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# Prostate Cancer Mortality and Metastasis under Different Biopsy Frequencies in North American Active Surveillance Cohorts

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Author Contributions:

ABA, DWL, LFN, BCT, BJT, HBC, MRC, PRC, JEC, and LHK contributed data to the study. JML and RBE conducted the study design. JML conducted the analysis. JML, RBE, and AAL wrote the manuscript. JML, RBE, AAL, DWL, DFP, and SVC edited the manuscript.

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## Abstract

**Background:** Active surveillance (AS) is an accepted means of managing low-risk prostate cancer. Due to rarity of downstream events, data from existing AS cohorts cannot yet address how differences in surveillance intensity affect metastasis and mortality. This study projects the comparative benefits of different AS schedules in men diagnosed with Gleason Score (GS) 6 or below with risk profiles similar to those in North American AS cohorts.

**Methods:** We simulated times of GS upgrading based on AS data from the University of Toronto (UT), Johns Hopkins University (JHU), University of California, San Francisco (UCSF) and the Canary Pass Active Surveillance Cohort (PASS). Times to metastasis and prostate cancer death, informed by models of the Scandinavian Prostate Cancer Group 4 trial, were projected under biopsy surveillance schedules ranging from watchful waiting (WW) to annual biopsies. Outcomes included risk of metastasis and death, remaining life years (LYs), and quality adjusted life years (QALYs).

**Results:** Compared to WW, annual surveillance biopsies reduced the risk of prostate cancer metastasis (death) at 20 years by 1.4–3.3% (death 1.0–2.4%) and 5 year biopsies by 1.0–2.4% (death .6–1.6%). There was little difference between annual and five year biopsy schedules in terms of LYs (range of differences 0.04–0.16), and QALYs (range −0.09–0.02).

**Conclusion:** In men diagnosed with GS≤ 6, biopsying every 3–4 years appears is an acceptable alternative to more frequent biopsies. Reducing surveillance intensity for those with low risk of progression reduces the number of biopsies while preserving the benefit of more frequent schedules.

## Precis:

A simulation study shows that biopsying every 3–4 years is an acceptable alternative to annual or biennial biopsies in active surveillance for low risk prostate cancer. Tailoring schedules by risk of grade progression has the potential to reduce mean number of biopsies while preserving benefit.

### Keywords

Prostate cancer; active surveillance; microsimulation

## Introduction

Active surveillance (AS) is now a widely accepted management option for newly-diagnosed low-risk prostate cancer.[1–4] AS offers men with low-risk prostate cancer the opportunity to avoid treatment that may be unnecessary while still offering curative treatment to those reclassifying as higher risk during surveillance. Its acceptance has increased dramatically in recent years. In the US, the Surveillance, Epidemiology, and End Results (SEER) database

documented an increase in the utilization of AS/watchful waiting (WW) among men with low-risk prostate cancer from 14.5% to 42.1% between 2010 and 2015.[5] This figure is significantly higher in countries such as Sweden, where, in 2014, 91% of men with very low risk prostate and 74% of men with low risk prostate cancer chose AS.[6]

Despite widespread acceptance of AS, uncertainties remain regarding preferred strategies and their effects on long-term outcomes. Differences in AS protocols across existing cohorts[7–10] present an opportunity to compare short-term outcomes. For example, frequency of biopsies ranges from annual (Johns Hopkins University (JHU)[11]) to every 3–4 years (University of Toronto (UT)[8]).

There are a number of challenges involved in using existing data for comparing AS protocols. First, patient populations may vary in underlying risk.[12,13] Second, there is limited information on downstream outcomes such as metastases and deaths, due to the low risk of progression and lengthy follow-up needed to accumulate an adequate number of events. Results so far suggest that intermediate and long-term risks of metastasis and prostate cancer death are low in men with GS6 at diagnosis,[7,8,10,14] but data are still inadequate to make firm conclusions about the comparative outcomes under different biopsy schedules.

The absence of long-term clinical outcomes in existing AS cohorts necessitates the use of modeling to fill the gaps. Models of AS versus immediate curative treatment[15,16] project that while AS results in a modest increase in risk of prostate cancer death, it has clear benefits in terms of quality adjusted life years (QALYs). AS spares patients years of long-term side-effects from curative treatment such as erectile dysfunction, bowel dysfunction and urinary incontinence. Models of AS versus WW have found benefits of AS over WW in terms of life years (LYs) and QALYs, but little difference in LYs and QALYs between AS schedules of different frequencies.[17,18]

This study reports results from a microsimulation model of the comparative downstream effects of different AS schedules, harnessing recent work on the underlying upgrading risk across four North American AS cohorts. We include WW and continuous surveillance for benchmarking purposes, but focus on the comparison of intermediate schedules.

Our goal is to produce results that reflect the range of risks encountered in contemporary cohorts, enabling us to ascertain the robustness of our findings to differences in risk of underlying upgrade. Those included in the present study are the multi-institutional Canary Prostate Active Surveillance Study (PASS) and cohorts from the University of California at San Francisco (UCSF), JHU, and UT.[13] Underlying upgrading is defined as the first point at which a biopsy with perfect sensitivity to detect grade progression would detect GS7 or higher in a man who was initially diagnosed with GS6 disease and chose AS. We superimpose multiple AS protocols and project metastases, deaths due to prostate cancer, and QALYs under each. In addition to schedules that are the same for all individuals, we also investigate tailored strategies that increase surveillance intensity for men who have a relatively high risk of underlying upgrading on AS. Our results apply to both very low-risk and low-risk AS populations.

# Methods

## Simulation inputs

**Underlying grade change—**The following low-risk cohorts were included in this analysis: 1) PASS[10] (1,067 men enrolled during 2008–2013), UT (1,104 men enrolled during 1995–2015),[8] and 3) UCSF (1,319 men enrolled during 1990–2015).[9] In addition, the JHU cohort was also included (913 men enrolled during 1994–2014.[7]), although this cohort primarily included men with very low-risk disease. In all cohorts, we excluded patients diagnosed before 1995, who were older than 80 years at enrollment, or who had GS ≥7 at diagnosis. Enrollment criteria, follow-up schedules, and number of men who were upgraded are provided in Table 1.

Our model of underlying upgrading from GS6 to GS7 based on the four cohorts has been described previously.[13] The estimation approach accommodates imperfect biopsy sensitivity and specificity in detecting GS7 disease and includes age at diagnosis, baseline PSA and PSA velocity as predictors of upgrading risk. Supplemental Materials Figure 1 demonstrates the average cumulative incidence of underlying upgrading in the four cohorts with 90% prediction intervals, assuming biopsy sensitivity of 0.6 (based on a prior study[19]) and specificity of 1.

**Metastasis and prostate cancer death—**To model time from underlying upgrading to metastasis and time from metastasis to prostate cancer death, we used data from the Scandinavian Prostate Cancer Group 4 (SPCG-4) trial of radical prostatectomy (RP) versus WW in men with localized prostate cancer.[20–22] We fit independent Weibull models for time from diagnosis to metastasis and time from metastasis to death in the SPCG-4 data, as a function of GS, age, and PSA and SPCG-4 study arm. (Supplemental Materials provides a description of these methods). The hazard ratio (HR) associated with RP, adjusted for age and GS, was 0.53 for metastasis and 0.76 for death following metastasis. The parametric Weibull model provided a similar fit to a Cox regression but allowed for projecting beyond the timeframe of the trial (Supplemental Materials Figure 2).

Since the SPCG-4 trial was largely conducted before the era of PSA screening, post-diagnosis survival times did not include lead time as would be expected in contemporary screen-detected cases on AS. Therefore, we added age-specific lead times sampled from previously estimated distributions[23] to times from diagnosis to metastasis and prostate cancer death generated using the SPCG-4-based models (Supplemental Materials Figure 3).

**Other-cause death—**Hazards of other cause death were derived from 2013 male US Social Security Actuarial Life Tables (https://www.ssa.gov/oact/STATS/table4c6.html), adjusted by a multiplicative factor of 0.45 to reflect a lower risk in men screened for prostate cancer.[24]

## Microsimulation Model

We generated four different populations (N=50,000 each) that reflected the baseline distribution of age and PSA characteristics and underlying risk of upgrading in the four North American cohorts.[13] N=50,000 was selected to minimize Monte Carlo error in

quantities of interest but allow for computational feasibility. Baseline factors were bootstrapped from the original cohorts. For each individual, we simulated a time of underlying upgrade, given cohort, age at diagnosis, PSA intercept, and slope. We then superimposed a range of biopsy schedules (Table 2) on the disease histories. For each schedule, we determined the time at which the biopsy detected the underlying upgrade, assuming a biopsy sensitivity of 60% for detecting GS7.[19]

Individuals were at risk of metastasis from the point of GS upgrade, with a hazard based on the GS7 cancers in the SPCG4 WW group. We assumed all upgraded cancers were GS7. Once the upgrade was detected, curative treatment was applied, multiplying the hazard of metastasis by 0.53.[22] The later the upgrade was detected, the later the hazard reduction was activated (Supplemental materials Figure 4). Less frequent biopsies led to a longer interval between underlying upgrade and treatment and, ultimately, a greater cumulative risk of metastasis than expected under more frequent biopsies.

We sampled a lead time from the appropriate age-specific distribution, adding it to the generated time from underlying upgrade to metastasis as described above. Finally, we generated times of competing other-cause death and prostate cancer death following metastasis.

**Surveillance schedules—**We considered eight fixed biopsy schedules and three risk-tailored biopsy schedules (Table 2). The ``risk-tailored" schedules assigned each individual to one of the fixed schedules based on their quartile in the simulated population with respect to a risk of upgrading. Risk of upgrading was derived from age, PSA at diagnosis, and PSA velocity and the corresponding coefficients based on previously estimated models of underlying upgrading.[13] The risk-tailored schedules assign individuals with higher risk of upgrading to more frequent biopsies and those with lower risk of upgrading to less frequent biopsies.

**Outcomes—**For each scenario/cohort, we calculated the time spent in AS before treatment, the delay between underlying upgrade and treatment, LYs, QALYs, and net (in the absence of other-cause death) cumulative probabilities of prostate cancer death and metastasis at 10 and 20 years.

To generate QALYs, we superimposed health states corresponding to events in a man's natural history (Figure 1) on the post-diagnosis time period. Each health state is associated with a utility ranging from 0 (dead) to 1.0 (perfect health). Table 3 provides the utilities and other model inputs from literature sources used in this analysis. A range of values was assigned according to the minimum and maximum values in published studies.

## Sensitivity Analyses

The base case assumed independence between times of underlying upgrade, metastasis, and death, conditional on age, grade, and PSA and used a value of 0.53 for the treatment hazard ratio for metastasis and .76 for metastasis to death. Sensitivity analyses considered each of the following:

- Strong correlation between times to underlying upgrade, metastasis, and death, achieved by assuming that the times to metastasis and death share the same percentile as the time to underlying upgrade, conditional on age and PSA at diagnosis.
- An enhanced benefit of primary treatment on time to metastasis, corresponding to treatment such as adjuvant or salvage radiation. Salvage radiation in RP patients is associated with HR of 0.41[25], so we assessed a benefit of combined surgery and radiation of 0.53*0.41 = 0.23.

We also conducted one-way sensitivity analyses varying the health-state utilities.

## Results

### Time to curative treatment and delay between upgrading and treatment

Figure 2 summarizes the times to upgrading and curative treatment under different biopsy schedules. JHU had the longest time until underlying GS upgrade (median 14.8 years for JHU years versus 1.7–2.8 years for other cohorts) and the longest time to treatment initiation.

The delay between underlying upgrade and curative treatment depended on the biopsy frequency. Delay distributions were relatively comparable across all cohorts.[12] Median delay ranged from 0.9 years under annual schedules to 4.1–4.4 years under biopsies every five years.

Under annual surveillance, mean counts of biopsies prior to treatment varied from 14.2 in JHU to 6.6–10 in the other cohorts. Under five-year biopsy surveillance, mean counts varied from 3.0 (JHU) to 1.7–2.2 in the other cohorts (Figure 3).

### Metastasis, mortality and quality of life

In general, all AS schedules performed favorably relative to WW in terms of metastases and prostate cancer deaths (Figure 3). Compared to WW, annual biopsies reduced the risk of prostate cancer metastasis (death) at 20 years by 1.4–3.3% (1.0–2.4%), and 5 year biopsies by 1.0–2.4% (death 0.6–1.6%). There was little marginal improvement in 20-year metastasis and death for annual and biennial schedules versus biopsies every 3–4 years (Figure 3).

LYs and QALYs, both of which account for other-cause death, were less sensitive than the net probabilities of death and metastasis to differences in schedules (Figure 4). Mean LYs under annual AS exceeded those under five year biopsies by 0.04 (JHU) and 0.08–0.16 (other cohorts). Relative to five year biopsies, mean QALYs under annual AS were 0.02 lower in JHU and 0.02–0.09 greater in the other cohorts.

### Sensitivity Analyses

Sensitivity analyses assuming an enhanced treatment effect yielded a relatively greater benefit of more frequent biopsies than in the base case. The LY difference between annual and five-year biopsies was 0.1 in JHU and 0.2–0.3 (other cohorts). QALYs differed by 0.02 in JHU and 0.11–0.18 (other cohorts). Assuming correlated outcomes, the LY difference

between annual and five-year biopsies was 0.11–0.13 across cohorts; QALYs varied by 0.05–0.07.

Figure 5 shows one-way sensitivity analyses for QALYs with respect to health state utilities. QALYs were most sensitive to the utilities of the pre-treatment/AS state and the long-term post-treatment state. The relative benefit of more intensive AS schedules decreased when the pre-treatment state had a higher utility and increased when the long-term treatment state had a higher utility.

### Risk-tailored schedules

The performance of risk-tailored schedules fell between schedules with biopsies every 2 and 5 years in terms of number of biopsies incurred and net percent with metastasis and death at 20 years (Figures 3). Relative to a biennial biopsy schedule, tailored schedules that reduced biopsy frequency to five years for the first or first and second quartiles of risk (Tailored Schedules 2 and 3) reduced the mean number of biopsies by 1.0–2.5 and 0.60–1.5, respectively, while only increasing 20 year risk of metastasis by 0.1%−0.5% and death by 0.2%−0.6% (Figure 3) and reducing LYs by <0.04 and QALYs by <0.01 (Figure 4).

## Discussion

Our goal in this study was to examine the likely impact of varying AS protocols while incorporating the natural heterogeneity that exists among published studies. We found that increasing biopsy frequency offered benefits versus WW in terms of downstream risk of metastasis and death, but there were only modest differences in LYs and QALYs between surveillance schedules that varied the biopsy interval from every one to five years. Furthermore, compared with 3-and 4-year biopsy schedules, the marginal declines in risk of metastasis and death for more frequent schedules were small relative to the mean increase in biopsies.

While other recent studies have projected downstream outcomes under different schedules,[17,18] ours is the first study to explicitly examine long-term outcomes as they pertain to existing North American AS cohorts. Prior work has indicated that the risk of underlying upgrading differs by cohort; in particular, JHU appears to have a much lower risk than the other three cohorts. These findings translate into differences in projected risks of downstream outcomes. We project that under annual biopsies, the net probability of prostate cancer death is 1.3% at 20 years in JHU versus 3.2–3.4% in the other cohorts.

Our projections of the relative differences in outcomes across candidate schedules are consistent with AS modeling studies that compared a variety of AS schedules.[17,18,26] Sathianathen et al[18] projected a LY difference of 0.02 between annual and five year schedules, and a difference in QALYs of 0.01. Similarly Loeb[17] found only minor differences in LYs and QALYs between annual and five-year biopsies. Loeb's study also found the marginal benefit of AS over WW in terms of LYs and QALYs was significantly greater for men who were younger at diagnosis. These findings are consistent with the age ordering in our cohorts. UCSF and PASS have an average age of 62–63 at diagnosis and

have a higher marginal benefit of more frequent biopsies relative to UT and JHU, whose average age was 66.

At this time, we have some ability to make comparisons of our projections with the observed downstream events in the longest running North American AS cohorts. In the JHU cohort, as of 2015, only 2/1,298 men have died of prostate cancer while on AS; cancer-specific, and metastasis-free survival rates were 99.9%, and 99.4%, respectively, at 15 years.[7] Our corresponding projections under annual biopsies were 99.7% and 99.4%, respectively. In the Toronto cohort, as of 2016, 2.0% (16/769) of those diagnosed with GS6 had developed metastasis.[14] Using this data and simulating biopsies every 3 years, our 10 and 15-year projections for metastasis were 1.2% and 2.9%, respectively. In practice, a higher fraction of men have curative treatment in actual cohorts compared to simulated ones due to volume criteria for progression and/or dropout due to patient choice. Ultimately, these differences may lead to lower rates of metastasis and death relative to those projected under the nominal schedules.

Our models allow us to examine the benefit of tailored approaches that are based on a known underlying risk of upgrading. The tailored schedules consisted of biennial surveillance for higher risk groups with a single biopsy or biopsies every 5 years for lower risk groups. These schedules did not significantly alter the risk of downstream outcomes compared with non-tailored biennial schedules, but did lower the biopsy burden for low-risk men. Therefore, accurate risk stratification has the potential to meaningfully reduce biopsies without sacrificing benefit.

## Clinical Perspective

Biopsies are burdensome and have a risk of potentially serious complications.[27] In men of similar risk and age to these cohorts (i.e., GS6, starting AS in their 60s), performing annual biopsies in men with no change in their disease state or PSA is clearly excessive, especially when taking into account the complications from multiple biopsies. Our results confirm that extending the interval between biopsies is appropriate in carefully selected low-risk men. It should be borne in mind that comparisons between strategies over the long term show greater differences than over the short term given the higher rate of prostate-specific mortality over time.[17] Therefore, men with greater life expectancy contemplating AS will likely receive greater benefit from more intensive surveillance.

## Limitations

As with all modeling studies, the validity of our results relies on many assumptions. The fact that our results are in line with other recent studies that made different assumptions suggests robustness of our major findings. Our QALY calculations were based on a simplified set of health states that did not incorporate treatment for PSA recurrence complications of biopsy. Our study also only considered biopsy-based protocols and did not include other elements of current AS practices, including MRI/fusion biopsies or dynamic schedules based on evolving biomarkers that may increase the sensitivity of biopsy. We assumed a biopsy sensitivity of 60%; a higher sensitivity would reduce the delay from underlying upgrade to detected upgrade under all schedules and would narrow further modest differences in benefit

between schedules that biopsy more versus less frequently. Our results also only apply to men with GS6 at diagnosis, not to men with GS 3+4=7 who are included in some protocols. While the SPCG-4 represents a high-quality data source for long term follow-up, it may not completely reflect the risk of metastasis and death in contemporary North American AS cohorts. In particular, the historical SPCG-4 WW cohort may not be directly comparable to contemporary patients due to GS grade inflation and migration that has occurred since the trial, which enrolled patients from 1989–1999. The risk of metastasis and prostate cancer death in contemporary patients with the same grading is lower than SPCG-4;[28] as such, our model may overstate the probability of these outcomes. The relative comparisons between biopsy schedules are likely robust to moderate differences in the overall risk of metastasis and death.

**Conclusion:** In men diagnosed with GS6 disease who are similar to those in existing AS cohorts, we project little marginal improvement for biopsying annually versus every 3–4 years. Until validated tools are available for accurate risk stratification, determining the exact frequency with which to biopsy each patient should depend on patient-specific risk factors and personal preferences.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Bibliography

1. Tosoian JJ, Carter HB, Lepor A. & Loeb S. Active surveillance for prostate cancer: contemporary state of practice. Nat. Rev. Urol. 116, 1477–1490 (2016).
2. Chen RC et al. Active surveillance for the management of localized prostate cancer (Cancer Care Ontario guideline): American society of clinical oncology clinical practice guideline endorsement. J. Clin. Oncol. 34, 2182–2190 (2016). [PubMed: 26884580]
3. Briganti A. et al. Active Surveillance for Low-risk Prostate Cancer: The European Association of Urology Position in 2018. Eur. Urol. 74, 357–368 (2018). [PubMed: 29937198]
4. Sanda M. et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. J. Urol. 199, 683–690 (2018). [PubMed: 29203269]
5. Mahal BA et al. Use of Active Surveillance or Watchful Waiting for Low-Risk Prostate Cancer and Management Trends Across Risk Groups in the United States, 2010–2015. JAMA E1–E3 (2019).
6. Loeb S. et al. Uptake of Active Surveillanc for Very-Low-Risk Prostate Cancer in Sweden. JAMA Oncol. 3, 1393–1398 (2017). [PubMed: 27768168]
7. Tosoian JJ et al. Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. J. Clin. Oncol. 33, 3379–3385 (2015). [PubMed: 26324359]

8. Klotz L. et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J. Clin. Oncol. 33, 272–277 (2015). [PubMed: 25512465]
9. Welty CJ et al. Extended followup and risk factors for disease reclassification in a large active surveillance cohort for localized prostate cancer. J. Urol. 193, 807–811 (2015). [PubMed: 25261803]
10. Newcomb LF et al. Outcomes of active surveillance for the management of clinically localized prostate cancer in the prospective, multi-institutional Canary PASS cohort. J. Urol. 195, 206–221 (2016). [PubMed: 26259991]
11. Tosoian JJ et al. Active surveillance program for prostate cancer: An update of the Johns Hopkins experience. Int. Braz J Urol 37, 278 (2011).
12. Inoue LYT et al. Comparative analysis of biopsy upgrading in four prostate cancer active surveillance cohorts. Ann. Intern. Med. 168, 1–9 (2018). [PubMed: 29181514]
13. Lange JM et al. Estimating and comparing cancer progression risks under varying surveillance protocols. Ann. Appl. Stat. 12, 1773–1795 (2018). [PubMed: 30627300]
14. Yamamoto T. et al. Metastatic prostate cancer in men initially treated with active surveillance. J. Urol. 195, 1409–1414 (2016). [PubMed: 26707510]
15. Hayes JH et al. Active Surveillance Compared With Initial Treatment for Men With Low-Risk Prostate Cancer. JAMA 304, 2373 (2010). [PubMed: 21119084]
16. Xia J. et al. Prostate cancer mortality following active surveillance versus immediate radical prostatectomy. Clin. Cancer Res. 18, 5471–5478 (2013).
17. Loeb S. et al. Active Surveillance Versus Watchful Waiting for Localized Prostate Cancer: A Model to Inform Decisions. Eur. Urol. 72, 899–907 (2017). [PubMed: 28844371]
18. Sathianathen NJ et al. Cost-effectiveness Analysis of Active Surveillance Strategies for Men with Low-risk Prostate Cancer. Eur. Urol. 1–8 (2018). at <https://linkinghub.elsevier.com/retrieve/pii/S0302283818308534>
19. Inoue LYT, Trock BJ, Partin AW, Carter HB & Etzioni R. Modeling grade progression in an active surveillance study. Stat. Med. 33, 930–939 (2014). [PubMed: 24123208]
20. Holmberg L. et al. Results from the scandinavian prostate cancer group trial number 4: A randomized controlled trial of radical prostatectomy versus watchful waiting. J. Natl. Cancer Inst. - Monogr. 2011, 230–233 (2012).
21. Holmberg L. et al. A Randomized Trial Comparing Radical Prostatectomy with Watchful Waiting in Early Prostate Cancer. N. Engl. J. Med. 347, 781–789 (2002). [PubMed: 12226148]
22. Bill-Axelson A. et al. Radical prostatectomy or watchful waiting in early prostate cancer. N. Engl. J. Med. 370, 932–942 (2014). [PubMed: 24597866]
23. Kaur D, Ulloa-Perez E, Gulati R. & Etzioni R. Racial disparities in prostate cancer survival in a screened population: Reality versus artifact. Cancer 124, 1752–1759 (2018). [PubMed: 29370459]
24. Xia J. et al. Overdetection of Recurrence after Radical Prostatectomy: Estimates Based on Patient and Tumor Characteristics. Clin. Cancer Res. 20, 5302–5310 (2014). [PubMed: 25320374]
25. Lange JM, Trock BJ, Gulati R. & Etzioni R. A Framework for Treatment Decision Making at Prostate Cancer Recurrence. Med. Decis. Mak. 37, (2017).
26. Barnett CL et al. Optimizing active surveillance strategies to balance the competing goals of early detection of grade progression and minimizing harm from biopsies. Cancer 124, 698–705 (2018). [PubMed: 29131319]
27. Loeb S. et al. Systematic review of complications of prostate biopsy. Eur. Urol. 64, 876–892 (2013). [PubMed: 23787356]
28. Cazzaniga W. et al. Mortality after radical prostatectomy in a matched contemporary cohort in Sweden compared to the Scandinavian Prostate Cancer Group 4 (SPCG-4) study. BJU Int. 4, (2018).
29. Heijnsdijk E. et al. Quality-of-life effects of prostate-specific antigen screening. N. Engl. J. Med. 367, 595–605 (2012). [PubMed: 22894572]
30. Stewart ST, Lenert L, Bhatnagar V. & Kaplan RM Utilities For Prostate Cancer Health States in Men Aged 60 and Older. Med. Care 43, 347–355 (2005). [PubMed: 15778638]

31. Calvert NW et al. Effectiveness and cost-effectiveness of prognostic markers in prostate cancer. Br. J. Cancer 88, 31–35 (2003). [PubMed: 12556955]
32. Sanda MG et al. Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors. N. Engl. J. Med. 358, 1250–61 (2008). [PubMed: 18354103]
33. Ku J. et al. Changes in health utilities and health-related quality of life over 12 months following radical prostatectomy. Can. Urol. Assoc. J. 3, 445–452 (2009). [PubMed: 20019969]
34. Matthew AG et al. Health-related quality of life following radical prostatectomy: long-term outcomes. Qual. Life Res. 23, 2309–17 (2014). [PubMed: 24609438]
35. Bremner K, Chong C, Tomlinson G, Alibhai S. & Krahn M. A review and meta-analysis of prostate cancer utilities. Med. Decis. Mak. 27, 288–298 (2007).
36. Lloyd AJ, Kerr C, Penton J. & Knerer G. Health-Related Quality of Life and Health Utilities in Metastatic Castrate-Resistant Prostate Cancer: A Survey Capturing Experiences from a Diverse Sample of UK Patients. Value in Health 18, 1152–1157 (2015). [PubMed: 26686802]
37. Konski A. et al. Economic analysis of a phase III clinical trial evaluating the addition of total androgen suppression to radiation versus radiation alone for locally advanced prostate cancer (Radiation Therapy Oncology Group protocol 86–10). Int. J. Radiat. Oncol. Biol. Phys. 63, 788–794 (2005). [PubMed: 16109464]
38. Moeremans K, Caekelbergh K. & Annemans L. Cost-effectiveness analysis of bicalutamide (CasodexTM) for adjuvant treatment of early prostate cancer. Value Heal. 7, 472–481 (2004).
39. Penson DF et al. The cost-effectiveness of combined androgen blockade with bicalutamide and luteinizing hormone releasing hormone agonist in men with metastatic prostate cancer. J. Urol. 174, 547–552 (2005). [PubMed: 16006889]
40. Ramsey S. et al. Is combined androgen blockade with bicalutamide cost-effective compared with combined androgen blockade with flutamide? Urology 66, 835–839 (2005). [PubMed: 16230148]

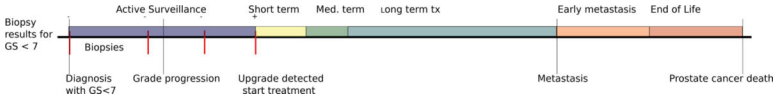


**Figure 1.**
Health states

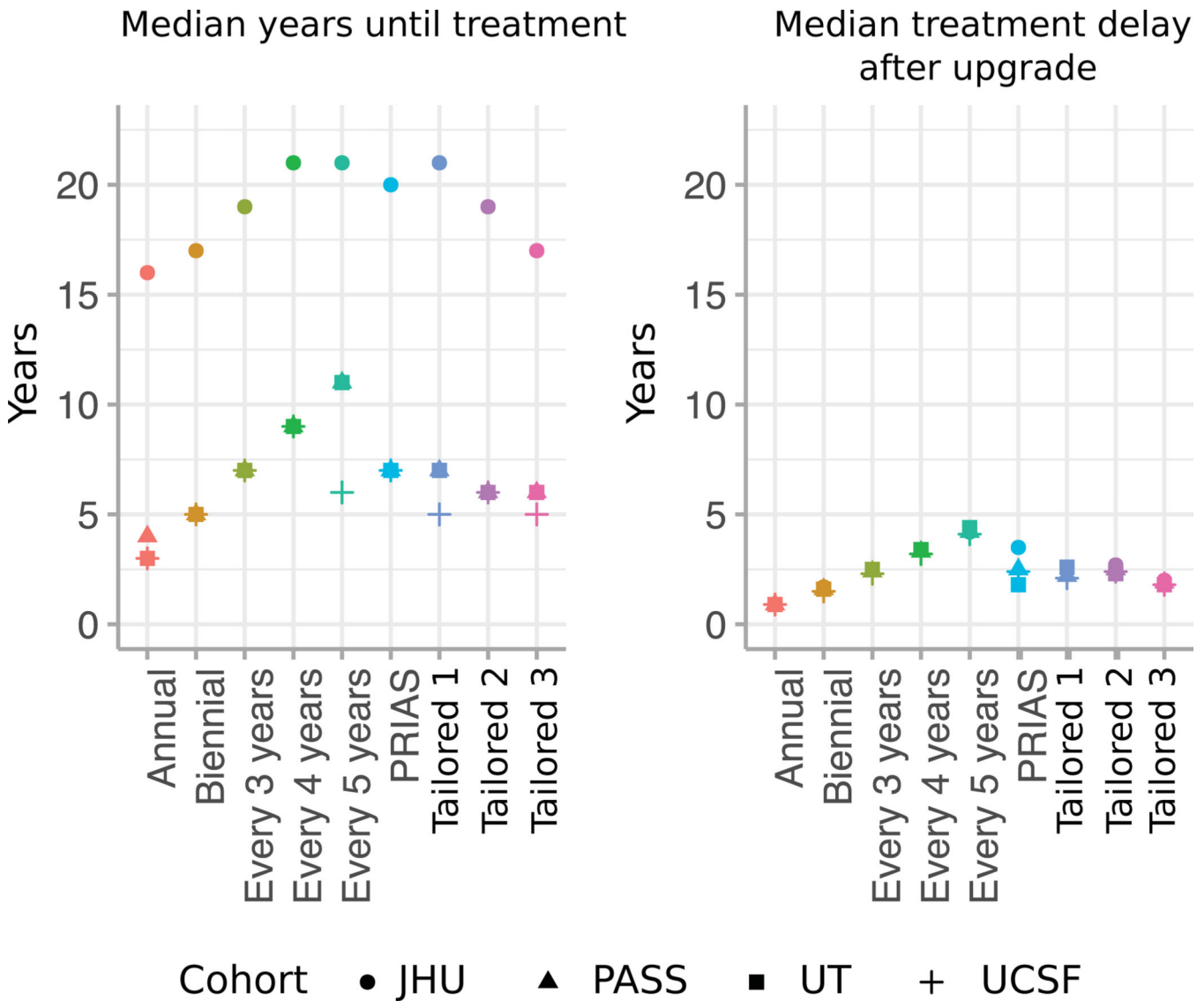


**Figure 2.**

Median years until treatment, median delay of treatment after upgrade, and mean number of biopsies under perfect AS compliance.

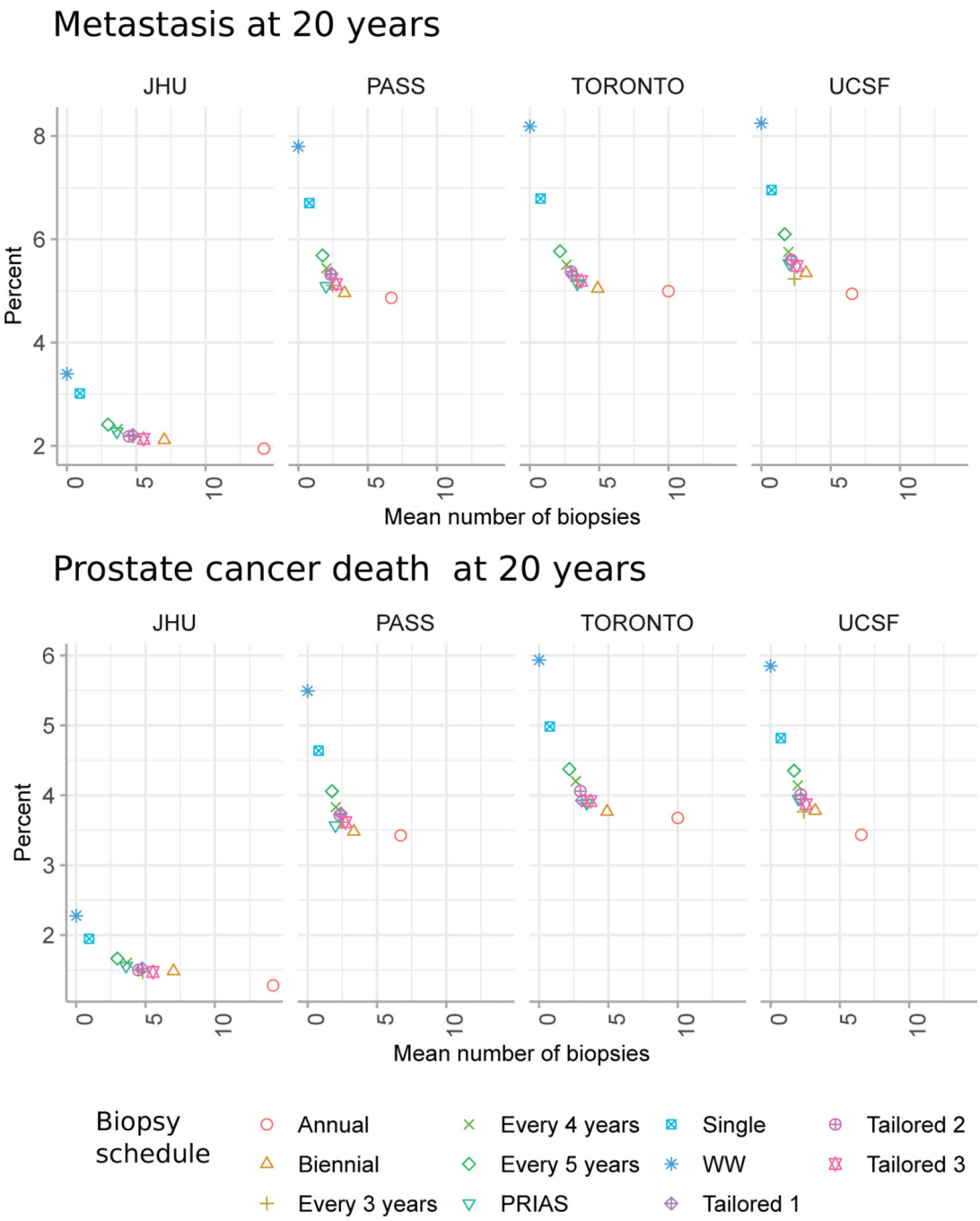


**Figure 3.**
Projected net cumulative probability of metastasis and death versus mean number of biopsies by cohort and schedule.

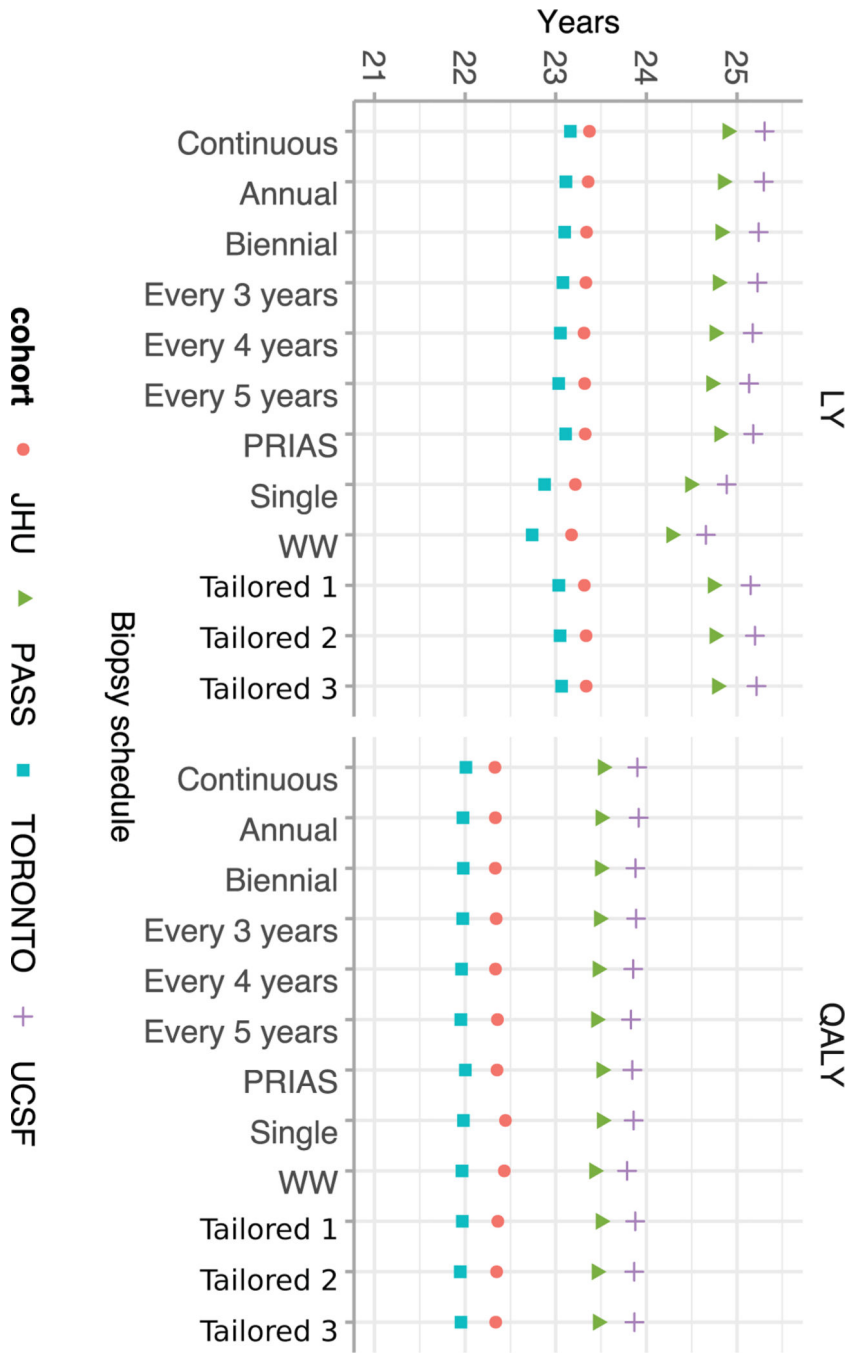


**Figure 4.**
Projected mean remaining LYs and QALYs by schedule and cohort.

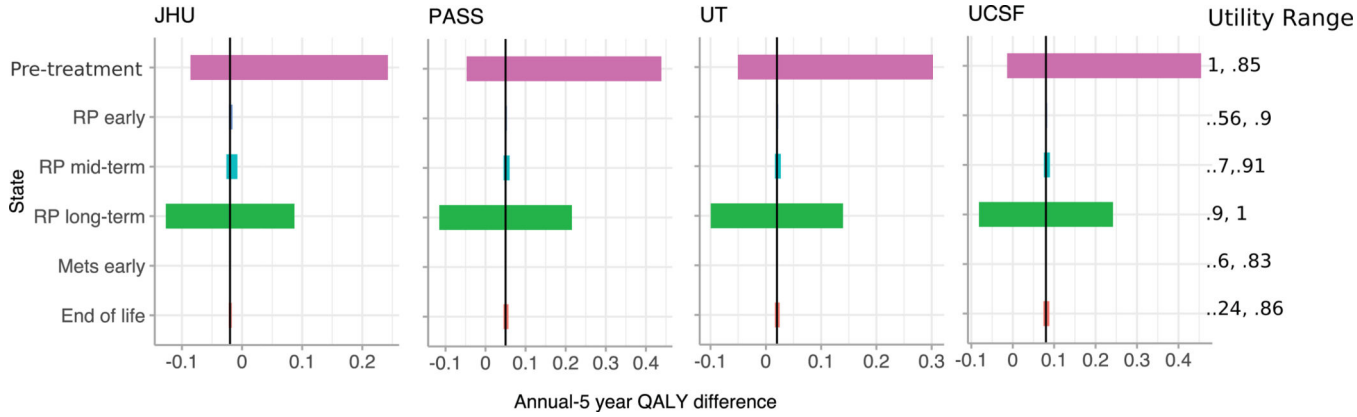


**Figure 5.**

Tornado plots for one-way sensitivity analyses, comparing the difference in QALYs between annual and five year based on the range of utilities in the literature. The vertical line represents the Annual-five year QALY difference under the base values.

**Table 1.**

Description of North American AS cohorts

| | JHU | PASS | Toronto | UCSF |
|---|---|---|---|---|
| Enrollment years | 2008–2013 | 1995–2015 | 1994–2014 | 1990–2015 |
| Enrollment criteria† | Very low risk | Low risk | Low and select intermediate risk | Low and select intermediate risk |
| PSA surveillance | 6 mo. | 4 mo. | 3 mo. | 3 mo. |
| Confirmatory biopsy | Yes | Yes | Yes | Yes |
| Subsequent biopsies | 1 year | 2 years | 4 years | 2 years |
| Triggers for intervention | | | | |
| Gleason score | >6 | >6 | >6 | >6 |
| Volume | | | | |
| Positive cores | >16% | >33% | NA | >33% |
| Max % core with cancer | >50% | NA | NA | >50% |
| Sample size after exclusions†† | 699 | 613 | 421 | 764 |
| Age at diagnosis, median (IQR)†† | 65.6 (62.0, 68.8) | 63 (58, 67) | 65.7 (60.1, 70.9) | 62 (57, 66) |
| Clinical Stage†† | | | | |
| T1 | 699 (100.0%) | 543 (88.6%) | 859 (77.8%) | 592 (77.5%) |
| T2 (Not Otherwise Specified) | 0 | 0 | 4 (0.4%) | 0 |
| T2a | 0 | 70 (11.4%) | 133 (12.0%) | 172 (22.5%) |
| T2b or higher | 0 | 0 | 42 (3.8%) | 0 |
| Missing | 0 | 0 | 66 (6.0%) | 0 |

† Risk based on Gleason score, clinical stage, tumor volume, PSA; JHU also included low PSA density criterion.

†† Exclusion of GS>6, Age>80

**Table 2.**

Biopsy schedules and schedules

| **Biopsy schedules** | **Years of biopsies** |
|---|---|
| Continuous | Hypothetical schedule with continuous biopsies |
| Annual | 1,2,3,4,… |
| Biennial | 1,3,5, … |
| Every 3 years | 1,4,7, … |
| Every 4 years | 1,5,9, … |
| Every 5 years | 1,6,11,16,… |
| PRIAS | 1,3,7,10,15,20,25, … |
| Single | 1 |
| WW | None |

**Tailored biopsy schedules**

| Name | Upgrading risk[†] | Biopsy schedule |
|---|---|---|
| Tailored 1 | 1st quartile | Single |
| | 2nd quartile | Biennial |
| | 3rd quartile | Biennial |
| | 4th quartile | Biennial |
| Tailored 2 | 1st quartile | Every 5 years |
| | 2nd quartile | Biennial |
| | 3rd quartile | Biennial |
| | 4th quartile | Biennial |
| Tailored 3 | 1st quartile | Every 5 years |
| | 2nd quartile | Every 5 years |
| | 3rd quartile | Biennial |
| | 4th quartile | Biennial |

[†]Updgrading risk based on baseline age, PSA, and PSA velocity.[13]

**Table 3.**

Utilities of health states

| Health State | Mean | Range | Duration | Reference |
|---|---|---|---|---|
| **Active Surveillance/Pre-treatment** | 0.97 | 0.85–1.00 | | [29] |
| ***Radical prostatectomy*** | | | | |
| Short-term treatment | 0.67 | 0.56–0.90 | 2 mo. | [30] |
| Mid-term treatment | 0.77 | 0.70–0.91 | 10 mo. | [31] |
| Long-term treatment | 0.95 | 0.90–1.0 | until other-cause death or metastasis | [29,30,32–34] |
| **Metastasis** | | | | |
| Early metastasis | 0.76 | 0.6–0.83 | from metastasis until 30 mo. before prostate death | [35,36] |
| Palliative therapy/end of life | 0.60 | 0.24–0.86 | 30 mo. | [37–40] |