

Prostate Cancer Mortality following Active Surveillance versus Immediate Radical Prostatectomy

Jing Xia¹, Bruce J. Trock⁴, Matthew R. Cooperberg⁶, Roman Gulati¹, Steven B. Zeliadt², John L. Gore³, Daniel W. Lin³, Peter R. Carroll⁶, H. Ballentine Carter⁵, and Ruth Etzioni¹

Abstract

Propose: Active surveillance has been endorsed for low-risk prostate cancer, but information about long-term outcomes and comparative effectiveness of active surveillance is lacking. The purpose of this study is to project prostate cancer mortality under active surveillance followed by radical prostatectomy versus under immediate radical prostatectomy.

Experimental design: A simulation model was developed to combine information on time from diagnosis to treatment under active surveillance and associated disease progression from a Johns Hopkins active surveillance cohort ($n = 769$), time from radical prostatectomy to recurrence from cases in the CaPSURE database with T-stage \leq T2a ($n = 3,470$), and time from recurrence to prostate cancer death from a T-stage \leq T2a Johns Hopkins cohort of patients whose disease recurred after radical prostatectomy ($n = 963$). Results were projected for a hypothetical cohort aged 40 to 90 years with low-risk prostate cancer (T-stage \leq T2a, Gleason score \leq 6, and prostate-specific antigen level \leq 10 ng/mL).

Results: The model projected that 2.8% of men on active surveillance and 1.6% of men with immediate radical prostatectomy would die of their disease in 20 years. Corresponding lifetime estimates were 3.4% for active surveillance and 2.0% for immediate radical prostatectomy. The average projected increase in life expectancy associated with immediate radical prostatectomy was 1.8 months. On average, the model projected that men on active surveillance would remain free of treatment for an additional 6.4 years relative to men treated immediately.

Conclusions: Active surveillance is likely to produce a very modest decline in prostate cancer-specific survival among men diagnosed with low-risk prostate cancer but could lead to significant benefits in terms of quality of life. *Clin Cancer Res*; 18(19): 5471–8. ©2012 AACR.

Introduction

Interest in active surveillance is increasing as an initial management approach for newly diagnosed, low-risk prostate cancer. In December 2011, the NIH convened a State-of-the-Science Consensus Conference on the role of active surveillance in the management of men with localized prostate cancer (<http://consensus.nih.gov/2011/prostate.htm>). The final statement from the conference panel concluded that forgoing immediate treatment with surgery or

radiation, both of which can have serious side effects, and instead actively monitoring the disease is a "viable option" for many men diagnosed with low-risk prostate cancer. However, currently, most men with low-risk prostate cancer undergo immediate treatment (1). There are significant barriers to adoption (2), principally a paucity of comparative data evaluating cancer-specific outcomes among contemporary, low-risk cases undergoing immediate treatment versus active surveillance. Indeed, the literature review commissioned for the consensus conference (3) did not find a single study reporting results from direct comparisons of active surveillance with immediate treatment.

Although direct estimates of the impact of active surveillance on prostate cancer mortality (PCM) are currently lacking, information is available on parts of the process from diagnosis to death under active surveillance versus immediate treatment. Several active surveillance studies are ongoing (4–8) and, although none are mature enough to assess PCM, they are now yielding distributions of times to treatment and the corresponding frequency of disease progression (e.g., biopsy upgrading). The implications of biopsy grade at treatment of disease recurrence are, in turn, well understood from cohort studies and nomograms (9, 10).

Authors' Affiliations: ¹Division of Public Health Sciences, Fred Hutchinson Cancer Research Center; ²VA Health Services Research & Development; ³Department of Urology, University of Washington, Seattle, Washington; ⁴Departments of Urology, Epidemiology, Oncology, and Environmental Health Sciences; ⁵James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland; and ⁶Department of Urology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California

Corresponding Author: Ruth Etzioni, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, M2-B230, Seattle, WA 98109-1024. Phone: 1-206-667-6561; Fax: 1-206-667-7264; E-mail: retzioni@fhcrc.org

doi: 10.1158/1078-0432.CCR-12-1502

©2012 American Association for Cancer Research.

Translational Relevance

Men diagnosed with low-risk prostate cancer face an agonizing decision about whether to be treated or to opt for active surveillance. Their dilemma is made even more challenging by the lack of information about the clinically relevant outcomes of active surveillance—primarily its effect on their risk of prostate cancer death. Ongoing active surveillance programs are not mature enough to provide results concerning disease-specific mortality. Also, they are single-arm studies so there is no comparison group to enable inferences about the comparative effectiveness of active surveillance. In this study we use the results from one of the leading active surveillance cohorts and, using a computer model as a virtual laboratory for translational research, we project disease-specific deaths under active surveillance versus immediate treatment. This information should enable patients and their clinicians to make better informed decisions about the most appropriate approach for managing newly diagnosed, low-risk prostate cancer.

And there are also several prognostic studies of the interval from disease recurrence to PCM (11, 12). Our goal is to integrate this information using a coherent model of the progression of disease through surveillance, treatment, recurrence, and death. Without modeling, any assessment of the effect of active surveillance will necessarily depend on a direct assumption about the impact of active surveillance on PCM [e.g., ref. (13)]. Such an assumption could critically influence inferences about the harms and benefits of active surveillance.

In this article we present a model that logically combines results from active surveillance and prognostic studies among prostate cancer patients receiving surgery. We use the model to project PCM among contemporary low-risk cases on active surveillance, followed by radical prostatectomy if disease progresses, and we compare our projections

with PCM had the cases received immediate radical prostatectomy. Our work provides a novel method for using data from active surveillance cohorts to inform practices that favorably balance harms and benefits in low-risk prostate cancer cases.

Methods

Our methods decompose the interval from diagnosis to PCM into phases, the duration of each of which can be projected based on published studies (Fig. 1). Among men on active surveillance, we model the time from diagnosis to radical prostatectomy, the time from radical prostatectomy to recurrence, and the time from recurrence to PCM. Among men treated immediately with radical prostatectomy, time spent in the first phase (active surveillance) is zero. We use the same model for time to PCM after radical prostatectomy whether it is conducted immediately or following active surveillance. However, the outcomes differ in the 2 scenarios because we allow disease to progress on active surveillance so that key prognostic predictors [i.e., Gleason score (GS) and prostate-specific antigen (PSA)] used in the model of time from treatment to recurrence and time from recurrence to death may have different values when men are treated immediately versus after the delay induced by a period on active surveillance.

We use a microsimulation modeling framework to project outcomes for the same cohort of cases under active surveillance or immediate radical prostatectomy. We consider cases who are low risk at diagnosis according to the most recent guidelines on prostate cancer from the National Comprehensive Cancer Network (<http://www.nccn.com/cancer-treatment/prostate-cancer/localized.html>), namely T-stage \leq T2a, GS \leq 6, and PSA \leq 10 ng/mL. This is generally consistent with ongoing active surveillance cohort studies as summarized by the State-of-the-Science Conference draft statement.

Data sources

To project the time to treatment under active surveillance, we use data from the Johns Hopkins Active Surveillance (JH-

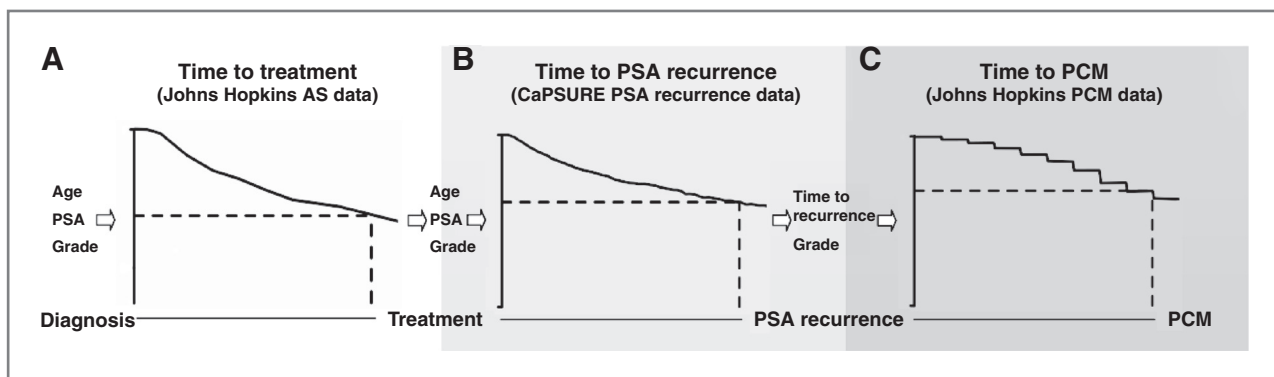


Figure 1. Framework for modeling of prostate cancer mortality following active surveillance versus immediate radical prostatectomy. Under immediate treatment, we model time to recurrence (B) followed by time from recurrence to prostate cancer mortality (C). Under active surveillance, these are preceded by a model of time to treatment (A). The figures show Kaplan-Meier curves for the relevant endpoints from the 3 data sets used in the model. AS, active surveillance; PCM, prostate cancer mortality.

AS) program (6). Patients enrolled are those with T-stage \leq T1c, GS \leq 6, PSA density \leq 0.15 ng/mL/cc, \leq 2 prostate needle biopsy cores with cancer, and cancer involvement of \leq 50% in any biopsy core. Cases are biopsied annually and referred to treatment based on any adverse change in prostate biopsy. Patients also self-refer for a variety of reasons, including rising PSA or anxiety. Using data for all cases in this program, we estimate time to treatment using a Kaplan–Meier curve and the frequency of biopsy GS progression under active surveillance using a logistic regression of whether GS is 7 or more at the final biopsy before treatment. Covariates include age at diagnosis, PSA at biopsy, annual percentage change in PSA between diagnosis and final biopsy, and time from diagnosis to treatment.

To project the time from radical prostatectomy to PSA recurrence or any secondary treatment ("recurrence"), we use data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database (14–16). CaPSURE was initiated in 1995 to document community trends in prostate cancer practice patterns, epidemiology, and outcomes. It is a longitudinal, observational database accruing data from 40 urologic practice sites over its history. There are currently 13,821 men enrolled in CaPSURE and CaPSURE collects approximately 1,000 clinical and patient-reported variables, including posttreatment PSA levels. We use data from cases diagnosed after 1994 because this was the year in which PSA screening rates in the population began to stabilize and cases diagnosed after this point are likely to be more reflective of contemporary diagnoses.

To model the time from recurrence to PCM, we use data from a Johns Hopkins PCM (JH-PCM) cohort, consisting of patients treated with radical prostatectomy who had a recurrence (i.e., PSA \geq 0.2 ng/mL) and who were followed for PCM (12). Approximately 55% were treated with salvage radiation, hormonal therapy, or both at the time of recurrence. To be consistent with the model of time from radical prostatectomy to recurrence, we only consider patients who received radical prostatectomy after January 1994. To their data on time from recurrence to death, we fit a Cox regression model adjusting for biopsy GS at the time of diagnosis and time from radical prostatectomy to recurrence (11, 17).

A simulation model of time from diagnosis to PCM

The simulation model first generates a virtual population of 1 million patients representative of contemporary U.S. prostate cancer cases by sampling age and PSA pairs from cases reported in the Surveillance, Epidemiology, and End Results (SEER) program (<http://seer.cancer.gov/>) with low-risk disease diagnosed after January 2004 (this was the date when PSA levels at diagnosis were added to the SEER database). For each simulated case we generate time to PCM under active surveillance versus immediate radical prostatectomy.

Given age and PSA, we simulate the time from immediate radical prostatectomy to recurrence for each case using a Cox model fit to low-risk CaPSURE cases (T-stage \leq T2a, GS \leq 6, and PSA \leq 10 ng/mL) and a time from recurrence to PCM from the Cox model fit to the JH-PCM data restricted to cases

with T-stage \leq T2a at radical prostatectomy. We use Weibull regression to extrapolate beyond the last observed failure times. We independently simulate times to other-cause mortality from life tables (<http://www.mortality.org/>) given age at diagnosis and birth year. The age at death is the minimum of the age at PCM and other-cause death, with cause of death assigned accordingly.

Under active surveillance, we simulate a time to treatment from the distribution of treatment times in the JH-AS cohort. To capture the intuition that disease that progresses quickly to treatment under active surveillance will also likely recur quickly after immediate radical prostatectomy, we generate the time to treatment under active surveillance at a percentile corresponding to the percentile used to generate the time from immediate radical prostatectomy to recurrence. To extrapolate beyond the last observed failure time we assume a constant failure rate (i.e., an exponential distribution), with risk of failure (proceeding to treatment) estimated based on the final year of observation. To each patient initiating treatment, we randomly assign a PSA growth rate and use this to project the PSA level at the time of treatment. PSA growth rates among cancer cases in the absence of treatment are estimated via linear, mixed-effects models fit to serial PSA measurements among participants enrolled in the JH-AS cohort. We impute biopsy GS (\leq 6 or \geq 7) at treatment from the GS progression model fit to the JH-AS data. Among cases upgraded on active surveillance, we assume that 86% have biopsy GS 7 at treatment and 14% have biopsy GS 8 or more at treatment based on observed frequencies from the JH-AS cohort.

Once age, PSA, and GS have been updated for cases treated on active surveillance, we simulate a time from treatment to recurrence for each treated case based on a Cox model fit to the cases in the CaPSURE cohort; we restrict to cases with T-stage \leq T2a because cases still have early stage disease despite possible progression of PSA and grade. We correlate the times from diagnosis to treatment and from treatment to recurrence by generating them at the same percentile within their respective distributions. For cases that recur within their lifetimes, we simulate a time from recurrence to PCM from the Cox model fit to the JH-PCM data with T-stage \leq T2a. We use Weibull regression to extrapolate beyond the last observed failure times in the models for time to recurrence and PCM. Death due to competing causes is simulated independently using contemporary life tables.

Using the simulated data, we compute the cumulative incidence of PCM and the difference in life years overall and after treatment of each patient under active surveillance versus immediate radical prostatectomy.

In addition, we conduct 3 sensitivity analyses to determine the robustness of our results to the model inputs and assumptions. The first 2 pertain to the delay in treatment and disease progression under active surveillance, which we anticipate could influence the prognosis and survival of men under active surveillance. The first considers outcomes given a different distribution of time to treatment under

active surveillance, representing a protocol with a different surveillance intensity. The JH-AS cohort represents a relatively intense surveillance protocol, and we consider a less intensive protocol, with the distribution of times to treatment modeled after that observed in the Toronto Active Surveillance study (7). The second sensitivity analysis pertains to the extent of upgrading to GS 7 versus GS 8 or more while on active surveillance; we consider how PCM mortality following active surveillance would change under more versus less extensive upgrading. The third sensitivity analysis varies the extent of the presumed correlation between time to treatment under active surveillance and time to recurrence after radical prostatectomy using 2 methods. First, we generate time to recurrence after radical prostatectomy using a percentile that is close but not exactly equal to that used to generate time to treatment under active surveillance. Second, we only match percentiles in these distributions to cases treated because of biopsy grade progression.

Result

The JH-AS cohort included data on 769 cases with a median follow-up time of 2.7 years (range from 4 days to 15.0 years). Among these cases, PSA grew by 3.1% per year on average with a standard error of 0.5%. A total of 253 patients initiated treatment by the time of analysis and another 66 had progressed but had not yet initiated treatment (and so are censored). The median time to treatment among those treated was 5.9 years; the failure rate in the last year of observation (0.10) was used for extrapolation beyond the last observed treatment time. Table 1 presents the results of the model for GS progression by the time of treatment. A longer time to treatment and older age were associated with a greater chance of biopsy upgrade while on active surveillance. PSA and the annual change in PSA from diagnosis to treatment were not significantly associated with biopsy upgrading, and excluding the PSA covariates did not materially change our projections. The majority of upgrades (86%) were to GS 7.

The T-stage \leq T2a CaPSURE cohort for analysis of recurrence under delayed radical prostatectomy includes data on 3,470 men diagnosed after January 1994 and treated with radical prostatectomy, of whom 385 (11.1%) recurred after radical prostatectomy. The average age at diagnosis was 60.8 (range 39–80) years, and the median follow-up time was

3.6 years (range from 5 days to 15.3 years). The cumulative incidence of recurrence was 10.1% at 5 years and 11.1% at 10 years. The Weibull regression model used to extrapolate beyond the follow-up period had a median time to recurrence of 68.2 years. The low-risk CaPSURE cohort for analysis of recurrence under immediate radical prostatectomy includes data on 2,150 (62.0%) men, of whom 163 (7.6%) recurred after radical prostatectomy. The average age at diagnosis was 60.2 (range 39–79) years, and the median follow-up time was 3.7 years (range from 7 days to 15.3 years). The cumulative incidence of recurrence was 6.8% at 5 years and 7.6% at 10 years. The Weibull regression model used to extrapolate beyond the follow-up period had a median time to recurrence of 86.1 years. Table 2 summarizes the characteristics of the T-stage \leq T2a CaPSURE cohort and low-risk CaPSURE cohort. Table 4 presents the Cox model results for recurrence following immediate and delayed radical prostatectomy.

The JH-PCM cohort includes 1,745 men, of whom 963 (55.2%) received radical prostatectomy after January 1994 and had T-stage \leq T2a. The average age at diagnosis was 58.7 (range 39–74) years. A total of 63 (6.5%) men died of prostate cancer and the cumulative incidence of PCM was 3.4% at 5 years and 5.9% at 10 years after recurrence. The Weibull regression model used to extrapolate beyond the follow-up period had a median time to PCM of 122.4 years. Table 3 summarizes the JH-PCM data, and Table 4 presents the results of our model of PCM. Table 4 shows the strong association between time to recurrence and PCM, with each additional year of recurrence-free survival reducing the risk of PCM following recurrence by 35%.

Our distributions of age and PSA at diagnosis were based on low-risk cases diagnosed after 2004 in SEER (mean age 60.6 years; mean PSA 4.9 ng/mL). The model projected that 63.7% of cases on JH-AS would progress to treatment before they died of other causes. The projected 20-year cumulative incidence of PCM was 2.78% under active surveillance and 1.64% under immediate radical prostatectomy. The reduced incidence of PCM under immediate radical prostatectomy amounted to an average of 1.8 months of life saved per case (Table 5). Compared with men initially treated with radical prostatectomy, men on active surveillance had on average 6.4 more years of life free from treatment and its side effects.

Table 1. Logistic regression model of biopsy upgrading for active surveillance patients who were diagnosed after 1995 and underwent treatment ($n = 237$)

Covariate	Coefficient	OR	Standard error	P value
Intercept	-7.91	0.00	1.99	<0.001
Age at diagnosis	0.10	1.11	0.03	<0.001
PSA at diagnosis	0.01	1.01	0.05	0.821
Time to treatment (yrs)	0.21	1.23	0.08	0.008
Annual change of PSA	0.06	1.06	0.07	0.372

Table 2. Characteristics of T-stage \leq T2a and low-risk (T-stage \leq T2a, Gleason score \leq 6, and PSA level \leq 10 ng/mL) CaPSURE patients diagnosed after 1994

Characteristic	T-stage \leq T2a (n = 3,470)		Low risk (n = 2,150)	
	Number of patients	Percentage	Number of patients	Percentage
Age				
<40	1	0.03	1	0.05
40–49	189	5.45	122	5.67
50–59	1,256	36.20	856	39.82
60–69	1,677	48.33	1,008	46.88
70–79	344	9.91	163	7.58
\geq 80	3	0.08	—	—
Gleason score				
\leq 6	2,545	73.34	2,150	100.00
7	738	21.27	—	—
\geq 8	121	3.49	—	—
Missing	66	1.90	—	—
PSA at diagnosis (ng/mL)				
0–2.5	203	5.85	162	7.54
2.51–4.0	362	10.43	287	13.35
4.1–6.0	1,369	39.45	1,031	47.95
6.1–10.0	953	27.46	670	31.16
>10.0	451	13.00	—	—
Missing	132	3.81	—	—

As a sensitivity analysis of the intensity of surveillance, we modified the simulated time to treatment on active surveillance by a HR of 0.5 to lengthen the interval from diagnosis to treatment. Our goal was to approximate a less intensive surveillance regimen; the HR of 0.5 was motivated by the published time to treatment on the Toronto Active Surveillance study (7), which reported 84%, 72%, and 62% remaining on surveillance at 2, 5, and 10 years, respectively, versus 81%, 56%, and 34%, respectively, in the JH-AS cohort. Under this setting, the model projected that about 54.8% patients would progress to treatment within their lifetimes (vs. 63.7% projected for the JH-AS cohort), and the corresponding 20-year PCM would increase from 2.78% to 2.82%.

As a second sensitivity analysis, we altered the assumed fraction upgrading to GS \geq 8 while on active surveillance. In our baseline model, projections of posttreatment survival assume that 14% of upgraded cases are treated with GS 8 or more, based on the observed grade distribution at treatment in the JH-AS cohort. In our sensitivity analysis, we changed this fraction to 25% and, as a consequence, projected that 20-year PCM would increase from 2.75% to 3.04%.

Our third sensitivity analysis relaxed the correlation between the time to treatment under active surveillance and the time to recurrence following surgery. Under baseline assumptions, the Spearman correlation was 0.94. We projected that 20-year PCM under active surveillance would decrease to 2.38% with a correlation of 0.5% and to 1.69% with no correlation, resulting in a more comparable survival outcome relative to immediate radical prostatectomy.

When we only correlate times in these phases for cases on active surveillance who were treated because of biopsy upgrading (Spearman correlation 0.94), we projected that

Table 3. Characteristics of T-stage T2a JH-PCM data diagnosed after 1994 (n = 963)

Characteristic	Number of patients	Percentage
Age		
<40	1	0.10
40–49	71	7.37
50–59	440	45.69
60–69	431	44.76
70–79	20	2.08
Gleason score		
\leq 6	468	48.60
7	366	38.01
\geq 8	128	13.29
Missing	1	0.00
PSA at diagnosis (ng/mL)		
0–2.5	30	3.12
2.51–4.0	54	5.61
4.1–6.0	247	25.65
6.1–10.0	316	32.81
>10.0	316	32.81
Time to recurrence		
\leq 3 years	636	65.01
>3 years	337	34.99

Table 4. Cox proportional hazards regression model for recurrence following immediate and delayed radical prostatectomy based on CaPSURE data and for prostate cancer death based on T-stage \leq T2a JH-PCM data

Endpoint	Covariate	Coefficient	HR	95% Confidence interval	P value
Recurrence under immediate radical prostatectomy (fit to low-risk CaPSURE cohort)	Age	0.01	1.01	(0.98, 1.03)	0.527
	PSA	0.15	1.16	(1.07, 1.25)	<0.001
Recurrence under delayed radical prostatectomy (fit to T-stage \leq T2a CaPSURE cohort)	Age	0.01	1.01	(1.00, 1.03)	0.187
	PSA	0.03	1.03	(1.02, 1.03)	<0.001
	Gleason score				
	≤ 6	Ref.			
Prostate cancer mortality	7	0.47	1.59	(1.25, 2.03)	<0.001
	≥ 8	1.43	4.16	(2.92, 5.93)	<0.001
	Time to recurrence	-0.44	0.65	(0.51, 0.82)	<0.001
	Gleason score				
≤ 6	Ref.				
7	0.56	1.75	(0.96, 3.17)	0.066	
≥ 8	0.89	2.43	(1.21, 4.86)	0.012	

NOTE: The immediate radical prostatectomy model was fit to 2,150 cases with low-risk disease (T-stage \leq T2a, Gleason score \leq 6, and PSA level \leq 10 ng/mL); the delayed radical prostatectomy model, used to simulate times to recurrence following active surveillance, was fit to 3,470 cases with T-stage \leq T2a disease.

20-year PCM under active surveillance would decrease to 2.08%.

All sensitivity analyses produced only modest differences in cumulative PCM under active surveillance, and supported our projections that active surveillance would have minimal impact on life expectancy for low-risk prostate cancer cases.

Discussion

The recent results from the Prostate cancer Intervention Versus Observation Trial (PIVOT) have reinforced the notion that men diagnosed with low-risk prostate cancer may not need to be treated for their disease (18). In this article, we have presented a novel modeling framework for projecting the long-term outcomes and comparative effectiveness of active surveillance, the emerging approach of choice for low-risk prostate cases. Several studies (8, 13, 19) have suggested that active surveillance may produce PCM similar to that under immediate treatment. In contrast, our modeling framework does not make any quantitative assumptions about the likely impact of active surveillance on PCM; rather, the estimated impact arises as a mechanistic consequence of the timing of treatment and extent of disease progression under active surveillance.

The impact of active surveillance on PCM arises by connecting the phases in the model, each of which is informed by published data that we consider to be sufficiently mature and high quality for modeling purposes. We have used specific data sources and inputs to inform the model and

produce the specific findings reported; however, the framework developed is designed to be applicable for use with other data sources and in other settings. In particular, we plan to use this framework to explore the consequences of a variety of active surveillance approaches, varying the surveillance intervals and criteria for referral to treatment. In the present article, we used data from the CaPSURE cohort to model the interval from radical prostatectomy to recurrence because of its size, quality, and multisite nature. Detailed information on disease progression under active surveillance is necessary for modeling and this was available in the JH-AS data. Finally, we used information on disease progression after recurrence from the JH-PCM cohort. Although studies of these cohorts are highly cited and they are recognized as valuable, high-quality data sources, they are subject to limitations. The JH-AS cohort includes very low-risk cases (6) with PSA density \leq 0.15 ng/mL/cc and very low-volume disease. Consequently, our inferences about the risk of progression and PCM based on the JH-AS data may be lower than what would be expected for other low-risk active surveillance cohorts. The JH-PCM cohort reflects a single clinical site and may not be broadly representative. Our sensitivity analyses indicate that our conclusions seem to be relatively robust, but further investigation of the impacts of different inputs and data sources will be important to confirm this result.

Our main finding is that the absolute difference between the projected PCM under active surveillance or immediate radical prostatectomy is likely to be very modest,

Table 5. Comparison of outcomes of following active surveillance or immediate radical prostatectomy

	Immediate radical prostatectomy	Active surveillance
Treated	100.00%	63.68%
Treated with Gleason score ≤ 6	100.00%	40.69%
Treated with Gleason score 7	0.00%	19.76%
Treated with Gleason score ≥ 8	0.00%	3.23%
Time to treatment		
≤ 3 years	—	27.75%
> 3 years	—	35.93%
PSA at treatment (ng/mL)		
0–2.5	14.43%	14.55%
2.51–4.0	14.05%	13.73%
4.1–6.0	43.23%	30.09%
6.1–10.0	28.29%	30.42%
> 10.0	0.00%	11.21%
Cumulative incidence of recurrence from diagnosis		
20-year	24.54%	31.13%
Lifetime	29.38%	37.61%
Cumulative incidence of prostate cancer death		
20-year	1.64%	2.78%
Lifetime	2.00%	3.40%
Cumulative incidence of other cause death		
20-year	51.60%	51.13%
Lifetime	98.00%	96.60%
Years of life per person from treatment	19.66	13.30
Total years of life per person from diagnosis	19.66	19.50
Years of life per person lost because of prostate cancer	0.25	0.40

NOTE: Outcomes are based on 1 million simulated patients.

corresponding to a number needed to harm of 88 after 20 years. The difference in PCM averages approximately 1.8 months of life saved per individual, but men on active surveillance are able to live an average of 6.4 years longer without treatment than those treated immediately. Ultimately, the model projects that approximately 64% of men on active surveillance would be treated within their lifetimes under a surveillance protocol similar to the JH-AS cohort. Thus, under active surveillance, 36% of men could avoid being treated.

We focus on PCM rather than all-cause mortality because radical prostatectomy is an intervention designed to reduce PCM and other-cause death is so much more frequent than PCM in this cohort. As a result, analyses of all-cause mortality are generally not sensitive to real differences in PCM under radical prostatectomy versus active surveillance.

We did not explicitly model quality of life because well-validated utilities under active surveillance are not yet available. However, if there was no loss in quality of life under active surveillance and the impacts of treatment on quality of life were to be included, the posttreatment utility would only have to be 0.9 or less each year in the 5 years following treatment of immediate radical prostatectomy to have a lower quality-adjusted life expectancy than active surveillance (19.2 years vs. 19.3 years, respectively).

The model rests on several key assumptions. The first is that the risk of disease recurrence following radical prostatectomy is not affected by the active surveillance process itself so that the likelihood of recurrence depends similarly on measured prognostic variables whether radical prostatectomy is conducted immediately or after surveillance. This conditional independence assumption is a key underpinning of our model. We assume that, conditional on prognostic variables measured at the time of radical prostatectomy, time from radical prostatectomy to recurrence does not depend on whether radical prostatectomy was done at diagnosis or after active surveillance. An additional assumption is that the fate of a tumor under active surveillance is linked with the fate of that tumor once it is treated. Although this is a reasonably intuitive assumption, the way in which we operationalize it in the model (by simulating times to treatment and recurrence using similar percentiles within their respective distributions) is only one method of quantitatively representing this intuition. We note that results are somewhat sensitive to the resulting correlation between time to treatment and time to recurrence, with 20-year PCM varying from 1.67% to 2.78% as the correlation ranges from 0 to 0.94.

Our results are similar to those from the PIVOT study (18), which found modest absolute difference in 12-year PCM in (primarily GS ≤ 6) cases treated immediately with

radical prostatectomy (4.4%) or assigned to watchful waiting (7.4%). They also reflect the findings of another modeling study (20), which projected 0% to 1% absolute difference in PCM at 15 years under conservative management versus immediate curative treatment (we estimate 1.14% at 20 years). Our projected mortality under immediate radical prostatectomy (1.64% over 20 years) is lower than population-based results for low-risk cases diagnosed after 1994 in the SEER registry who received immediate radical prostatectomy (3.4% died of prostate cancer within 14 years), possibly reflecting selection of cases with more favorable risk profiles into the CaPSURE and JH-PCM cohorts.

The final statement from the 2011 NIH Consensus Conference on Active Surveillance (<http://consensus.nih.gov/2011/prostate.htm>) concluded that active surveillance has emerged as a viable option that should be offered to patients with low-risk cancer, but that there are many unanswered questions that require further research. Answering these questions via prospective, randomized studies is infeasible. Despite their limitations, alternative types of studies will have to be used and modeling should play an important role in this setting. The present work exemplifies how the power of modeling can be harnessed to project the long-term outcomes of active surveillance and should be useful in determining best practices for men with low-risk prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Welch H, Albertsen P. Prostate cancer diagnosis and treatment after the introduction of prostate. *J Natl Cancer Inst* 2009;101:1325–9.
2. Cooperberg M, Carroll P, Klotz L. Active surveillance for prostate cancer: progress and promise. *J Clin Oncol* 2011;29:3669–76.
3. Ip S, Dahabreh I, Chung M, Yu W, Balk E, Iovin R, et al. An evidence review of active surveillance in men with localized prostate cancer. Evidence report. AHRQ Publication No 12E003EF 2011;204:1–21.
4. Dall'Era M, Cowan J, Simko J, Shinohara K, Davies B, Konety B, et al. Surgical management after active surveillance for low-risk prostate cancer: pathological outcomes compared with men undergoing immediate treatment. *BJU Int* 2010;107:1232–7.
5. Tilling K, Garmo H, Metcalfe C, Holmberg L, Hamdy F, Neal D, et al. Active surveillance for localized prostate cancer. *Eur Urol* 2010;57:446–52.
6. Tosoian J, Trock B, Landis P, Feng Z, Epstein J, Partin A, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J Clin Oncol* 2011;29:2185–90.
7. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol* 2010;28:126–31.
8. van den Bergh R, Steyerberg E, Khatami A, Aus G, Pihl C, Wolters T, et al. Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? *Cancer* 2010;116:1281–90.
9. Stephenson A, Scardino P, Eastham J, Bianco F, Dotan Z, Fearn P, et al. Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. *J Natl Cancer Inst* 2006;98:715–7.
10. Kattan M, Wheeler T, Scardino P. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. *J Clin Oncol* 1999;17:1499–507.
11. Boorjian S, Thompson R, Tollefson M, Rangel L, Bergstralh E, Blute M, et al. Long-term risk of clinical progression after biochemical recur-

Authors' Contributions

Conception and design: B.J. Trock, M.R. Cooperberg, S.B. Zeliadt, H.B. Carter, R. Etzioni

Development of methodology: J. Xia, R. Gulati, S.B. Zeliadt, R. Etzioni
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B.J. Trock, P.R. Carroll, H.B. Carter, R. Etzioni
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Xia, R. Gulati, S.B. Zeliadt, H.B. Carter, R. Etzioni

Writing, review, and/or revision of the manuscript: J. Xia, B.J. Trock, M.R. Cooperberg, R. Gulati, S.B. Zeliadt, J.L. Gore, D.W. Lin, P.R. Carroll, H.B. Carter, R. Etzioni

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H.B. Carter

Study supervision: R. Etzioni

Acknowledgments

The authors thank Drs. Andrew Vickers and Pamela McMahon for helpful comments on the draft of this manuscript and Dr. Lurdes Y. T. Inoue for estimating the PSA growth parameters for the JH-AS data set.

Grant Support

This work was supported by Award Number U01CA157224 of the National Cancer Institute and the Centers for Disease Control. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute, the National Institutes of Health, or the Centers for Disease Control.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received May 22, 2012; revised July 23, 2012; accepted July 24, 2012; published OnlineFirst September 24, 2012.

rence following radical prostatectomy: the impact of time from surgery to recurrence. *Eur Urol* 2011;59:893–9.

12. Trock B, Han M, Freedland S, Humphreys E, DeWeese T, Partin A, et al. Prostate cancer-specific survival following salvage radiotherapy vs. observation in men with biochemical recurrence after radical prostatectomy. *JAMA* 2008;299:2760–9.
13. Hayes J, Ollendorf D, Pearson S, Barry M, Kantoff P, Stewart S, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer. *J Am Med Assoc* 2010;304:2373–80.
14. Lubeck D, Litwin M, Henning J, Stier D, Mazonson P, Fisk R, et al. The CaPSURE database: a methodology for clinical practice and research in prostate cancer. CaPSURE research panel. Cancer of the prostate strategic urologic research endeavor. *Urology* 1996;48:773–7.
15. Cooperberg M, Broering J, Litwin M, Lubeck D, Mehta S, Henning J, et al. The contemporary management of prostate cancer in the United States: lessons from the cancer of the prostate strategic urologic research endeavor (CaPSURE), a national disease registry. *J Urol* 2004;171:1393–401.
16. Porten S, Cooperberg M, Konety B, Carroll P. The example of CaPSURE: lessons learned from a national disease registry. *World J Urol* 2011;29:265–71.
17. Freedland S, Mangold L, Walsh P, Partin A. The prostatic specific antigen era is alive and well: prostatic specific antigen and biochemical progression following radical prostatectomy. *J Urol* 2005;174:1276–81.
18. Wiit T, Brawer M, Jones K, Barry M, Aronson W, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012;367:203–13.
19. Warlick C, Trock B, Landis P, Epstein J, Carter H. Delayed versus immediate surgical intervention and prostate cancer outcomes. *J Natl Cancer Inst* 2006;98:355–7.
20. Parker C, Muston D, Melia J, Moss S, Dearnaley D. A model of the natural history of screen-detected prostate cancer, and the effect of radical treatment on overall survival. *Br J Cancer* 2006;94:1361–8.

Clinical Cancer Research

Prostate Cancer Mortality following Active Surveillance versus Immediate Radical Prostatectomy

Jing Xia, Bruce J. Trock, Matthew R. Cooperberg, et al.

Clin Cancer Res 2012;18:5471-5478. Published OnlineFirst September 24, 2012.

Updated version Access the most recent version of this article at:
doi:[10.1158/1078-0432.CCR-12-1502](https://doi.org/10.1158/1078-0432.CCR-12-1502)

Cited articles This article cites 19 articles, 4 of which you can access for free at:
<http://clincancerres.aacrjournals.org/content/18/19/5471.full#ref-list-1>

Citing articles This article has been cited by 4 HighWire-hosted articles. Access the articles at:
<http://clincancerres.aacrjournals.org/content/18/19/5471.full#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.