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Long-Term Follow-Up of a Large Active Surveillance Cohort of Patients With Prostate Cancer

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Long-Term Follow-Up of a Large Active Surveillance Cohort of Patients With Prostate Cancer

Laurence Klotz, Danny Vesprini, Perakaa Sethukavalan, Vibhuti Jethava, Liying Zhang, Suneil Jain, Toshihiro Yamamoto, Alexandre Mamedov, and Andrew Loblaw

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ABSTRACT

Purpose

Active surveillance is increasingly accepted as a treatment option for favorable-risk prostate cancer. Long-term follow-up has been lacking. In this study, we report the long-term outcome of a large active surveillance protocol in men with favorable-risk prostate cancer.

Patients and Methods

In a prospective single-arm cohort study carried out at a single academic health sciences center, 993 men with favorable- or intermediate-risk prostate cancer were managed with an initial expectant approach. Intervention was offered for a prostate-specific antigen (PSA) doubling time of less than 3 years, Gleason score progression, or unequivocal clinical progression. Main outcome measures were overall and disease-specific survival, rate of treatment, and PSA failure rate in the treated patients.

Results

Among the 819 survivors, the median follow-up time from the first biopsy is 6.4 years (range, 0.2 to 19.8 years). One hundred forty-nine (15%) of 993 patients died, and 844 patients are alive (censored rate, 85.0%). There were 15 deaths (1.5%) from prostate cancer. The 10- and 15-year actuarial cause-specific survival rates were 98.1% and 94.3%, respectively. An additional 13 patients (1.3%) developed metastatic disease and are alive with confirmed metastases ($n = 9$) or have died of other causes ($n = 4$). At 5, 10, and 15 years, 75.7%, 63.5%, and 55.0% of patients remained untreated and on surveillance. The cumulative hazard ratio for nonprostate-to-prostate cancer mortality was 9.2:1.

Conclusion

Active surveillance for favorable-risk prostate cancer is feasible and seems safe in the 15-year time frame. In our cohort, 2.8% of patients have developed metastatic disease, and 1.5% have died of prostate cancer. This mortality rate is consistent with expected mortality in favorable-risk patients managed with initial definitive intervention.

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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 patients who are reclassified over time as higher risk.

Beginning in 1995, we initiated 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. Our initial cohort was first reported in 2002,^{1,2} and a follow-up was reported in 2010 of 450 patients with 8-year follow-up.³ This report represents a reanalysis with 993 patients and up to 16 years of follow-up.

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 using PSA kinetics and/or histologic progression as triggers for intervention. Favorable and selected intermediate-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 within 12 months of the initial biopsy and then every 3 to 4 years until the patient reached 80 years old. Biopsies were performed according to the Vienna nomogram.⁴ Patients were reclassified as higher risk and offered radical intervention if they met the following criteria:

PSA doubling time (DT) of less than 3 years (from 1996 to 2008). Beginning in 2009, adverse PSA kinetics were discontinued as a sole trigger for intervention; rather,

they were an indication for closer scrutiny, either with repeat biopsies or a multiparametric magnetic resonance imaging (MRI).

Histologic upgrade on repeat prostate biopsy. Patients had an eight- to 14-core biopsy within a year after the initial biopsy. This targeted the site of the original positive core and the anterior and anterolateral zones. Subsequent biopsies were performed every 3 to 4 years.

Clinical progression as defined by development of an unequivocal palpable nodule during surveillance confirmed histologically to be disease progression.

Between 1995 and 1999, the study was offered to all low-risk patients (Gleason score ≤ 6 and PSA ≤ 10 ng/mL) and to patients older than age 70 years with PSA ≤ 15 ng/mL or Gleason score $\leq 3+4$ (7). Since January 2000, the study was restricted to low-risk patients (Gleason score ≤ 6 and PSA ≤ 10 ng/mL) or patients with favorable intermediate-risk disease (PSA 10 to 20 ng/mL and/or Gleason score 3+4) with significant comorbidities and a life expectancy of less than 10 years. The phase II clinical trial was approved by the Sunnybrook Research Ethics Board. From 1995 to 2002, informed consent was obtained from each participant. Beginning in 2003, active surveillance was offered as a management option to patients without a formal consent form. The same data were collected prospectively (also approved by the Research Ethics Board).

Statistical Methods

Survival analysis was performed in all patients, including Kaplan-Meier overall survival (OS), cause-specific survival (CSS), time to stopping surveillance, and time to PSA failure. Median follow-up time was calculated using the reverse Kaplan-Meier method.⁵ PSA failure was defined as a PSA more than 0.2 ng/mL after surgery and PSA nadir plus 2 ng/mL after radiation.

PSA DT was calculated using the general linear mixed model method.⁶ The Hosmer-Lemeshow test was performed for goodness-of-fit. Internal validation of the two final multivariable models was performed using the non-parametric bootstrap method.

RESULTS

Patient Population

The current cohort (data lock was May 5, 2013) comprises 993 patients. Median age is 67.8 years (range, 41 to 89 years). Two hundred six patients have been observed for more than 10 years and 50 patients for more than 15 years. Among all 993 patients, 149 died, 819 were alive, and 25 (2.5%) were lost to follow-up. The median follow-up time from the initial cancer diagnosis is 6.4 years (range, 0.2 to 19.8 years). Ten percent of patients were entered onto the study within the previous 2 years.

The distribution of patients by stage, grade, and PSA is shown in [Appendix Table A1](#) (online only) and [Table 1](#). Five percent of patients were diagnosed after a transurethral resection of the prostate, 74% had T1c disease, 17% had a palpable nodule, and 4% were classified as

having unknown stage. Baseline PSA was less than 2.5 ng/mL in 14%, 2.5 to 5 ng/mL in 30%, 5 to 10 ng/mL in 43%, greater than 10 ng/mL in 11%, and unknown in 2% of patients. Eighty-four percent of patients had a Gleason score of ≤ 6 , and 13% had a Gleason score of 7 (3+4). Baseline Gleason score could not be ascertained in 2% of patients (whose original biopsies were performed outside of our institution > 10 years ago). Twenty-one percent of patients were intermediate risk, of whom 3% had both PSA more than 10 ng/mL and Gleason score of 7.

Mortality Outcomes

OS is shown in [Figure 1](#). Among 993 patients, 149 patients (15%) died, and 844 patients were alive (censored rate, 85%). The OS range was 0.2 to 20.2 years. The 10- and 15-year OS rates were 80% and 62%, respectively. In univariable and multivariable Cox proportional hazards regression analyses, four significant predictive factors at baseline were found and remained in the multivariable model, namely, age ≥ 70 years (hazard ratio [HR], 2.87; 95% CI, 1.88 to 4.38; $P < .001$), transrectal ultrasonography volume (HR, 0.983; 95% CI, 0.973 to 0.993; $P = .001$), Gleason score more than 6 (HR, 1.70; 95% CI, 1.14 to 2.55; $P = .010$), and PSA values (log scale; HR, 1.52; 95% CI, 1.00 to 2.31; $P = .048$).

CSS is shown in [Figure 2](#). Among 993 patients, there were 15 deaths (1.5%) from prostate cancer, and 978 patients were alive or suffered death from other causes. All 15 patients who died of prostate cancer had confirmed metastases before death. An additional 13 patients (1.3%) with confirmed metastases are alive ($n = 9$) or died of well-documented other causes ($n = 4$). Thus, 2.8% ($n = 28$) of the entire cohort has developed metastatic disease. Median follow-up time for the patients with metastatic disease was 9.6 years (range, 2.3 to 16.4 years). Median time to metastasis was 7.3 years (95% CI, 5.81 to 8.76 years). Twelve (44%) of the 28 patients with metastases had a Gleason score of 3+4 (7) at diagnosis (v 13% of the overall cohort). Seven patients (26%) fulfilled Epstein criteria for very low risk.

Of the 15 patients who died of prostate cancer, seven patients received radiotherapy (RT), two had a radical prostatectomy (RP), four received androgen-deprivation therapy as sole therapy, and two refused treatment until metastatic disease developed. The 10- and 15-year actuarial CSS rates were 98%, and 94%, respectively. CSS did not differ between patients less than or greater than age 70 years ([Appendix Fig A1](#), online only; $P = .18$). Only two of 28 patients who developed metastasis were not upgraded to Gleason score ≥ 7 before developing metastatic disease. Neither of these two patients had surgical grading.

Table 1. Baseline Gleason score and PSA of Patients

| Gleason Score | Patients by PSA | | | | | | | | | | Patients by Age | | | | | | | |
|---------------|-----------------|----|------------------|----|-----------------|----|------------------|----|------------|----|-----------------|----|-------|----|------------|----|-----------------|----|
| | 0 to 2.5 ng/mL | | > 2.5 to 5 ng/mL | | > 5 to 10 ng/mL | | > 10 to 15 ng/mL | | > 15 ng/mL | | Unknown | | Total | | < 70 Years | | ≥ 70 Years | |
| | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| ≤ 6 | 124* | 89 | 267* | 90 | 349* | 82 | 62 | 70 | 15 | 71 | 20 | 80 | 837 | 84 | 536 | 90 | 301 | 75 |
| 7 | 13 | 9 | 21 | 7 | 64 | 15 | 25 | 27 | 5 | 23 | 4 | 16 | 132 | 13 | 45 | 8 | 87 | 22 |
| Not available | 3 | 2 | 9 | 3 | 9 | 2 | 1 | 1 | 1 | 5 | 1 | 4 | 24 | 24 | 14 | 2 | 10 | 3 |
| Total | 140 | | 297 | | 422 | | 88 | | 21 | | 25 | | 993 | | 595 | | 398 | |

Abbreviation: PSA, prostate-specific antigen.

*Low-risk group.

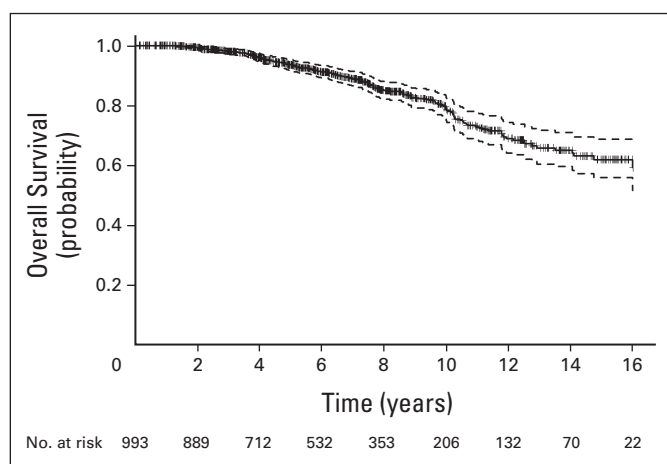


Fig 1. Kaplan-Meier overall survival curve with 95% CIs in all patients.

Univariable analysis was used to determine which factors were associated with early development of metastasis. Those with a PSA DT of less than 3 years experienced progression earlier than the group with longer PSA DT (median, 5.12 v 9.23 years, respectively; $P = .002$). The finding of a Gleason score of 8 to 10 on confirmatory biopsy was associated with early progression to metastasis (Gleason score of 6 v 8, $P = .034$; Gleason score of 7 v 8, $P = .023$).

The cumulative HR for non-prostate cancer to prostate cancer death in all patients was 9.2 (95% CI, 5.4 to 15.6; Appendix Fig A2, online only). Appendix Figure A3 (online only) shows this HR stratified by age \geq or less than 70 years. As expected, the risk of non-prostate cancer mortality was higher in men \geq 70 years old (HR, 11.5; 95% CI, 5.8 to 22.8), although even in men younger than age 70, the risk of non-prostate cancer mortality was almost six times higher than that of prostate cancer mortality (HR, 5.8; 95% CI, 2.4 to 13.8).

Intervention

To date, 267 (27%) of the 993 patients have been treated. Time to treatment is shown in Figure 3. At 5, 10, 15, and 20 years, 75.7%, 63.5%, 55.0%, and 55.0% of patients remain untreated and on surveillance, respectively. The reasons for discontinuing surveillance are listed in Table 2. PSA DT and grade of progression were the most

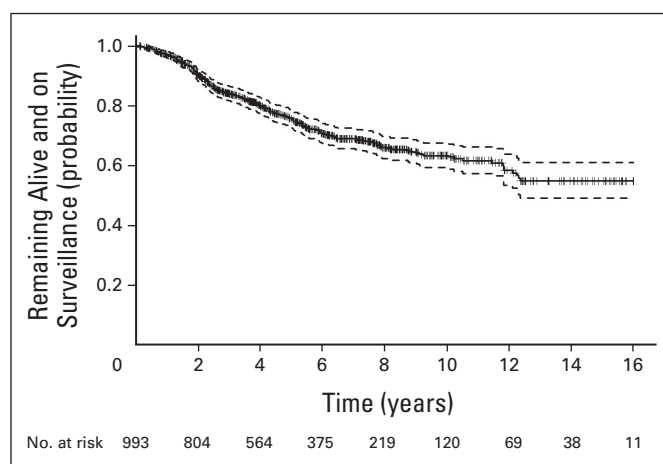


Fig 3. Time to intervention with 95% CIs in all patients.

common reasons for starting treatment. The choice of RT, RP, or androgen-deprivation therapy was based on age, general health, and patient preference.

Appendix Table A2 (online only) shows the univariable and multivariable analysis of factors predicting for the likelihood of being reclassified as higher risk. Age, tumor stage ($< v \geq T2$), PSA values, Gleason score ($\leq v > 6$), number of cores involved at baseline and on confirmatory biopsy, and prostatitis on biopsy all correlated with risk reclassification. The likelihood of being treated was related to Gleason score ($P = .005$; odds ratio [OR], 1.72) and baseline tumor category $\geq T2a$ ($P < .001$; OR, 1.96) but not to baseline PSA ($> v \leq 10$ ng/mL; $P = .59$) in the univariable analysis. In the multivariable analysis, Gleason score at 1 year ($P < .001$) and baseline PSA values (log scale; $P = .046$) were significantly predictive for intervention. This final multivariable model showed no evidence of lack of fit based on the Hosmer-Lemeshow statistic ($P = .235$). The probability of misclassification was 21.2%.

Post-treatment PSA levels were available for 249 patients (93%) treated after a period of surveillance, whereas the remaining 18 patients were treated elsewhere and post-treatment PSA levels could not be obtained. PSA failure has been calculated both from the date of diagnosis of prostate cancer, using the entire cohort as the denominator, and from the

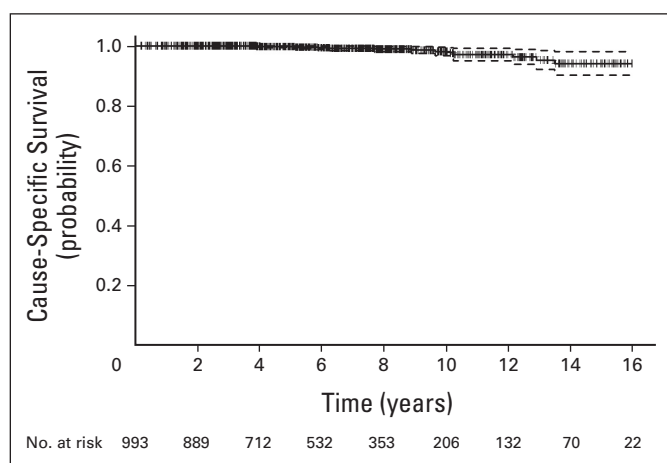


Fig 2. Kaplan-Meier cause-specific survival curve with 95% CIs in all patients.

| Reason for Intervention/ Treatment | No. of Patients | % of Patients | |
|--|--------------------|-------------------------------|---------------------------|
| | | Treated Patients (n = 267) | Total Cohort (N = 993) |
| Short PSA doubling time | 116 | 43.5 | 11.7 |
| Grade progression | 94 | 35 | 9.5 |
| Patient preference | 16 | 6 | 1.6 |
| Stage progression | 8 | 3 | 0.8 |
| Biopsy volume progression | 6 | 2 | 0.6 |
| Ureteral obstruction | 3 | 1 | 0.3 |
| Ultrasound lesion volume increase $> 2\times$ | 1 | 0.4 | 0.1 |
| Other | 2 | 0.8 | 0.2 |
| Not reported | 21 | 7.9 | 2 |
| Total | 267 | 100 | 27 |

Abbreviation: PSA, prostate-specific antigen.

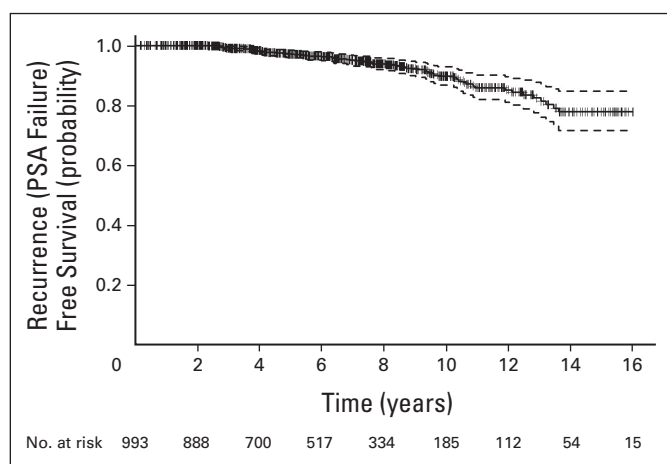


Fig 4. Time from diagnosis to prostate-specific antigen (PSA) failure (as proportion of all patients).

date of treatment using the treated patients as the denominator. Of the 249 patients, 63 (25%) experienced a PSA failure, representing 6% of the overall cohort (63 of 993 patients). As a proportion of the entire surveillance cohort (Fig 4), the 5- and 10-year biochemical disease-free survival rates from the time of diagnosis were 97.2% and 89.8%, respectively. The 5- and 10-year biochemical disease-free survival rates from the time of treatment as a proportion of the treated patients were 77% and 60%, respectively (Appendix Fig A4, online only). Of the 75 patients treated with RP and 148 patients treated with RT, 25% and 24% experienced PSA failure, respectively. The biochemical no evidence of disease survival rates after RP at 5, 10, and 15 years from the date of treatment were 80%, 65%, and 54%, respectively; in patients treated with RT, the rates were 79%, 60%, and 48%, respectively. This difference in biochemical no evidence of disease failure between RP and RT was not significant ($P = .60$), notwithstanding the difference in definitions of PSA failure between these groups. The PSA failure rates in the treated patients at 5, 10, and ≥ 14 years from the date of diagnosis as a proportion of the whole cohort were 3%, 10%, and 22%, respectively.

Appendix Table A3 lists the univariable and multivariable factors predicting for biochemical failure after intervention. Factors predicting for PSA failure were age, tumor stage, log PSA at baseline, baseline Gleason score, PSA DT, and percentage and number of cores involved on the initial biopsy. Neither the presence of prostatic intraepithelial neoplasia nor atypical small acinar proliferation predicted for biochemical failure after treatment. Biopsy findings were a trigger for intervention in 35% of the treated patients. However, number of biopsies, Gleason score, and number of cores involved on the biopsy triggering intervention were not significantly predictive for biochemical failure after treatment. Patients with longer duration of surveillance had a lower risk of biochemical failure after treatment (OR, 0.82; 95% CI, 0.74 to 0.89). A PSA DT of less than 3 years was associated with a 7.8-fold (95% CI, 4.4 to 13.7-fold) greater likelihood of biochemical recurrence after treatment compared with a PSA DT of ≥ 3 years. Among patients with a PSA DT of 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. In the multivariable analysis, duration of active surveillance ($P < .001$) and baseline PSA values (log scale; $P = .014$) were significantly predictive for PSA failure after definitive therapy. This final multivariable model showed no evidence of lack of fit based on the Hosmer-

Lemeshow statistic ($P = .902$). The probability of misclassification was only 6.5%.

DISCUSSION

Active surveillance has been increasingly accepted as a safe approach to favorable-risk prostate cancer in the 5- to 10-year time frame. In this series, follow-up is extended to 16 years. Two hundred six patients have been observed for more than 10 years and 60 patients for more than 15 years. The 10- and 15-year actuarial CSS rates are 98.1% and 94.3%, respectively. Only 15 patients in this cohort of 993 patients have died of prostate cancer, and an additional 13 patients have developed metastatic disease. The OS rate is 85.0%. Younger patients were not at increased risk for prostate cancer mortality. Post hoc power analysis determined that our study achieved greater than 99% power to contrast the 15-year prostate cancer mortality between 5.7% (Fig 2) in our study and 22% in the study by Albertsen et al.⁷

There are seven active surveillance series in the literature, including this one (Table 2), constituting more than 4,000 patients.^{3,8-12} OS in the combined cohort is 93%, and the disease-specific survival is 99.7%. One third of patients have been treated definitively. The data reported here extend the confidence regarding the indolent and non-lethal nature of most favorable-risk prostate cancer beyond 15 years.

Twenty-five percent of the patients in this study fulfilled the D'Amico criteria for intermediate risk. Nonetheless, the 15-year prostate cancer mortality is low. This supports the concept that in a screened population, selected men older than age 70 years with intermediate-risk prostate cancer are candidates for surveillance.

Popiolek et al¹³ reported prostate cancer mortality in low-grade patients managed with watchful waiting (with no option of radical intervention) observed for more than 30 years. In the low-risk group, prostate cancer mortality was 13% overall and was 11% and 28% at 15 and 20 years, respectively. These patients, importantly, were not offered delayed definitive intervention. This likely explains the two-fold greater 15-year prostate cancer mortality in the experience of Popiolek et al¹³ compared with this active surveillance cohort (11% v 5.7%, respectively).

The PSA progression rates among the 249 evaluable patients offered definitive local therapy 5 and 10 years after the therapeutic intervention were 23% and 41%, respectively. More meaningfully, the rates of all patients on surveillance who were treated and went on to experience subsequent PSA failure were 2.8% and 10.2% at 5 and 10 years after diagnosis, respectively. This is comparable to the outcome of radiation and surgery for favorable-risk disease.

A PSA DT of less than 3 years as the trigger for intervention was associated with a 7.8-fold greater risk of PSA progression after definitive therapy compared with patients with a PSA DT ≥ 3 years (in whom grade progression was the usual indication for intervention). This supports the concept that a PSA DT of less than 3 years is a marker for aggressive disease. It demonstrates sensitivity but lacks specificity.¹⁴ We previously reported that in 300 men who remained on surveillance long term, none of whom had clinical or pathologic progression, 50% had at least one trigger for intervention at some point during the follow-up period.¹⁵ Therefore, relying on PSA kinetics to determine who to treat would result in significant overtreatment.

The PSA failure rate of 25% in the treated patients at 10 years compares favorably with our previous report, where it was approximately

50%.³ That included many patients from the late 1990s. Because confirmatory biopsies were not mandatory until 2002, those men who were risk reclassified with higher-grade disease were diagnosed later. They were treated in most cases with 66 Gy of radiation, a dose that today is considered subtherapeutic, and were managed on surveillance in a period when experience with this approach was limited and decision making more ad hoc. Ten percent of the overall cohort experienced post-treatment PSA failure, consistent with PSA failure after radiation or surgery in a favorable-risk cohort.^{16,17} Furthermore, most of the surgically treated patients with PSA failure received effective salvage RT. Over 1,000 bootstrap samples, the SEs of coefficients for significant factors predicting for therapeutic intervention and for PSA failure after definitive therapy in the final multivariable models can be found in [Appendix Tables A2 and A3](#). Compared with the original model estimates (SE) for those significant predictive factors in the multivariable analyses, the bias of estimator or SE was similar between the original SE and the bootstrapping SE for the two models. Therefore, the reproducibility of the models was confirmed. We conclude that these clinical parameters contributed significantly to the therapeutic intervention and to the PSA failure after treatment after validation by the bootstrap approach.

Active surveillance is an evolving strategy. The major limitation is that a significant proportion of patients diagnosed with Gleason score 6 cancer harbor higher-grade disease. The ability to identify earlier and more accurately those patients with occult Gleason pattern 4 and 5 cancer is likely to result in improved results, including a decrease in PSA failure rates in the risk-reclassified patients and lower metastasis and mortality rates. This would also offer reassurance to those patients not found to have higher-risk disease. Both multiparametric MRI and molecular biomarkers show promise in providing this opportunity. We and others have incorporated MRI into patient decision making. However, the cohort described here, 97% of whom remained free of metastatic disease or prostate cancer mortality and 55% of whom avoided any treatment, was largely managed without the benefit of MRI.

This study had some limitations. Patients were graded according to the Gleason grading system at the time of diagnosis. We did not perform International Society of Urological Pathology–standard regrading. Thus, many of the patients graded as Gleason score 6 during the period from 1996 to 2005 might be graded as Gleason score 7 using the modified Gleason system.

Active surveillance for favorable-risk and select early intermediate-risk prostate cancer is feasible and seems to be safe over 15 years. This strategy provides the benefit of a personalized approach based on the demonstrated risk of clinical or biochemical progression with time. In this cohort, the likelihood of dying of other causes was 9.2 times greater than the likelihood of prostate cancer death. Although prostate cancer mortality increased with longer follow-up, only 2.8% of patients have developed metastatic disease and 1.5% have died of prostate cancer. These findings are consistent with expected mortality in favorable-risk patients managed with initial definitive intervention.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Laurence Klotz, Danny Vesprini, Andrew Loblaw

Collection and assembly of data: Laurence Klotz, Perakaa Sethukavalan, Vibhuti Jethava, Suneil Jain, Toshihiro Yamamoto, Alexandre Mamedov, Andrew Loblaw

Data analysis and interpretation: Laurence Klotz, Danny Vesprini, Liying Zhang, Suneil Jain, Andrew Loblaw

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

- 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
- Klotz L: Active surveillance for prostate cancer: For whom? *J Clin Oncol* 23:8165-8169, 2005
- Klotz L, Zhang L, Lam A, et al: Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol* 28:126-131, 2010
- 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
- Altman DG, De Stavola BL, Love SB, et al: Review of survival analyses published in cancer journals. *Br J Cancer* 72:511-518, 1995
- Zhang L, Loblaw A, Klotz L: Modeling prostate specific antigen kinetics in patients on active surveillance. *J Urol* 176:1392-1397, 2006
- Albertsen PC, Hanley JA, Fine J: 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA* 293:2095-2101, 2005
- 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
- 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
- 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
- Roemeling S, Roobol MJ, de Vries SH, et al: Active surveillance for prostate cancers detected in three subsequent rounds of a screening trial: Characteristics, PSA doubling times, and outcome. *Eur Urol* 51:1244-1250, 2007
- 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
- Popiolek M, Rider JR, Ondren O, et al: Natural history of early localized prostate cancer: A final report from three decades of follow up. *Eur Urol* 63:428-435, 2013
- Vickers AJ, Savage C, O'Brien MF, et al: Systematic review of pretreatment prostate-specific antigen velocity and doubling time as predictors for prostate cancer. *J Clin Oncol* 27:398-403, 2009
- Loblaw A, Zhang L, Lam A, et al: Comparing prostate specific antigen triggers for intervention in men with stable prostate cancer on active surveillance. *J Urol* 184:1942-1946, 2010
- Kane CJ, Im R, Amling CL, et al: Outcomes after radical prostatectomy among men who are candidates for active surveillance: Results from the SEARCH database. *Urology* 76:695-700, 2010
- Lukka H, Hayter C, Julian JA, et al: Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. *J Clin Oncol* 23:6132-6138, 2005
- Efron B: Bootstrap methods: Another look at the jackknife. *Ann Statist* 7:1-26, 1979

GLOSSARY TERMS

active surveillance: an approach to management of suspected or proven malignancy felt to pose a low risk of progression in the short to intermediate term. Tumors are observed closely with blood tests, imaging, and/or serial biopsy, and intervention is undertaken if/when there is evidence of tumor growth or progression.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Long-Term Follow-Up of a Large Active Surveillance Cohort of Patients With Prostate Cancer**

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Appendix

Table A1. Clinical Stage Distribution

| Clinical Tumor Stage at Baseline | Total Patients | | Patients by Age | | | |
|----------------------------------|----------------|------|-----------------|------|------------|------|
| | | | < 70 Years | | ≥ 70 Years | |
| | No. | % | No. | % | No. | % |
| T1a | 17 | 1.7 | 12 | 2.0 | 5 | 1.2 |
| T1b | 31 | 3.1 | 17 | 2.9 | 14 | 3.5 |
| T1c | 739 | 74. | 462 | 77.5 | 277 | 69.6 |
| T2 | 3 | 0.3 | 2 | 0.3 | 1 | 0.2 |
| T2a | 126 | 12.7 | 61 | 10.2 | 65 | 16.3 |
| T2b | 25 | 2.5 | 8 | 1.3 | 17 | 4.2 |
| T2c | 15 | 1.5 | 7 | 1.1 | 8 | 2.0 |
| Unknown | 37 | 3.7 | 26 | 4.3 | 11 | 2.7 |
| Total | 993 | | 595 | | 398 | |

Table A2. Univariable and Multivariable Logistic Regression Analysis of Factors Predicting for Therapeutic Intervention and Comparing Final Multivariable Model Estimations on SE of Predictive Factors Using the Original Data and 1,000 Bootstrapping Samples

| Predictive Factor | P | Odds Ratio | 95% CI |
|---|--------|------------|-----------------|
| Univariable analysis | | | |
| Age at baseline | .0042 | 1.026 | 1.008 to 1.044 |
| T stage at baseline ($\geq v < T2$) | .0002 | 1.955 | 1.377 to 2.762 |
| Gleason score at baseline ($> v \leq 6$) | .0053 | 1.724 | 1.170 to 2.517 |
| Log of PSA at baseline (continuous variable) | < .001 | 1.721 | 1.294 to 2.306 |
| Gleason 4 pattern (yes v no) | .0029 | 1.795 | 1.216 to 2.628 |
| Gleason score on confirmatory biopsy at 1 year | < .001 | 3.771 | 2.439 to 5.996 |
| Short PSA DT ≤ 3 years (yes v no) | < .001 | 6.286 | 4.012 to 10.020 |
| Greatest % of cores involved at first biopsy | < .001 | 1.013 | 1.005 to 1.021 |
| Prostatitis on first biopsy (yes v no) | .0531 | 0.681 | 0.456 to 0.996 |
| No. of cores on confirmatory biopsy at 1 year | < .001 | 1.400 | 1.244 to 1.583 |
| Greatest % of cores on confirmatory biopsy at 1 year | .0204 | 1.012 | 1.002 to 1.022 |
| Multivariable analysis* | | | |
| Gleason score on confirmatory biopsy at 1 year | < .001 | 3.375 | 2.171 to 5.399 |
| Log of PSA at baseline (continuous variable) | .0461 | 1.781 | 1.018 to 3.180 |
| Internal validation using original data and 1,000 bootstrapping samples | | | |
| Gleason score on confirmatory biopsy at 1 year | | | |
| Original SE | | | 0.232 |
| Bootstrap SE | | | 0.247 |
| Log of PSA at baseline (continuous variable) | | | |
| Original SE | | | 0.289 |
| Bootstrap SE | | | 0.328 |

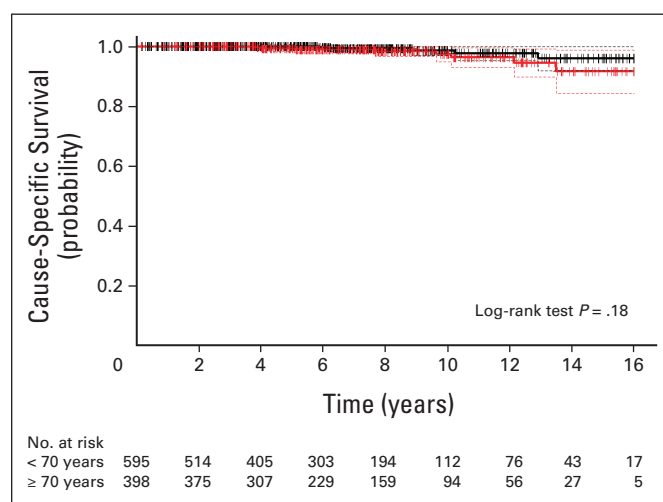
Abbreviation: DT, doubling time; PSA, prostate-specific antigen.

*Short PSA DT ≤ 3 years was excluded in the multivariable logistic regression analysis because it was a criteria for treatment.

Table A3. Univariable and Multivariable Logistic Regression Analysis of Factors Predicting for PSA Failure After Definitive Therapy After Initial Surveillance and Comparing Final Multivariable Model Estimations on SE of Predictive Factors Using Original Data and 1,000 Bootstrapping Samples

| Variable | P | Odds Ratio | 95% CI |
|--|----------|------------|-----------------|
| Univariable analysis | | | |
| Age at baseline | .0224 | 1.038 | 1.006 to 1.073 |
| T stage at baseline ($\geq v < T2$) | .0085 | 2.139 | 1.190 to 3.714 |
| Log of PSA at baseline (continuous variable) | .0109 | 1.999 | 1.185 to 3.444 |
| Gleason score at baseline | .3174 | 1.279 | 0.774 to 2.022 |
| Gleason score $> v \leq 6$ at baseline | .0145 | 2.150 | 1.129 to 3.885 |
| Gleason score on confirmatory biopsy at 1 year | .0081 | 2.266 | 1.221 to 4.171 |
| Gleason score before intervention | .9902 | 0.998 | 0.698 to 1.413 |
| No. of biopsies | .7571 | 1.043 | 0.793 to 1.349 |
| Short PSA DT ≤ 3 years (yes v no) | $< .001$ | 7.801 | 4.393 to 13.667 |
| Duration on active surveillance (years) | $< .001$ | 0.817 | 0.738 to 0.894 |
| No. of cores involved on confirmatory biopsy at first time | .1356 | 1.070 | 0.962 to 1.162 |
| No. of cores involved before intervention | .8792 | 0.996 | 0.918 to 1.036 |
| Greatest % of cores involved at first time | .0719 | 1.012 | 0.998 to 1.026 |
| No. of cores involved on confirmatory biopsy at 1 year | .0074 | 1.308 | 1.069 to 1.592 |
| Greatest % of cores on confirmatory biopsy at 1 year | .0305 | 1.018 | 1.001 to 1.035 |
| Multivariable analysis* | | | |
| Duration of active surveillance | $< .001$ | 0.809 | 0.730 to 0.887 |
| Log of PSA at baseline (continuous variable) | .0140 | 1.945 | 1.156 to 3.344 |
| Internal validation using original data and 1,000 bootstrapping samples | | | |
| Duration of active surveillance | | | |
| Original SE | | | 0.050 |
| Bootstrap SE | | | 0.051 |
| Log of PSA at baseline (continuous variable) | | | |
| Original SE | | | 0.271 |
| Bootstrap SE | | | 0.252 |

Abbreviation: DT, doubling time; PSA, prostate-specific antigen.

*Short PSA DT ≤ 3 years was excluded in the multivariable logistic regression analysis because it was a criteria for treatment.**Fig A1.** Kaplan-Meier cause-specific survival curves stratified by age less than or ≥ 70 years (log-rank test, $P = .13$).

Long-Term Follow-Up of a Large Active Surveillance Cohort

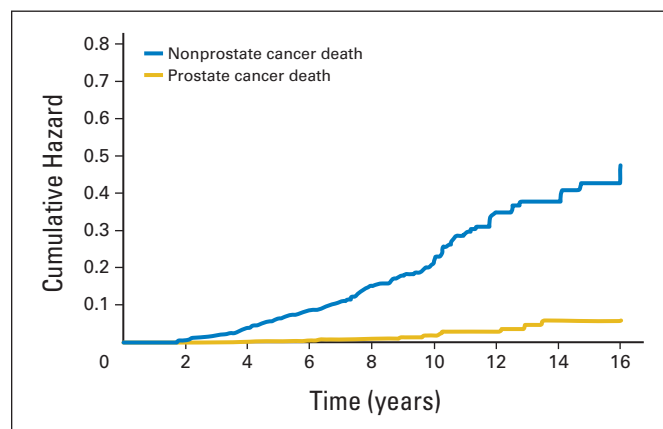


Fig A2. Cumulative hazard ratio of non-prostate cancer death (blue line) to prostate cancer death (gold line).

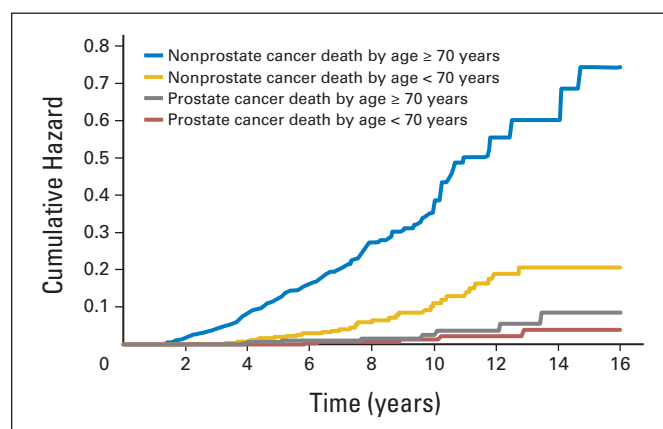


Fig A3. Cumulative hazard of non-prostate cancer death stratified by age ≥ 70 years (blue line) or by age less than 70 years (gold line) and of prostate cancer death stratified by age ≥ 70 years (gray line) or by age less than 70 years (red line).

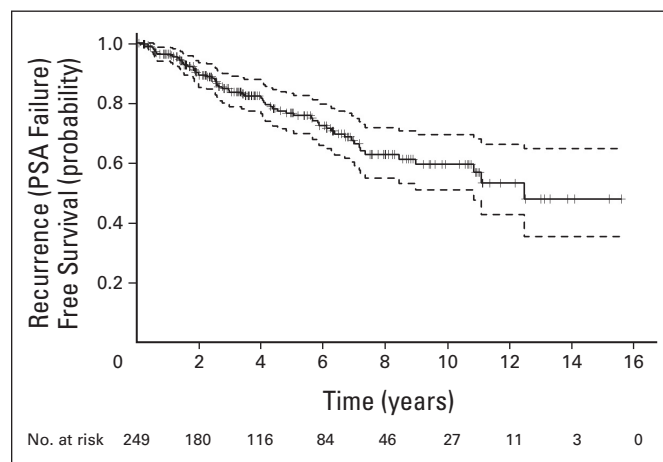


Fig A4. Time from treatment to prostate-specific antigen (PSA) failure (treated patients only).