VOLUME 28 · NUMBER 1 · JANUARY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Clinical Results of Long-Term Follow-Up of a Large, Active Surveillance Cohort With Localized Prostate Cancer

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Submitted May 28, 2009; accepted September 9, 2009; published online ahead of print at www.jco.org on November 16, 2009.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2801-126/$20.00

DOI: 10.1200/JCO.2009.24.2180

## ABSTRACT

### Purpose
We assessed the outcome of a watchful-waiting protocol with selective delayed intervention by using clinical prostate-specific antigen (PSA), or histologic progression as treatment indications for clinically localized prostate cancer.

### Patients and Methods
This was a prospective, single-arm, cohort study. Patients were managed with an initial expectant approach. Definitive intervention was offered to those patients with a PSA doubling time of less than 3 years, Gleason score progression (to 4 + 3 or greater), or unequivocal clinical progression. Survival analysis and Cox proportional hazard model were applied to the data.

### Results
A total of 450 patients have been observed with active surveillance. Median follow-up was 6.8 years (range, 1 to 13 years). Overall survival was 78.6%. The 10-year prostate cancer actuarial survival was 97.2%. Overall, 30% of patients have been reclassified as higher risk and have been offered definitive therapy. Of 117 patients treated radically, the PSA failure rate was 50%, which was 13% of the total cohort. PSA doubling time of 3 years or less was associated with an 8.5-times higher risk of biochemical failure after definitive treatment compared with a doubling time of more than 3 years ($P < .0001$). The hazard ratio for nonprostate cancer to prostate cancer mortality was 18.6 at 10 years.

### Conclusion
We observed a low rate of prostate cancer mortality. Among the patients who were reclassified as higher risk and who were treated, PSA failure was relatively common. Other-cause mortality accounted for almost all of the deaths. Additional studies are warranted to improve the identification of patients who harbor more aggressive disease despite favorable clinical parameters at diagnosis.

*J Clin Oncol 28:126-131. © 2009 by American Society of Clinical Oncology*

## INTRODUCTION

Active surveillance for favorable-risk, localized prostate cancer may reduce the risk of overtreatment of clinically insignificant prostate cancer while retaining the option of definitive therapy for those patients who are reclassified over time as higher risk.

Estimates in autopsy studies indicate that 50% of men older than 50 years of age have prostate cancer.[1,2] In the United States and Canada, the likelihood of being diagnosed is approximately 18%. The estimated lifetime probability of dying as a result of prostate cancer is 2.8%.[3] The incidence-to-mortality ratio is 6.4. The most common cause of death in men diagnosed with prostate cancer is cardiovascular disease.

The recently published European Randomized Study of Screening[4] demonstrated a 20% reduction in prostate cancer mortality in the screened arm. The number needed to treat for each death avoided was 48. These data emphasize that, although screening and early detection offer benefits in terms of reduced mortality, there is a significant risk of overtreatment. This dilemma is the rationale for a selective approach to treatment.

We performed a prospective, clinical trial to evaluate active surveillance, in which the decision to intervene was determined by prostate-specific antigen (PSA) kinetics and/or histologic progression. This strategy offers the attraction of individualizing therapy according to the biologic behavior of cancer. Patients with a slowly growing malignancy would be spared the adverse effects of radical treatment, whereas those with more rapidly progressive cancer would still potentially benefit from curative therapy. Our initial cohort was first reported in 2002.[5,6] This report represents an update and reanalysis of that experience.

 

**Table 1.** Clinical Stage Distribution

| Clinical Stage at Baseline | Total Patients | | Patients by Age (years) | | | |
|---|---|---|---|---|---|---|
| | | | < 70 | | ≥ 70 | |
| | No. | % | No. | % | No. | % |
| T1a | 1 | 0.2 | 1 | 0.5 | 0 | 0 |
| 1b | 26 | 5.8 | 16 | 7.3 | 10 | 4.3 |
| 1c | 302 | 67 | 157 | 71.7 | 145 | 62.8 |
| T2 | 3 | 0.7 | 0 | 0 | 3 | 1.3 |
| 2a | 80 | 18 | 32 | 14.6 | 48 | 20.8 |
| 2b | 22 | 5 | 6 | 2.7 | 16 | 6.9 |
| 2c | 12 | 3 | 5 | 2.3 | 7 | 3.0 |
| T3 | 4 | 0.9 | 2 | 0.9 | 2 | 0.9 |
| Total | 450 | | 219 | | 231 | |

## PATIENTS AND METHODS

A prospective, single-arm, cohort study was initiated in November 1995 to assess the feasibility of an observation protocol with selective, delayed intervention by using PSA kinetics and/or histologic progression as triggers for intervention. Favorable-risk patients were offered an initial surveillance approach. PSA was performed every 3 months for 2 years and then every 6 months in stable patients. A confirmatory biopsy was performed 6 to 12 months after the initial biopsy and then every 3 to 4 years until the patient reached 80 years old. Patients were reclassified as higher risk and offered radical intervention for the following criteria: PSA doubling time (DT) of less than 3 years; histologic upgrade on repeat prostate biopsy; and clinical progression.

For the first 4 years of the study, a PSA DT of 2 years was used as a trigger. However, this proved to be overly stringent, insofar as it identified only 10% of patients as high risk. In 1999, the trigger was increased to 3 years. Approximately 20% of patients in the cohort were offered intervention for a PSA DT less than 3 years.

Patients had an 8- to 14-core biopsy within a year after the initial biopsy (on the basis of the Vienna nomogram).[7] This confirmatory biopsy was intended to identify higher-grade cancer that had been missed on the original biopsy. When possible, particular attention was paid to the site of the previous positive biopsy and to the anterolateral horn. Subsequent biopsies were intended to identify biologic progression and were performed every 3 to 4 years. Patients with a borderline PSA DT underwent biopsy more frequently at the discretion of the managing physicians.

Clinical progression was defined as development of an unequivocal palpable nodule during surveillance. Histology of the nodule was evaluated by directed biopsies. If the nodule was confirmed as evidence of cancer progression, patients were offered definitive therapy.

Between 1995 and 1999, the study was offered to all favorable-risk patients (ie, Gleason 6 or less, PSA 10 ng/mL or less) and to patients older than age 70 years with PSA up to 15 ng/mL or Gleason up to 3 + 4.[5] Since January 2000, the study was restricted to favorable-risk patients only. This decision was based on the publication of more convincing evidence of a significant difference in natural history between Gleason 6 and 7[8] and an interest in studying a more homogeneous population. The phase II clinical trial was approval by the Sunnybrook Health Sciences Centre Research Ethics Board. From 1995 to 2002, informed consent was obtained from each participant. Beginning in 2003, the phase II study was terminated as a formal clinical trial, and active surveillance was offered as a treatment option to patients. The same data were collected prospectively.

### *Statistical Methods*

Survival analysis was performed in all patients and included Kaplan-Meier overall survival, cause-specific survival (CSS), time to stopping surveillance, and time to PSA failure. The 95% CI was calculated with the curves. The log-rank test was used to detect the difference in overall survival between patients who remained on surveillance and those who were reclassified and treated radically, or in time to PSA failure between patients with surgery treatment and patients with radiation. PSA failure was defined as a PSA greater than 0.2 ng/mL for patients who underwent surgery and the PSA nadir + 2 ng/mL for patients who received radiation. Patients who did not experience PSA failure until the last contact had PSA failure censored times.

The cumulative hazard ratio was calculated for nonprostate cancer to prostate cancer mortality. Hazard function is defined as the event rate at time $t$ conditional on survival until time $t$, $S(t)$, or later. It alternatively can be represented in terms of the cumulative hazard function, $-\log S(t)$. Cox proportional hazards regression analysis was applied to determine the hazard ratio between non–prostate cancer mortality and prostate cancer mortality. Stratification of age groups (≥ 70 or < 70 years) was considered in the cumulative hazard ratio analysis.

PSA DT was calculated by using the general linear mixed-model method previously described.[9] Univariate logistic regression analysis of the likelihood of being treated was performed on the three risk factors (ie, PSA at baseline $> 10$ ng/mL $v \leq 10$ ng/mL; stage at baseline $\geq 2$ $v < 2$; and Gleason score at baseline $> 6$ $v \leq 6$). A similar analysis was performed on the relationship between PSA DT and eventual post-treatment biochemical failure.

## RESULTS

The cohort consisted of 450 patients. Median age was 70.3 years. Median follow-up was 6.8 years. The distribution by grade, stage, and PSA is summarized in Tables 1, 2, and 3. Overall, 83% of patients had Gleason score of 6 or less, and 17% had Gleason 3 + 4 = 7. In addition,

**Table 2.** PSA Distribution

| PSA at Baseline, ng/mL | Total No. | | Patients by Age (years) | | | |
|---|---|---|---|---|---|---|
| | | | < 70 | | ≥ 70 | |
| | No. | % | No. | % | No. | % |
| 0-2.5 | 54 | 12 | 31 | 14 | 23 | 10 |
| > 2.5-5 | 112 | 25 | 73 | 33 | 39 | 17 |
| > 5-10 | 216 | 48 | 93 | 43 | 123 | 53 |
| > 10-15 | 56 | 12 | 18 | 8 | 38 | 16 |
| > 15 | 10 | 2 | 3 | 1.4 | 7 | 3 |
| Unknown | 2 | 0.4 | 1 | 0.5 | 1 | 0.4 |
| Total | 450 | | 219 | | 231 | |

Abbreviation: PSA, prostate-specific antigen.

**Table 3.** Stratification by Baseline Gleason Score and PSA

| Gleason Score | No. of Patients by PSA Range (ng/mL) | | | | | | No. of Patients by Age (years) | |
|---|---|---|---|---|---|---|---|---|
| | 0-2.5 | > 2.5-5 | > 5-10 | > 10-15 | > 15 | Total | < 70 | ≥ 70 |
| 3 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 |
| 4 | 5 | 1 | 2 | 1 | 0 | 9 | 7 | 2 |
| 5 | 7 | 11 | 20 | 5 | 1 | 44 | 27 | 17 |
| 6 | 32 | 74 | 141 | 35 | 8 | 290 | 144 | 148 |
| 7 | 6 | 13 | 40 | 13 | 0 | 72 | 19 | 53 |
| Total | 50 | 99 | 204 | 54 | 9 | 416 | 197 | 221 |

Abbreviation: PSA, prostate-specific antigen.

**Table 4.** Reasons for Intervention on Surveillance

| Reason for Treatment | No. of Patients | Patients (%) | |
|---|---|---|---|
| | | Treated (n = 135) | Total Cohort (n = 450) |
| Short PSA doubling time | 65 | 48 | 14 |
| Grade progression | 36 | 27 | 8 |
| T1 to T2 progression | 6 | 4 | 1 |
| Volume progression | 4 | 3 | 0.9 |
| Ureteral obstruction | 2 | 2 | 0.4 |
| Patient preference | 14 | 10 | 3 |
| Unknown | 8 | 6 | 2 |
| Total | 135 | 100 | 30 |

Abbreviation: PSA, prostate-specific antigen.

85% had PSA ≤ 10 ng/mL, and 12% had a PSA between 10 and 15 ng/mL. Seventy-one percent of patients were favorable risk by D'Amico criteria. The intermediate-risk patients either were older than 70 years or had significant comorbidity. Among the 450 patients, 97 patients (21.6%) died, and 353 are alive. The 10-year overall survival was 68% (95% CI, 62% to 74%; Fig 1A). There was no difference in overall survival between patients who remained on surveillance and those who were reclassified and treated radically ($P = .25$).

CSS is shown in Figure 1B. The 5- and 10-year CSS rates were 99.7% and 97.2%. All prostate cancer–related mortalities (n = 5) occurred in men who had been reclassified as higher risk and who were offered radical treatment. These deaths occurred at 3.7, 5.2, 5.3, 8.7, and 9.6 years after diagnosis.

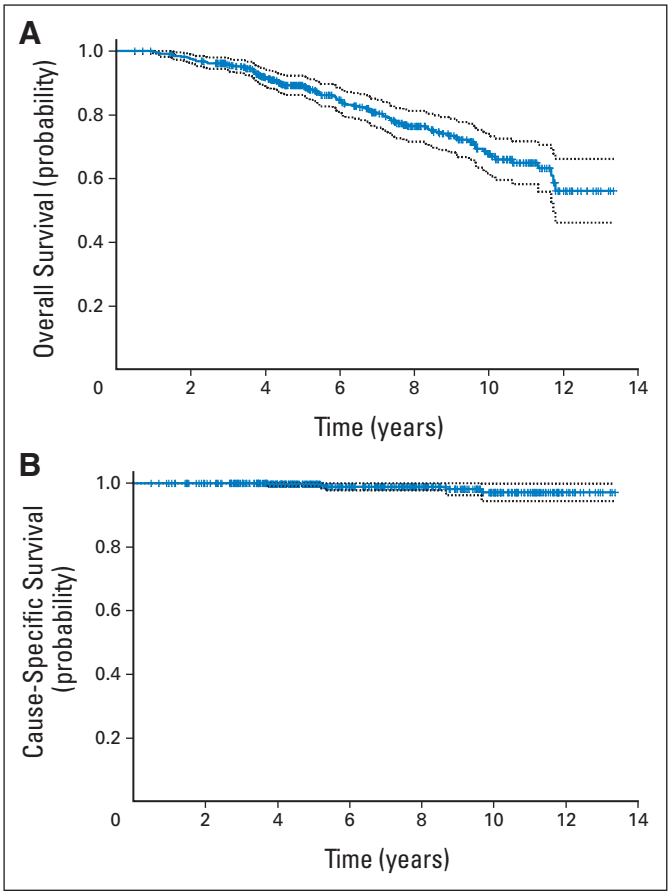


**Fig 1.** (A) Overall and (B) cause-specific survivals.

All five patients had a PSA DT less than 2 years that triggered a recommendation of radical therapy as per protocol. Radical intervention was undertaken in three of the five patients (radiation, n = 2; prostatectomy, n = 1). Two patients refused treatment. One of the patients who received radiation had Gleason 7 at baseline. Of the two radically treated patients who had Gleason 6, one had a radical prostatectomy within a year of diagnosis. His PSA continued to increase after surgery, and no nadir was observed. He experienced recurrence with metastatic disease within 1 year of treatment, and he experienced progression rapidly to hormone-refractory disease and death.

One patient, who was age 74 years at diagnosis, was upgraded to Gleason 8 on confirmatory biopsy at 20 months after diagnosis. His PSA DT at that point was 1.3 years. He received radiation therapy and adjuvant androgen deprivation therapy (ADT) approximately 2 years after study entry. At 6 years, he was found to have liver and bone metastases and was treated with ADT. At 7 years, he developed hormone-refractory disease and received docetaxel. He died 9 years and 8 months after entering on the study.

Thus, the cohort of 450 men contains only a single patient who was treated after a relatively prolonged period of observation (> 2 years) and subsequently experienced progression to metastatic disease and death.

### *Reasons for Discontinuing the Surveillance Protocol*

The reasons for discontinuing surveillance are summarized in Table 4. The choice of radiotherapy, surgery, or ADT was based on age, general health, and patient preference. Table 5 shows the treatments administered to patients who came off surveillance and their current

**Table 5.** Treatment and Status of Patients Coming Off Surveillance

| Vital Status | Treatment | | | |
|---|---|---|---|---|
| | XRT ± ADT | ADT Alone | Surgery | Total |
| Alive | 51 | 3 | 25 | 79 |
| Dead | 22 | 6 | 4 | 32 |
| Lost to Follow-up | 17 | 1 | 6 | 24 |
| Total | 90 | 10 | 35 | 135 |

Abbreviations: XRT, radiation therapy; ADT, androgen deprivation therapy.

  

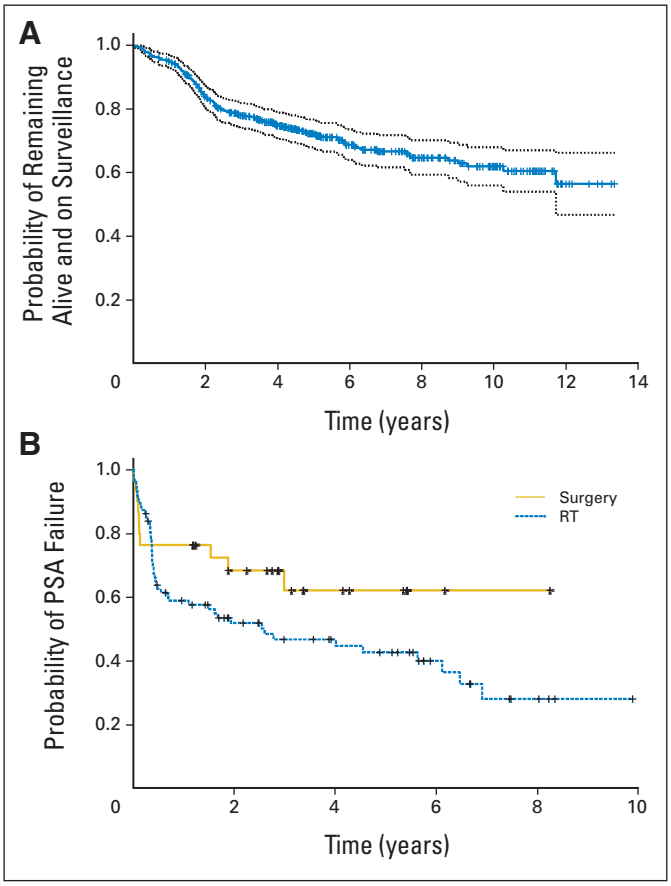


**Fig 2.** (A) Likelihood of remaining alive and on surveillance. (B) Prostate-specific antigen (PSA) failure in 117 patients treated with surgery or radiation after a period of surveillance.

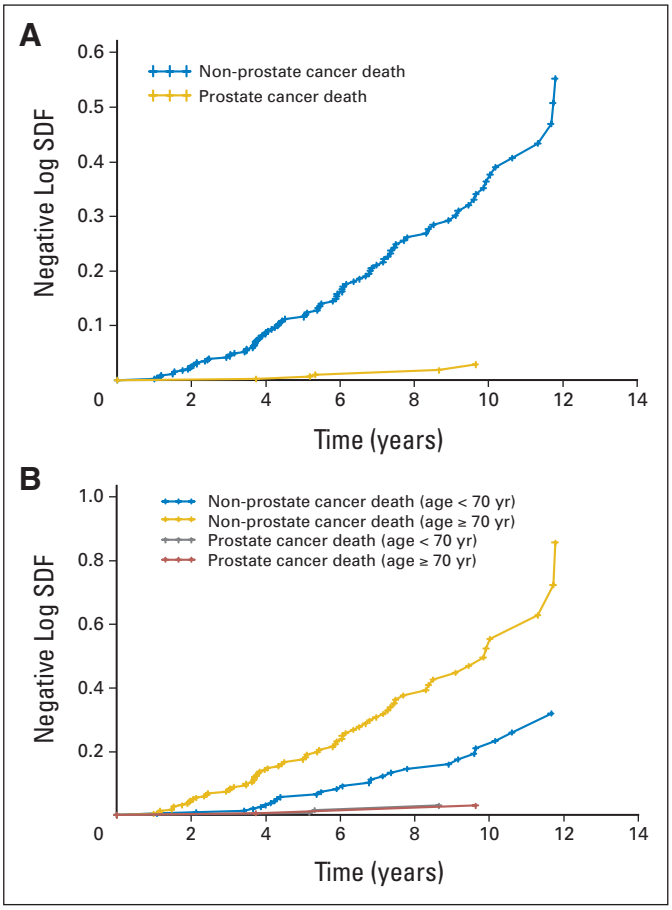


**Fig 3.** (A) Cumulative hazard ratio for non–prostate cancer to prostate cancer mortality. (B) Cumulative hazard ratio for mortality by cause and age, stratified around age 70 years.

statuses. Figure 2A shows the time to stopping surveillance with 95% CIs for the 450 patients. At 2, 5, and 10 years, the likelihood that a patient remained on surveillance was 84, 72, and 62%, respectively. Overall, 135 patients (30%) have been treated definitively. Figure 2B shows, in the treated patients, the time to PSA failure. One hundred twenty-five patients were treated radically; 90 received radiation therapy, and 35 underwent surgery. An additional 10 patients received ADT alone. PSA failure was defined as a PSA greater than 0.2 ng/mL for surgery patients and PSA nadir + 2 ng/mL for patients who received radiation. Of 117 patients on whom post-treatment PSAs were available, 59 patients (50.4%) had PSA failure. This represents 13% of the overall cohort. The 5-year recurrence-free survival was 47%. The median time to PSA failure was 48 months. PSA-free survival at 5 years was 62% in the patients treated with surgery and was 43% in patients treated with radiation. Log-rank test showed no difference finding between patients with surgery treatment and patients with radiation ($P = .12$).

Figure 3A shows the hazard ratio for non–prostate cancer mortality versus prostate cancer mortality over time. By using Cox proportional hazard model, the hazard ratio between two groups was 18.6, and the 95% CIs were 7.6 to 45.7. The hazard ratio is assumed to be constant, so it is independent of time.

Figure 3B shows this hazard ratio stratified by age ≥ 70 years or younger than 70 years. For men ≥ 70 years, the hazard ratio for non–prostate cancer to prostate cancer mortality was 33.3, and the 95% CI was 8.2 to 136. In men younger than 70 years, the hazard ratio was 8.76, and the 95% CI was 2.65 to 28.9. As expected, the risk of nonprostate cancer mortality is higher in older men. However, even in the men younger than 70 years, the risk of non–prostate cancer mortality was far higher than that of prostate cancer mortality.

Tables 6 show the univariate analysis of factors predicting for the likelihood of being treated: PSA at baseline greater than 10 versus ≤ 10 ng/mL; stage at baseline ≥ 2 versus less than 2; and Gleason score at baseline greater than 6 versus ≤ 6. The likelihood of being treated was related to Gleason score (odds ratio, 1.83; $P = .0233$), and T stage ≥ T2a (odds ratio, 2.02; $P = .0016$) but not to baseline PSA ($> 10$ *v* $\leq 10$; $P = .128$).

**Table 6.** Univariate Analysis of Predictive Baseline Factors for Definitive Intervention

| Variable | *P* | OR | 95% CIs |
|---|---|---|---|
| Stage at baseline (≥ T2a *v* < T2a) | .0016 | 2.022 | 1.305 to 3.133 |
| PSA at baseline (> 10 *v* ≤ 10) | .1275 | 1.527 | 0.886 to 2.633 |
| Gleason score at baseline (> 6 *v* ≤ 6) | .0233 | 1.834 | 1.086 to 3.097 |

Abbreviations: OR, odds ratio; PSA, prostate-specific antigen.

**Table 7.** Univariate Logistic Regression Analysis of the Relationship Between PSA DT and the Likelihood of Biochemical Failure After Radical Intervention

| PSA DT Variable, Years | *P* | OR | 95% CIs |
|---|---|---|---|
| 0-1 *v* 2-3 | .8902 | 1.114 | 0.240 to 5.180 |
| 1-2 *v* 2-3 | .2356 | 1.907 | 0.656 to 5.539 |
| 2-3 *v* ≥ 3 | .0042 | 3.362 | 1.465 to 7.718 |
| 0-2 *v* 2-3 | .3190 | 1.655 | 0.615 to 4.454 |
| < 3 *v* ≥ 3 | < .0001 | 8.500 | 4.840 to 14.926 |

Abbreviations: PSA, prostate-specific antigen; DT, doubling time; OR, odds ratio.

Among 450 patients in the study, there were 85 patients (18.9%) who were intermediate risk at baseline, defined as either PSA greater than 15 ng/mL, Gleason score of 7, or stage T3. Forty-nine patients (11%) remained untreated, and 36 patients (8%) were eventually treated. Among the 49 untreated patients, no patient had disease progression. Among the 36 who were treated, only one had experienced progression to metastatic disease and death.

Table 7 shows the univariate analysis in the patients who were treated with definitive local therapy of the relationship between subsequent PSA failure and PSA DT before treatment. PSA DT less than 3 years was associated with an 8.5-times greater likelihood of biochemical recurrence after treatment compared with a PSA DT ≥ 3 years (95% CI, 4.8 to 14.9; $P < .0001$). Among patients with a PSA DT less than 3 years, the absolute value of the DT (ie, 0 to 1, 1 to 2, or 2 to 3 years) was not predictive of biochemical failure after treatment.

## DISCUSSION

The updated data in this study contain a number of outcome measures that were not available when the first publication of this cohort was written (ie, in 2002). The overall survival is 78.6%, and the 10-year prostate cancer–specific survival is 97%. The hazard ratio for non–prostate cancer to prostate cancer mortality is 18.6.

At the date of preparation of this manuscript, there are six published, active surveillance series, including this one (Appendix Table A1, online only).[10-14] All rely on PSA kinetics and repeat biopsy to identify a subset of patients for definitive therapy. The cohorts constitute 2,168 patients in total, and the median follow-up was 43 months. More than 200 patients have greater than 10 years of follow-up. The overall survival in the cohort is 93%, and the disease-specific survival is 99.7%. About one third of patients have been treated definitively.

Seventy-one percent of the patients in this study fulfilled the D'Amico criteria for favorable risk. The remainder either had Gleason 3 + 4 cancer or had a PSA greater than 10 ng/mL. These patients were older than 70 years or had significant comorbidity. Despite a significant proportion of intermediate-risk patients in the cohort, the 10-year prostate cancer mortality is low. This supports the concept that, in a screened population, even intermediate-risk prostate cancer in men older than 70 years may present a relatively low risk of prostate cancer mortality.

Most watchful-waiting series (of observation with no treatment option) were initiated in the pre-PSA era and represent a nonscreened cohort.[15-17] A major feature of widespread PSA screening has been stage and volume migration. Thus, those early watchful-waiting patients would be expected to have had a significantly higher volume of cancer than a cohort of typical, screen-detected, favorable-risk patients and, if anything, a worse prognosis with conservative management.

A key concern in advocating for a policy of active surveillance is the risk that a patient, who appears favorable at diagnosis, will experience progression to incurability during the period of observation and will suffer avoidable prostate cancer mortality as a result of the delay in definitive treatment. The low mortality of favorable-risk prostate cancer suggests that this event is likely to be unusual. However, critics of the surveillance approach point to the Swedish observation series, reported by Johannson et al.[17] This series consisted of 223 patients managed with watchful waiting (no salvage option). Median follow-up, remarkably, was 21 years. CSS was 79% at 15 years and was 54% at 20 years. The annual risk of prostate cancer mortality was calculated at 15 per 1,000 people during the first 15 years but at 44 per 1,000 after 15 years on the basis of the 49 patients observed for more than 15 years. The implication is that, in younger patients with a long life expectancy, prostate cancer mortality will increase to unacceptable levels eventually.

However, in that cohort, the prostate cancer mortality among the patients with grade 1 disease was 8% at 7 years. In contrast, the 7-year cancer-specific mortality in our surveillance cohort is 1.1%. This suggests that the relative risk for prostate cancer mortality in a non screened, pre-PSA, watchful-waiting cohort (with no salvage option) is as much as seven times higher than a contemporary, screen-detected group managed with surveillance and selective, delayed intervention. Thus, the increase in prostate cancer mortality seen after 15 years of follow-up in the unscreened watchful waiting series of Johansson et al[17] may not be recapitulated in a screened, active surveillance cohort.

The PSA progression rate among the 125 patients offered definitive local therapy was 53% at 5 years. There was no significant difference between patients treated with surgery or radiation. A PSA DT of less than 3 years as the trigger for intervention was associated with an 8.5-times greater risk of PSA progression after definitive therapy compared with patients who had a PSA DT ≥ 3 years (in whom grade progression was the usual indication for intervention). This supports the concept that a PSA DT less than 3 years is a reliable marker for aggressive disease.

We believe this PSA failure rate in the treated patients should be interpreted in the following context: First, none of the stable cohort of untreated patients have experienced progression clinically. Thus, the appropriate denominator for PSA failure is the 450 patients in the total cohort. Therefore, the real PSA failure rate in the cohort is 59 of 450 patients, or 13%. This is comparable to PSA failure rates for radical prostatectomy or radiation for favorable-risk patients. Second, PSA DT less than 3 years and Gleason upgrading clearly identify a group of high-risk patients, despite favorable prognostic criteria at diagnosis. Third, PSA failure does not mean death as a result of prostate cancer.[18] In the Hopkins cohort, the 15-year prostate cancer mortality in men with Gleason 6 and 7 who had PSA recurrence before 3 years was 19%. Extrapolating this to the current cohort gives an overall cancer mortality of 3% at 15 years after recurrence (19% × 13%). In addition, the patients who underwent prostatectomy have, in most instances, been managed with early salvage radiation therapy, and the expectation is that half or more will have a complete response. A detailed description of the outcome of the treated patients will be the subject of a subsequent manuscript. Fourth, the mortality rate, with a median follow-up

  

of longer than 6.8 years, is extremely low (1%), and the ratio of other-cause to prostate cancer mortality is 18.6 to 1. Although the rate of cancer mortality may increase with longer follow-up, so will the rate of non–prostate cancer mortality. We believe the ratio of other-cause mortality to prostate cancer mortality is likely to remain stable over time. Finally, longer follow-up will be required to determine the impact of the PSA failure rate in this cohort on disease-specific survival.

In conclusion, active surveillance for favorable-risk prostate cancer and intermediate-risk disease in men older than 70 years is feasible and appears safe in the 10- to 15-year time frame. This strategy provides the benefit of an individualized approach on the basis of the demonstrated risk of clinical or biochemical progression with time. In this cohort, the likelihood of dying as a result of other causes was 18.6 times greater than the likelihood of prostate cancer death. Uncertainty remains regarding the long-term impact of delayed treatment in men reclassified as higher risk after a period of observation and repeat biopsy. This will require results from a prospective, randomized trial comparing surveillance to radical treatment (currently underway).

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Laurence Klotz, Andrew Loblaw
**Administrative support:** Laurence Klotz, Alexandre Mamedov, Andrew Loblaw
**Provision of study materials or patients:** Laurence Klotz, Andrew Loblaw
**Collection and assembly of data:** Laurence Klotz, Liying Zhang, Alexandre Mamedov, Andrew Loblaw
**Data analysis and interpretation:** Laurence Klotz, Liying Zhang, Andrew Loblaw
**Manuscript writing:** Laurence Klotz, Liying Zhang, Adam Lam, Robert Nam
**Final approval of manuscript:** Laurence Klotz, Liying Zhang, Adam Lam, Robert Nam, Alexandre Mamedov, Andrew Loblaw

## REFERENCES


1. Franks LM: Proceedings: Etiology, epidemiology, and pathology of prostatic cancer. Cancer 32: 1092-1095, 1973
2. Hølund B: Latent prostatic cancer in a consecutive autopsy series. Scand J Urol Nephrol 14:29-35, 1980
3. Canadian Cancer Statistics 2000. National Cancer Institute of Canada, Toronto, Canada, 2001
4. Schröder FH, Hugosson J, Roobol MJ, et al: Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 360:1320-1328, 2009
5. Choo R, Klotz L, Danjoux C, et al: Feasibility study: Watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J Urol 167:1664-1669, 2002
6. Klotz L: Active surveillance for prostate cancer: For whom? J Clin Oncol 23:8165-8169, 2005
7. Remzi M, Fong YK, Dobrovits M, et al: The Vienna nomogram: Validation of a novel biopsy strategy defining the optimal number of cores based on patient age and total prostate volume. J Urol 174:1256-1260, 2005
8. Fryback DG, Albertsen PC, Storer BE: Prostatectomy and survival among men with clinically localized prostate cancer. JAMA 276:1723-1724, 1996
9. Zhang L, Loblaw A, Klotz L: Modeling prostate specific antigen kinetics in patients on active surveillance. J Urol 176:1392-1397, 2006; discussion 1397-1398
10. van As NJ, Norman AR, Thomas K, et al: Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. Eur Urol 54:1297-1305, 2008
11. Carter HB, Kettermann A, Warlick C, et al: Expectant management of prostate cancer with curative intent: An update of the Johns Hopkins experience. J Urol 178:2359-2364, 2007
12. Soloway MS, Soloway CT, Williams S, et al: Active surveillance: A reasonable management alternative for patients with prostate cancer—The Miami experience. BJU Int 101:165-169, 2008
13. van den Bergh RC, Roemeling S, Roobol MJ, et al: Outcomes of men with screen-detected prostate cancer eligible for active surveillance who were managed expectantly. Eur Urol [e-pub ahead of print on September 17, 2008]
14. Khatami A, Aus G, Damber JE, et al: PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: Results from the European randomized study of screening for prostate cancer, Sweden section. Int J Cancer 120:170-174, 2007
15. Fleming C, Wasson JH, Albertsen PC, et al: A decision analysis of alternative treatment strategies for clinically localized prostate cancer: Prostate Patient Outcomes Research Team. JAMA 269:2650-2658, 1993
16. Wasson JH, Cushman CC, Bruskewitz RC, et al: A structured literature review of treatment for localized prostate cancer: Prostate Disease Patient Outcome Research Team. Arch Fam Med 2:487-493, 1993
17. Johansson JE: Expectant management of early stage prostatic cancer: Swedish experience. J Urol 152:1753-1756, 1994
18. Johansson JE, Andrén O, Andersson S, et al: Natural history of early, localized prostate cancer. JAMA 291:2713-2719, 2004