When should active surveillance for prostate cancer stop if no progression is detected?

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Background: A significant proportion of screen-detected men with prostate cancer may be overdiagnosed. Active Surveillance (AS) has emerged as a way to mitigate this problem, by delaying treatment of men who are at low-risk until this becomes necessary. However, it is not known after how much time or biopsy rounds should patients stop AS and transition to conservative management (CM), if no progression is detected.

Methods: We used a microsimulation model with natural history of prostate cancer based on ERSPC and SEER data. We modeled referral to treatment while in AS, based on Johns Hopkins treatment-free survival data. We projected lifetime costs and effects of AS (and radical treatment, if progression is detected) under different biopsy follow-up schedules compared to CM, where radical treatment only occurs when men would be clinically diagnosed in absence of screening.

Results: For men with low-risk disease in younger age groups (55-65), AS is cost-effective for up to 7 yearly biopsy rounds. For men older than 65, even one biopsy round results in quality adjusted life years (QALYs) lost, though it may result in QALYs gained for men without previous screening. For men with intermediate-risk disease AS is cost-effective even for men in 65-75 age group.

Conclusions: The benefit of AS when compared to CM is strongly dependent on life expectancy and disease risk. Clinicians should take this into account when selecting men to AS, deciding on biopsy frequency and when to stop AS surveillance rounds and transition to CM.

KEYWORDS
active surveillance, microsimulation model, overtreatment, prostate cancer

1 INTRODUCTION

Active Surveillance (AS) has emerged as a way to minimize overtreatment due to frequent PSA-based prostate cancer screening. It consists on the monitoring of newly diagnosed and not yet treated men through PSA tests and/or repeat biopsies. The goal of AS is to delay or avoid radical treatment in patients who are unlikely to become symptomatic. In the conservative management (CM) regimen patients are also monitored, although not with invasive procedures like, prostate biopsies, and without curative intent, unless the patient becomes symptomatic. It is similar to watchful waiting, though this term often refers only to older men, or with major comorbidities.

The majority of clinical cohorts following men on AS have a limited follow-up, which is not long enough to establish the long-term effects, however, there is an emerging consensus regarding the safety of AS for low-risk men and the rate of low-risk men assigned to AS is increasing rapidly. Still there is substantial uncertainty about what is the most optimal way of performing AS, namely about whom to include and the follow-up protocol.

Computer modeling has been used to make projections of the potential effects of AS on prostate cancer mortality (PCM) and overtreatment. Previous studies found that compared to immediate treatment, AS results in a modest increase in PCM (1.4% and 1.8%, respectively). Others have compared the costs or cost-effectiveness of AS and/or CM to immediate treatment and found that AS seems to be more advantageous. As far as we know, no simulation study has tried to optimize the age to stop AS and start CM.

There are virtually no clinical studies on when can a patient safely discontinue AS, if no progression is detected and stop being considered for radical treatment, which may potentially lead to
treatment decisions to depend on personal or physician’s preferences. In the PRIAS cohort, the compliance with PSA testing during AS was relatively high, however, the compliance with prostate biopsies is relatively low and decreases rapidly over time from 81% at 1 year to 33% after 10 years. A recent study using SEER data found that only 13% of men underwent prostate biopsy after 2 years, in a community setting. For older patients or men suffering from significant comorbidities, this is probably reasonable, however, for patients with a longer life expectancy there could be a danger of progression to advanced disease, due to non-adherence to the biopsy protocol.

The aim of this study is to determine at which age it is safe and more cost-effective to leave AS and transition to a CM context, for different age and disease risk groups. We use a previously validated microsimulation model of prostate cancer screening and AS, and compare the incremental cost-effectiveness of each additional AS biopsy round, compared to CM.

2 | METHODS

2.1 | Simulation model

MISCAN is a microsimulation model designed to evaluate the lifetime effects of prostate cancer screening. A detailed description is available in the Supplemental Information, in http://cisnet.cancer.gov/prostate/profiles.html and in previously published studies.

Men may experience onset of prostate cancer, based on a constant hazard per age group. In each disease stage, a man may transition to a higher T-stage, a higher grade, become metastasized or clinical diagnosed. We modeled 18 health states corresponding to the combination of three stages (T1, T2, and T3), three grades (Gleason less than 7, 7, and more than 7) and whether or not cancer is metastasized. Additional states were created specifically to model AS. Men in T2-stage, Gleason 6 were classified as T2a or T2bc and Gleason 7 men as classified as Gleason 3 + 4 or 4 + 3, depending on their remaining lead-time (ie, time to clinical diagnosis in absence of screening) and age group, based on ERSPC data. We also modeled PSA growth from onset until detection. The parameters of the natural history, which include onset of the disease, durations, transition probabilities between health states, and PSA growth were calibrated to observed ERSPC’s PSA distribution data and SEER incidence data and Supplemental Information Fig. S1.

At clinical detection, a baseline survival is assigned, which depends on Gleason score (<8 or ≥8) and was estimated based on SEER data from the pre-PSA era (1983-1986). This was adjusted, for improvements on survival not directly associated with screening or primary treatment, by adding a hazard ratio for prostate cancer survival of 0.82, which was calibrated to the observed PCM in the ERSPC control (no screening) group (Supplemental Information Table S1).

We add a benefit of treatment and a benefit of screening (in case the patient is screen-detected) to the baseline survival. The hazard ratio for the benefit of treatment equals 0.56 for radical prostatectomy. For radiation therapy this equals 0.63 using the same rationale as in. The effect of screening is modeled through a lead-time dependent cure rate for non-metastatic cases.

\[
\text{Cure probability} = \exp(\text{cure parameter} \times \text{lead} - \text{time}).
\]

The cure parameter was calibrated based on the observed prostate cancer mortality reduction due to screening in the ERSPC trial and Supplemental Information Table S1.

When the patient is referred to AS, natural history progresses as if the patient was not screen-detected. Referral to radical treatment may occur due to detection of Gleason or volume progression (which is assumed to occur after an increase in stage) at each biopsy round, due to personal preference (randomly selected from all men in AS) or due to clinical detection at the time. The probabilities of referral to radical treatment for low-risk men are estimated based on JH-AS observed treatment-free survival data 4 (Table 1). For intermediate-risk men, we assume that given the risk of progression (which is Gleason and T-stage dependent), the probabilities of referral to treatment are the same as for low-risk men.

At the time of referral to treatment, survival differs compared to what would have happened if the patient would be treated at the time of screening diagnosis, by assuming a decrease in the benefit of screening, depending on the remaining lead-time for the patient.

2.2 | Active surveillance

We simulate a cohort of 10 million men, based on US life tables. In the basecase, men are screened between 55 and the upper bound of the age group selected for AS (with an attendance rate of 90%), with a PSA threshold for biopsy referral of four and biopsy compliance equal to 41%, based on the PLCO trial. Biopsy Compliance during AS is based on the PRIAS study and Supplemental Information Table S2.

We only follow men who are selected for AS in a particular age group (55-59, 60-64, 65-69, 70-74). Men selected for AS have either low-risk (Gleason 6, ≤ T2 stage, PSA <10) or intermediate-risk (up to Gleason 3 + 4, T2 stage, and PSA < 20) disease (Table 1). We compare AS protocols differing by follow-up (1, 4, 7, and 10 biopsy rounds) and biopsy frequency (annual or triannual) with CM, where men are only treated when clinical diagnosis would occur in absence of screening (See Fig. 1, for an example).

Initially, the rate of clinical diagnosis in absence of screening was based on the control group and interval cancers in the screening group of the ERSPC trial. Since the model was adapted to US, an extra hazard of clinical diagnosis was added, reflecting an earlier probability of detection. This was calibrated to SEER incidence data from before the introduction of PSA-based screening.

We assume that the main difference between AS and CM surveillance regimens is that AS includes prostate biopsies, that is, we assume a similar rate of PSA tests or visits to the doctor between the two regimens. We also assume that the main driver of referral to treatment while in AS is the result of the prostate biopsy.
2.3 | Quality of life and costs

QALYs were calculated by using utility estimates ranging between 0 (death or worst imaginable health) and 1 (pre-diagnosis health, which is assumed to be full health). Estimates for the utilities and its durations for all stages of AS, including, prostate biopsies, radical treatment, post-recovery, and palliative therapy are based on27–29 (Table 2). QALYs were calculated by multiplying the loss in utility with the duration of the phase and the number of men who experienced the event, as predicted by MISCAN.

Costs of AS compared to CM include the cost of prostate biopsies and the extra cost of radical treatment, since in CM regimen only men who are clinically diagnosed are treated. The cost of immediate treatment is the average lifetime cost for men treated at age 65, including adverse events, indirect costs, and post-treatment surveillance.30 Costs of palliative therapy are based on.31 All costs were inflated to 2015 US Dollars.

We calculate the cost per QALY using a 3% discount rate for all costs and effects. The most efficient AS policies are determined based on their incremental cost-effectiveness ratio (ICER). An AS protocol is considered to be cost-effective if its ICER is below $100 000.

2.4 | Outcomes

We estimated the cost-effectiveness of each AS protocol compared to CM (no treatment) for men who are selected to AS. The main outcome is cost per QALY gained of the AS protocol compared to CM. Other important outcomes include overtreatment, prostate cancer mortality, life years gained (LYG), and costs.

2.5 | Sensitivity analyses

We analyzed the effects of some plausible alternative scenarios. For the age groups 55-59 and 60-64, we studied whether a lower biopsy frequency (triannual after the first year) or a higher biopsy compliance (81% for the whole follow-up) would have a large impact on QALYs gained. For the age group 65-69, we projected the effects of starting screening at age 65, and we split the age group in smaller intervals (65-66, 65-67, 65-68). In order to assess the effect of uncertainty around the parameter estimates on the outcomes, several multivariate sensitivity analyses were performed, including the utility and cost estimates for each event, the parameters of the model related to treatment benefit, the benefit due to early detection, and the rate of clinical diagnosis.

3 | RESULTS

3.1 | Effects

In Fig. 2 LYG compared to the CM situation are plotted against overtreated men per 1000. Both outcomes are highly dependent on the age group of selection for AS. In the age group 55-59, performing four biopsy rounds results in 723 LYG at a cost of 120 overtreated men per 1000 men in AS. By contrast, for the age group 70-74, four biopsy rounds result in only 98 LYG with 224 overtreated men per 1000.
In Table 3, all effects are shown, with QALYs and LYG discounted at 3%. AS results in life years gained for all age groups. However, after adjusting life years for quality life, our model projects that for men older than 65, even one biopsy round results in QALYs lost, relative to CM situation. For men aged between 55 and 59 after four biopsy rounds, the model projects about 264 QALYS gained and for men aged between 60 and 64, 118 QALYS gained.

### 3.2 Costs

In Table 3, the total cost of AS is shown. Cost of AS increases with number of biopsy rounds and age group. Cost varied between $0.9 million, per 1000 men in AS, for one biopsy for 55-59 men, and $8.2 million for men aged 70-74 after 10 biopsy rounds.

### 3.3 Cost-effectiveness

We show the cost-effectiveness of AS compared to CM in Table 3. For low-risk men in age groups 65-69 and 70-74 AS is not effective. For men in age group 55-59, the estimated ICER after 10 yearly biopsy rounds (yearly biopsies) is $16 199. For the age group 60-64 the ICER is $113 909.

### 3.4 Other scenarios

Under the assumption that biopsy compliance during AS remains 81% for the whole follow-up (observed biopsy compliance in the first year of the PRIAS 14), we see that after four biopsy rounds QALYS gained increase from 264 to 300 for the 55-59 age group, and from 118 to 131 for the 60-64 age group (Table 4). If the biopsy frequency becomes triannual after the 1st year, QALYS gained decrease from 264 to 196, for the 55-59 age group, and from 118 to 71 for the 60-64 age group (Table 4). For men aged between 70 and 74 with intermediate-risk prostate cancer, AS may be cost-effective up to seven biopsy rounds. For men aged 65-69 the ICER is only $21 299 after 10 biopsy rounds. AS for low-risk men aged 65-69 may results in QALYS gained if screening only started at age 65 or if AS is restricted for men younger than 68 (Supplemental Information Table S6).

### 3.5 Sensitivity analyses

Our sensitivity analyses focus on the age group 60-65. At four biopsy rounds we find a range for the ICER between $15 842 (50% higher costs) and $78 709 (unfavorable utilities for prostate biopsies and treatment). At seven biopsy rounds the ICER ranges between $20 329
and $217 517. Of all the sets of parameters considered, utilities have the largest effect on the cost per QALY (Supplemental Information Tables S7 and S8). The only scenario where AS after seven biopsy rounds was not cost-effective was when we applied unfavorable utilities toward screening and treatment procedures. By contrast, if we would apply more favorable utilities, lower costs, lower treatment benefit, and a higher rate of clinical diagnosis then AS would become cost-effective after 10 biopsy rounds (Supplemental Information Tables S7 and S8).

### Table 3: Costs and effects of active surveillance (AS) for low-risk men per number of biopsy rounds\(^a\)

<table>
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<th>Age group</th>
<th>Biopsy rounds</th>
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<th>Overtreatment</th>
<th>PCM (%)</th>
<th>LYs</th>
<th>QALY’s</th>
<th>Total cost(^c)</th>
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\(^a\)Effects per 1000 screened men (unless denoted otherwise). Costs and effects (LYs and QALYs) are discounted at 3%. Costs are shown in millions of 2015 US dollars. QALYs were calculated by multiplying the loss in utility with the duration of the phase and the number of men who experienced the event, as predicted by MISCAN.

\(^b\)Includes men who become symptomatic (modeled as clinical diagnosed in absence of screening) during and after AS follow-up.

\(^c\)Includes the cost of prostate biopsy, treatment costs and palliative therapy costs, which we assume was given to all men who died of prostate cancer. Net costs were calculated as the difference in total costs in the AS and conservative management situation.

\(^d\)Weakly D denotes a weakly dominated strategy.

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\(4\) | **DISCUSSION**

In this study, we tried to determine for the first time, how much time should men stay on AS and be considered for treatment. Previous clinical studies have ascertained AS is relatively safe for low-risk men.\(^2-7,11,12\) Additionally, most studies\(^14-17\) found that AS is less expensive or cost-effective than immediate treatment. However, no clinical cohort or simulation study has examined how much time should men be on AS or how the age group or life expectancy could determine the intensity of the follow-up schedule.

In this study, we find that AS with 7 yearly biopsy rounds for low-risk men is cost-effective compared to CM, but only for age group 55-65 and for men up to age 75 with intermediate-risk disease. We performed this by calculating the cost-effectiveness of AS with different follow-up biopsy schedules (1, 4, 7, and 10 yearly biopsy rounds) compared to a CM group where men can only be treated if they would be clinically diagnosed in absence of screening.

The inclusion of low-risk men younger than 60 in AS is not consensual.\(^10\) These are the best candidates for immediate treatment and have a relatively low probability of being overtreated.\(^32,33\) We find that if these men are included on AS, they require an intensive yearly biopsy schedule, which should continue for at least 10 yearly biopsy rounds. A low biopsy compliance or biopsy frequency may result in QALYs lost and in a significant increase in PCM.

By contrast, for men older than 70, AS is not cost-effective, and does not result in QALYs gained, though some lives are saved. For men aged between 60 and 64, AS appears to be cost-effective up to seven biopsy rounds, and for men aged 65-69 AS results on QALYs lost. With a finer analysis, we find that for men aged 65-67, and for men who started screening after age 65 AS results in QALYs gained but it is still not cost-effective. Just like for men younger than 60, selecting intermediate-risk men for AS is still under debate.\(^34\) We find that if these men are selected, an intensive AS regime with many follow-up biopsies is recommended (for men younger than 70, at least 10 yearly biopsy rounds).

Sensitivity analyses found that the results in this study are the most sensitive to the utilities. For instance, using more unfavorable utilities about biopsies and treatment made the ICER become higher than $100 000 at 7 years for the age group 60-65. However, there were more scenarios (higher cure rate, lower treatment effect, favorable utilities), where AS with 10 yearly biopsy rounds became cost-effective.
This study is subject to some limitations. Our AS model uses a simplification of the criteria of selection for AS and to be referred to treatment compared to most clinical cohorts. For instance, we do not model the number of positive biopsy cores and we assume volume progression can only occur, if there is an increase in T-stage. The probabilities of referral to treatment are based on the JH cohort, which has slightly different selection criteria to AS and referral to treatment criteria than other cohorts like PRIAS or the Toronto cohort. The JH cohort does contain mostly very-low risk men and no intermediate-risk men. We assume that given progression which is not dependent on JH data, the probability of referral to treatment is the same as for intermediate-risk men, low-risk men, and very low-risk men (Except for volume progression which has higher probability of detection for low and intermediate-risk men than for very low-risk men). We also assume that all men whose progression is detected are referred to radical treatment, which may not happen in clinical practice.4

Changes in the rate of clinical diagnosis could affect the cost-effectiveness of the intervention. We examined the effect of parametric uncertainty around the hazard of clinical diagnosis parameters in predicted QALYs and costs. We found that while the proportion of men treated may change significantly (Supplemental Information Table S8) the cost per QALY did not vary substantially when we changed the values of the clinical diagnosis parameters by 20%.

These results apply for the average US population. Populations at higher risk, for instance African-Americans, may need a more intensive schedule compared to their Caucasian peers, for the same age and disease group. Comorbidity level should also be taken into account when building a personalized AS biopsy schedule.

From a safety perspective, we found that life years gained per each additional round of AS biopsies substantially decreases with age. Importantly, men younger than 65 (or older men with intermediate-risk disease) should be aware when deciding between AS and immediate treatment, that if they choose for AS, they may need to follow an intensive biopsy follow-up schedule, and that non-compliance with the biopsy schedule (ie, implicitly choosing Conservative Management) could result in missing their opportunity for cure.

While most clinical cohorts find that AS for low-risk men is safe, there is still some debate about the most optimal way to perform AS.

### Table 4: Costs and effects of active surveillance (AS) per number of biopsy rounds under different scenarios

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<th>Age group and scenario</th>
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<td>4.0</td>
<td>56 149</td>
<td>69 588</td>
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<tr>
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<td>754</td>
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<td>182</td>
<td>74</td>
<td>4.5</td>
<td>60 373</td>
<td>173 882</td>
</tr>
</tbody>
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<sup>a</sup>Effects per 1000 screened men. Costs and effects are discounted at 3%. Costs are shown in millions of 2015 US dollars. QALYs were calculated by multiplying the loss in utility with the duration of the phase and the number of men who experienced the event, as predicted by MISCAN.

<sup>b</sup>Compliance” denotes a scenario where biopsy compliance remains at 81% instead of decreasing through time as observed in. Triannual” denotes a scenario where biopsies occur every 3 years after the 1st year in AS, similar to the PRIAS cohort. “Intermediate-risk” denotes men who are Gleason 3 + 4 and/or have a PSA at diagnosis between 10 and 20.

<sup>c</sup>Includes the cost of prostate biopsy, treatment costs and palliative therapy costs, which we assume was given to all men who died of prostate cancer. Net costs were calculated by the difference in total costs in the AS and CM situation.

<sup>d</sup>Weakly D” denotes a weakly dominated strategy.

<sup>e</sup>Includes men whose cancer becomes symptomatic, during and after AS follow-up.
In particular, it is not known, when should a person stop AS, if no progression is detected. We conclude that the AS protocol for younger low-risk men (55-65) and for older (65-75) intermediate-risk men could consist of at least 7 yearly biopsy rounds. For older (65-75) low-risk men, AS is not effective compared to CM, after taking into account quality of life outcomes. Therefore, for these men, there is no need for an intensive yearly biopsy schedule or to remain for many years on AS.

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CONFLICTS OF INTEREST
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REFERENCES


**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information tab for this article.

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