, we assumed 100% compliance with protocol-recommended biopsies and that all men found to have disease reclassification (increases in tumor grade) underwent treatment.

Table 1 shows the model inputs (see Supplementary material for details). Transition probabilities between states were estimated from the literature. Previously published "utilities" (ie, QOL weights reflecting quantitative health preferences) were used to quantify QOL implications for each disease state [16].

One- and two-way deterministic sensitivity analyses were performed to assess the implications of uncertainty for key variables. Tornado diagrams were used to summarize results of one-way sensitivity analysis. Since previous studies showed an impact of time preference on PCa treatment selection, we also performed sensitivity analysis using discounting (ie, assigning lower weights to future events) [17]. We also estimated the risk of radical treatment, metastasis, and PCa death. Model validation was performed based on ISPOR–SMDM recommendations and comprised the following: (1) expert consensus on face validity of model inputs, structure, and results; (2) verification through extensive sensitivity and extreme value analysis; (3) cross validation to previous models; and (4) blinded external validation to partially dependent and independent published studies with >5 yr follow-up [18]. All analyses were performed using TreeAge Pro version 2014 (TreeAge Software, Inc., Williamstown, MA, USA).

## 3. Results

### 3.1. Main base case analysis

Table 2 shows the base case results of the decision analysis. In a cohort of men starting at age 50 with low-risk PCa undergoing conservative management, AS using the Johns Hopkins strategy yielded more LYs compared with WW (35.21 vs 34.55 LYs, or a difference of 0.66 life-years; Table 2). Lifetime risks of PCa death and metastasis were, respectively, 5.42% and 6.40% with AS versus 8.72% and 10.30% with WW. Men on AS had a 50% lifetime risk of undergoing radical treatment.

Using the outcome of quality-adjusted life expectancy, AS yielded more QALYs (33.89) than WW (33.36 QALYs, an expected difference of 0.53 life-years).

For a cohort starting at age 40 yr (Table 2), AS yielded more LYs and QALYs compared with WW. By contrast, among men aged ≥65 yr, WW had more QALYs than AS (Table 2). Supplementary Table 1 shows LYs and QALYs for men with very low–risk PCa.

### 3.2. Alternative AS protocols

In men aged ≥50 yr, using PRIAS, MRI-based, and 5-yr biopsy strategies yielded 35.12, 35.20, and 34.99 LYs, respectively. Lifetime risks of PCa death and metastasis

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