**Estimating the risks and benefits of Active Surveillance protocols for Prostate Cancer: A microsimulation study.**

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**Abstract**

**Objective:** To estimate the increase in prostate cancer mortality (PCM) and the reduction in overtreatment resulting from different Active Surveillance (AS) protocols, compared to treating men immediately.

**Subjects and Methods:** We use a microsimulation model (MISCAN-Prostate), with natural history based on ERSPC data. We estimate probabilities of referral to radical treatment while on AS, depending on disease stage, with data from John Hopkins AS cohort**.** We sample 10 million men representative of the US population and we project the effects of applying AS protocols differing by time between biopsies, compared to treating men immediately.

**Results:** AS with yearly follow-up biopsies for low-risk patients (≤ T2a-stage and Gleason 6) increases the probability of PCM to 2.6% (1% increase) and reduces overtreatment from 2.5% to 2.1% (18.4% reduction). With biopsies every three years after the first year, PCM increases by 2.3% and overtreatment reduces from 2.5% to 1.9% (30.3% reduction). Including intermediate-risk men ( > T2a-stage or Gleason 3+4) in AS increases PCM by 2.7% and reduces overtreatment from 2.5% to 2.0% (23.1% reduction). These results may not apply to African-American men.

**Conclusions:** Offering AS for low-risk patients is relatively safe. Increasing the biopsy interval from yearly to up to every 3 years after the first year, will significantly reduce overtreatment among low-risk men, with limited PCM risk.

## Introduction

In a time of widespread debate about prostate specific antigen (PSA) screening for prostate cancer, Active Surveillance (AS) has emerged as a way to prevent the unnecessary treatment of some patients with prostate cancer, or at least, to delay the treatment of the disease [1]. The benefit of not treating a patient immediately is the avoidance of the side-effects of radical treatment.

AS consists of the carefully monitoring of men diagnosed with prostate cancer, but not yet treated, with PSA tests or repeat biopsies. What still needs to be determined is whether the benefits of avoiding side effects outweigh the risk that a patient misses his cure window by not treating immediately.

Currently, there are some AS cohort studies designed to answer this question: Prostate Cancer Research International Active Surveillance (PRIAS) [2], UCSF cohort [3], John Hopkins (JH) [4] or the Toronto cohort [5] among others [6,7]. However, with the exception of the Toronto cohort, their median follow-up times are shorter than 5 years. In their latest publications, very few prostate cancer deaths were reported [2-5,7].

Most AS cohorts contain only one AS protocol, usually selecting low-risk patients, with stage <T2a and Gleason Score 6 or lower (T2GS6) [6,7]. While in some cohorts follow-up biopsies occur yearly (JH [4]), in others biopsy occurs up to every 3 years after the first year (PRIAS [2]).

It is not yet clear whether AS is safe for intermediate risk patients. While in the UCSF cohort [3] it was found that the 4-year treatment-free survival (TFS) did not significantly differ

between low-risk and intermediate risk men, intermediate risk patients had significantly worse outcomes in the Toronto cohort [5].

Given the multitude of possible avenues for selecting and following men during AS, and the limited follow-up data, the use of modeling to evaluate the outcomes of AS protocols is necessary. Previously, Xia et al [9] compared immediate radical prostatectomy (RP) and AS for low-risk patients in a simulation study and found that AS has a modest effect on prostate cancer mortality (PCM).

In this article we use a well-validated simulation model (MISCAN) of natural history of prostate cancer, that uses JH-AS data to predict TFS, gleason and volume progression. We project the lifetime risk of PCM and overtreatment in the situation where AS is given to newly screen-detected low and intermediate risk men, under different follow-up biopsy intervals, and we compare these strategies with treating all men immediately.

## Methods

### *Simulation Model*

MISCAN is a microsimulation model, which simulates individual life-histories. A detailed description is available in http://cisnet.cancer.gov/prostate/profiles.html and in previously published studies [10-13].

Before detection or death, the model contains 18 health states corresponding to the combination of 3 stages (T1, T2 and T3), 3 grades (Gleason less than 7, 7, and more than 7) and whether or not cancer is metastasized. Additionally, T2-stage Gleason 6 men are classified as T2a or T2bc and Gleason 7 men are classified as 3+4 or 4+3, depending on their remaining lead-time and age

group, with their respective proportions based on European Randomized Study of Screening for Prostate Cancer (ERSPC) data. Some natural history parameters were calibrated to ERSPC data (durations, transition probabilities, among others), while PSA growth parameters were calibrated to jointly to SEER incidence and ERSPC PSA distribution. [13].

In case the patient is detected outside of screening ("clinically detected") we assume that he is immediately treated. If screen-detected he can either be immediately treated or be assigned to AS.

If immediately treated, we assume an equal chance of being referred to RP or radiation therapy (RT). The prostate cancer survival without treatment is assigned at clinical detection and depends on stage and grade. It was estimated based on SEER data from the pre-PSA era (1983-1986). In order to correct for improvements on the survival not directly associated with screening or primary treatment, we add a hazard ratio for prostate cancer survival of 0.82, which was calibrated to the observed PCM in the ERSPC control (no screening) group (Supplementary Table 1).

The hazard ratios for prostate cancer survival after radical treatment equal 0.56 for RP based on [14] and 0.63 for RT (maintaining the same ratio of benefit between RP and RT from [15]). The effect of early detection is applied through an additional probability of cure which decreases exponentially with lead-time for non-metastatic cases,

Cure probability = 1 - exp(cure parameter * lead-time).

The cure parameter was calibrated to the observed PCM reduction in the ERSPC trial after 11 years of follow-up and equals -0.22. (Supplementary Table 1-2, Supplementary Figure 1)

*Modelling referral to treatment in AS*

A patient in AS may be referred to treatment in four ways: volume progression, gleason upgrade, clinical detection and in absence of evidence of biopsy progression. If any of these events occurs then we assume that all men are treated. (Table 1)

Since the benefit of screening is dependent on lead-time, men who are referred to AS will experience a smaller benefit of screening, depending on how much time they are on AS. For instance, a patient with a lead-time of 10 years at screen-detection, referred to immediate treatment, will have a probability of cure as follows: $1- \exp(-0.22 * 10) = 0.89$. That is, there is an 89% probability that he is cured, and an 11% probability that he dies from prostate cancer. If the patient would choose AS and be referred to treatment 6 years later, its corresponding cure would become, $1- \exp(-0.22 * 4) = 0.59$.

TFS is defined as time from screen-detection to radical treatment. We validate TFS projected by the model, together with the number of men who experienced volume or gleason upgrade, with data from the JH-AS study (Table 2). We simulated the study 100 times, by selecting patients to AS, with approximately the same age distribution and entrance criteria close to the JH cohort (maximum disease state T1 stage and GS6 and PSA $\leq$ 10) (Table 2).

*Screening and Active Surveillance Policies*

We sample 10 million men representative of the US age distribution based on US life tables. In the basecase, we screen men yearly between 55 and 69, with a PSA threshold for biopsy referral

(PSAt) equal to 4, biopsy compliance based on the PLCO trial and every screen-detected man is immediately treated.

We compare the outcomes of treating every man immediately, with admitting low risk patients (≤ T2a, Gleason 6, PSA <10) in AS. We run a set of AS protocols where after the first year, biopsy frequency reduces to every 2, 3 or 5 years. We also project the effects of AS, with a reduced (biannual) and increased (annual, up to age 74) screening schedule. Assuming that the referral rates from AS to radical treatment, for intermediate risk men (≤ T2-stage and 3+4 Gleason) are similar to those of low risk men, given [7], we also project the effects of admitting low and intermediate risk men (≤ T2-stage, 3+4 Gleason) in AS. (Table 3)

*Outcomes*

The main outcome measures are the lifetime risk of PCM, treatment free life years (TFLY), which is the duration from onset of the disease until treatment and the probability of overtreatment (defined as the risk that a man is referred to radical treatment, and would not be clinically detected in absence of screening, or in other words, an ovediagnosed man who goes through radical treatment). Additionally we report the average number of years spent on AS, the probability of PCM due to entering AS and the proportion of men in AS left untreated.

*Sensitivity Analyses*

We run the no AS, yearly and every 3-year biopsy protocols, in combination with differential screening intensities and referral rates to treatment while in AS. We also examine the effect of no efficacy of treatment, and referring men only to either RP or RP (Table 2). Since the model parameters are subject to uncertainty, we run a multivariate probabilistic sensitivity analysis including, the cure parameter, hazard ratios for treatment and the probabilities of detection in AS

(Table 3). We also examined the assumption of an exponentially decreasing cure benefit, by comparing the best fit, with the fit of a linearly decreasing cure benefit. (Supplementary Table 2).

**Results**

*Active Surveillance with different entrance and follow-up protocols*

Screening yearly between ages 55 and 69, with a PSAt of 4 (basecase) and treating every man immediately results in a lifetime risk of PCM of 2.6%. This strategy amounts to 7.4 treatment free life years (TFLY) per person, which contrasts with 8.7 TFLY per person (17.3% increase) if no PSA-based screening is performed and treat every men immediately. However, no screening results in a lifetime risk of PCM of 3.3% (Table 5).

On average, patients who entered AS remained untreated between 5.8 and 9.0 years depending on the screening and AS policy. If one refers patients in disease state T2aGS6 to AS then PCM increases to 2.6% (1.0% increase), TFLY from 7.4 to 7.7 and overtreatment reduces from 2.5% to 2.1% (18% reduction). About 27% of all AS men referred to AS remained untreated and the probability of dying due to AS is 1.8%.

Increasing the biopsy interval after the first year of follow-up from yearly, to two, three or five years increases PCM to about 2.6% (respectively, from 1.0% to 1.7%, 2.3% and 3.2% increase), and the proportion of men who die from prostate cancer due to AS rises from 1.8% to 3.0%, 4.1% and 5.9%, respectively. On the other hand, the probability of overtreatment reduces from 2.1% to 2.0% (25% reduction), 1.9% (30% reduction) and 1.8% (36% reduction). Average years spent on AS increases from 5.9 to 9.0.

Referring intermediate risk men to AS increases PCM to about 2.6% (2.7% increase), while overtreatment decreases from 2.5% to 2.0% (23.1% decrease). The risk of PCM due to AS is 3.6%. By contrast if we only admit low-risk men and a with biennial biopsies after the first year, the risk of PCM due to AS is only 3.0%, but with a higher overdiagnosis reduction (25.4% decrease). For univariate and multivariate sensitivity analyses see Supplementary Table 2-5 and Supplementary Figure 2.

*Active Surveillance with different screening intensities*

In the situation where every men is immediately treated, increasing the stopping age to 74 or increasing biopsy compliance lowers the PCM from 2.6% to 2.4% (7.4% and 6.1% decrease, respectively). On the other hand, probability of overtreatment increases from 2.5% to 3.9% (35.3% increase) or 3.1% (18.5% increase). Introducing AS, with the more intensive screening schedule seems to result in a larger effect both on overtreatment reduction and PCM increase (Table 5).

**Discussion**

In this study we use a novel approach to model AS, by modelling rates of volume and Gleason progression, instead of modelling durations [9] or by using a simplistic assumption of reduced treatment benefit for men in AS [17].

Introducing AS for screen-detected men results, on average, in an interval of between 5.8 and 9.0 years free of treatment, depending on the AS protocol. If we accept T2aGS6 men in AS with yearly biopsies or a biopsy every 3 years after the first year, overtreatment reduces from 2.5% to 2.1% (18.4% reduction) or 1.9% (30.3% reduction), PCM remains about 2.6% (1.0% or 2.3%

increase), with a probability of dying from prostate cancer due to AS of 1.8% or 4.1%, respectively.

To put these numbers in perspective, in 2014, about 233000 men were expected to be diagnosed with prostate cancer in the US [18]. Assuming half of them are screen-detected between ages 55 and 69 (116500) and that 30% of these men are low-risk and are referred to AS (34950), our model predicts that for men with yearly biopsies or a biopsy every three years after the first year, either about 9250 or 14250 men will not be overtreated and an extra 625 or 1450 men will die of prostate cancer due to entering AS, respectively.

Our sensitivity analyses showed that these effects will become larger if the intensity of screening increases (increased stopping age or higher biopsy compliance), as more screen-detected men are classified as low-risk and have a longer lead-time. Admitting intermediate risk men in AS seems not to be as efficient as increasing the biopsy interval in AS for low-risk men.

Our modelling of AS uses a previously validated model of the natural history of prostate cancer [10-14], which is mostly based on ERSPC data [19], with US incidence validated to SEER [13,14]. By calibrating the sensitivity to Gleason Progression and the probability of detecting volume progression given that there is an increase in stage, we are able to match the treatment free survival and the number of men experiencing volume and gleason progression during AS to observed data in JH AS cohort.

This has some advantages relative to calibration based only on an AS cohort. First, durations and transitions between health states (which in large part determine time on AS) are based on a large randomized control trial. Second, the median follow-up of the ERSPC trial is much larger than most AS cohorts, which makes our PCM projections potentially more reliable.

On the other hand, MISCAN makes some simplifications of the AS protocol compared with the current practice in most AS cohorts. The entrance criteria for AS used in MISCAN include T-stage, GS and PSA but not the number of positive cores or PSA density. Additionally, there is some variability regarding TFS, and number of men experiencing volume and/or gleason progression across AS cohorts [6,7].

The results in this study may not apply to African-American population [20], as the benefit of screening is estimated based on an European cohort, and the probabilities of referral to treatment while in AS are estimated based on a cohort with very few African-American men [4].

In contrast, with [9], where AS was modelled as duration from diagnosis to treatment, our approach for modelling AS allows one to project the effects of multiple AS strategies, without resorting to multiple AS cohort datasets. An additional advantage of this framework is that it allows us to jointly model screening and AS strategies. The main disadvantage of this approach is that given the difficulty of modelling directly volume progression, we need to make the assumption that volume progression can only occur, if there is an increase in T-stage in the model.

Our validation shows that MISCAN is slightly more pessimistic than the observed data in JH cohort (2 against 0 observed prostate cancer deaths). Other cohorts showed no PCM at 5 years except [21] with 1 prostate cancer death at 3.7 years of follow-up. This is likely due to the very low risk selection of patients in most AS cohorts, which contrasts with the ERSPC population used to inform natural history in MISCAN.

Importantly, we verify that a key statistic, probability of dying due to AS, which equals 1.8% in our model, is in line with previous studies where no benefit of early detection is assumed, and

where AS was modelled as duration from diagnosis to treatment (Xia et al [9]: 1.2%) or as an assumption about reduced benefit (Hayes et al [17]: 2%). This rate is also comparable with the observed PCM (1.5%) in the Toronto cohort, after 10 years of follow-up [6].

In this study we did not model quality of life. Heijnsdijk et al [22] finds that introducing quality of life adjusted years (QALY's) reduces the screening benefit by 23%. Delaying treatment with AS is a way to mitigate this reduction, due to the avoidance of side-effects. For instance, Hayes et al [17] compared AS with several forms of radical treatment and found that AS gives the highest expected QALY's. Using QALY's will likely favor AS protocols that are less biopsy intensive, given the increased risk of biopsy complications [23-25].

As previously suggested [1-9], our model predicts that AS for low-risk men is relatively safe. We project the harms of benefits of several AS strategies and we find that if we increase the interval between biopsies after the first year to three years, which is close to the strategy used in the PRIAS cohort [2], overtreatment may reduce up to 30%, though with a small increase in PCM. These results apply mostly to US population of European ancestry.

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**Conflicts of Interest Statement**

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