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# Long-term Outcomes Following Active Surveillance of Low-grade Prostate Cancer: A Population-based Study Using a Landmark Approach

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**Study Need and Importance:** Treatment options for low-risk prostate cancer (PC) commonly include active surveillance (AS), surgery, and radiation therapy, but no high-level evidence has shown any one treatment strategy to be superior to another in low-grade PC. Although reports from single academic institutions on long-term outcomes for AS have been promising, with excellent PC-specific survival of 99%-100% at 10 years, cogent population-level data are lacking. Generally, published studies feature highly selected patients with very low–risk PC, protocol-based follow-up, and median follow-up of roughly 5 years. No study has published long-term oncologic outcomes of AS at a population level.

**What We Found:** In this retrospective, population-based study, we compared long-term cancer outcomes of 21,282 men with low-grade PC managed with AS to those with initial treatment. We used 2 complementary analytical approaches to reduce bias. Our results (with a median follow-up of 10 years) suggest that AS was associated with slightly worse long-term metastasis-free survival, overall survival, and PC-specific survival compared with initial treatment (see Table).

**Limitations:** Our study lacks data on some prognostic variables such as cancer staging and PSA that may influence treatment choice and outcome.

**Interpretation for Patient Care:** In this real-world study of long-term outcomes in men with low-grade PC, AS is associated with excellent long-term metastasis-free survival and overall survival. However, long-term PC-specific survival was slightly inferior to initial treatment (1% worse at 10 years with AS); this must be balanced against known harms of over-treatment. Minor differences in long-term outcomes may be due to less restrictive inclusion criteria, less rigid follow-up, or the effects of initial treatment. With more contemporary use of MRI and transperineal biopsy, the results of AS will also likely improve and reduce any differences with radical treatment.

**Table.** *Cox Proportional Survival Model of Metastasis, Overall Mortality, and Prostate Cancer–specific Mortality (Landmark Analysis and Propensity Score Matched Analysis)*

| Variables | Primary landmark analysis | | Propensity score matched analysis | |
|---|---|---|---|---|
| | Hazard ratio (95%CI) | *P* value | Hazard ratio (95%CI) | *P* value |
| | *Outcome 1: Metastasis* | | | |
| Active surveillance vs initial treatment | 1.34 (1.15-1.57) | < .001 | 1.28 (1.08-1.51) | < .001 |
| | *Outcome 2: Overall mortality* | | | |
| Active surveillance vs initial treatment | 1.12 (1.01-1.24) | .038 | 1.12 (1.01-1.25) | .036 |
| | *Outcome 3: Prostate cancer–specific mortality* | | | |
| Active surveillance vs initial treatment | 1.66 (1.15-2.39) | .007 | 1.87 (1.24-2.82) | .003 |

Abbreviation: CI, confidence interval.
Each analysis was adjusted for age, diagnosis year, Johns Hopkins Adjusted Clinical Groups comorbidity score, disease characteristics at diagnosis (PSA, positive core, and maximum % of core), rurality, patient income, and provider-related characteristics (hospital type, physician type, physician and institution volume tertile).


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# Long-term Outcomes Following Active Surveillance of Low-grade Prostate Cancer: A Population-based Study Using a Landmark Approach

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**Purpose:** Active surveillance is widely used to manage low-risk prostate cancer, but population-level long-term outcomes are limited. Our objective was to determine long-term population-level oncological outcomes in active surveillance patients. A secondary objective examined the active surveillance discontinuation rate.

**Materials and Methods:** In this retrospective, population-based study using linked administrative databases from Ontario, Canada, we identified low-grade prostate cancer patients managed with active surveillance or initial treatment between 2002-2014. The 10- and 15-year metastasis-free survival, overall survival, and cancer-specific survival were compared between active surveillance and initial treatment. A landmark of 24 months was selected for the primary analysis. Long-term outcomes were examined using multivariable proportional hazards models and a propensity-based approach.

**Results:** The cohort consisted of 21,282 low-grade prostate cancer patients with a median follow-up of 9.8 years. At 10-year follow-up the survival rate of remaining on active surveillance was 39%, metastasis-free survival was 94.2%, overall survival 88.7%, and cancer-specific survival 98.1%. In adjusted models active surveillance was associated with higher risk of metastasis (HR 1.34, 95%CI 1.15-1.57), overall mortality (HR 1.12, 95%CI 1.01-1.24), and prostate cancer–specific mortality (HR 1.66, 95%CI 1.15-2.39) compared to initial treatment. Survival analysis using 7,525 propensity-matched pairs was consistent with the primary analysis for metastasis-free survival, overall survival and cancer-specific survival.

**Conclusions:** In this large population-based study of long-term outcomes in men with low-grade prostate cancer, active surveillance is associated with excellent long-term metastasis-free survival and overall survival. However, long-term cancer-specific survival was slightly inferior (1% worse at 10 years with active surveillance), and this must be balanced against known harms of overtreatment.

**Key Words:** watchful waiting, prostatic neoplasms

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Ethics Statement: This study received Institutional Review Board approval (IRB No. 12-5583).

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**Editor's Note: This article is the third of 5 published in this issue for which Category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 647 and 648.**

Active surveillance (AS) for low-risk prostate cancer (PC) is recommended as a preferred treatment option.[1,2] Reports on AS from single academic institutions have been promising, with very high 10-year cancer-specific survival (CSS) of 99%-100%.[3,4] However, academic centers include highly-selected cohorts with protocol-based follow-up. While the PRIAS network, the U.S. Veterans Affairs system, and the Swedish studies report on less-selected patients with less stringent "real life" follow-up, they predominantly focus on AS uptake. We lack data on long-term oncological outcomes in a well-defined


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AS cohort at the population level. Moreover, many published studies do not distinguish between AS and watchful waiting (WW). This is problematic since WW and AS are dissimilar approaches and result in different oncological outcomes. Additionally, selection of treatment approach (AS or initial definitive intervention) is driven by complex patient and provider factors that affect outcomes,[5] yet none of the studies reporting on long-term oncological outcomes adjusted for these factors. Our primary objective was to examine long-term oncologic outcomes with AS and initial curative treatment in low-grade PC at a population level using a landmark approach.

## METHODS

We carried out an observational, population-based study using linked administrative databases in Ontario, Canada.[6] We included men diagnosed from 2002-2014 with de novo PC (codes: ICD-9 185, ICD-10 C61, histology 8140) that was low-grade (Grade Group 1) based on a diagnostic procedure (transrectal ultrasound biopsy) within 30 days of diagnosis. Patients were excluded if the Gleason score at diagnosis was not abstracted, or if they had medical or surgical castration within 365 days of diagnosis. All data sources are described in Supplemental Table 1 (https://www.jurology.com) and in prior studies.[7,8]

### Study Cohort

Men were classified as starting initial AS if they had low-grade PC, did not receive any definitive treatment (ie, surgery, radiotherapy, or brachytherapy) within 6 months of diagnosis, and had a confirmatory biopsy within 2 years from diagnosis (details of cohort creation in Supplemental Figures 1 and 2, https://www.jurology.com).

Initial treatment cohort was defined as patients with low-grade PC who received definitive treatment within 6 months of diagnosis.

### Outcomes

***Primary outcomes.*** Given the long natural history of low-risk PC, development of metastasis is an intermediate endpoint and a good surrogate for cancer-specific mortality.[9,10] We used a previously-validated algorithm to identify metastasis in PC patients from Canadian Institute for Health Information-Discharge Abstract Database procedure codes and Ontario Health Insurance Plan claims.[11] Time to metastasis was calculated starting at the landmark date (2 years from diagnosis) until metastasis or censoring.

Overall mortality was defined as all-cause mortality during follow-up. Survival time was calculated from the landmark date (2 years from diagnosis) until death.

PC-specific mortality was defined as death from PC (code C61) during follow-up. We used cause of death provided by the Ontario Cancer Registry. Patients with mortality from other causes were censored at the date of death.

***Secondary outcome: transition to definitive treatment and treatment type after initial AS.*** The date of AS discontinuation was defined as the date of receipt of subsequent treatment after initial AS.

### Statistical Analyses

Continuous and categorical variables were compared between cohorts with Wilcoxon tests and $\chi^2$ tests, respectively. We performed a landmark analysis at 24 months to avoid immortal time bias[12] in the primary analysis (rationale in Supplemental Figure 3, https://www.jurology.com). The survival rates at 5-, 10-, and 15 years for metastasis-free survival (MFS), CSS, and overall survival (OS) were estimated using the Kaplan-Meier method, and the log-rank test was used to compare between cohorts. For the landmark analysis, follow-up time started at 2 years post diagnosis; therefore, the 5-, 10- and 15-year timepoints approximate 7, 12, and 17 years post diagnosis. Missing data for PSA, number of positive cores, and maximum percentage of core were imputed using multiple imputations (m = 20 data sets). Multivariable Cox proportional hazards (PH) models were used to evaluate associations between MFS, CSS, and OS, adjusting for age and year of diagnosis, adjusted clinical groups comorbidity score, disease characteristics at diagnosis (PSA: 0-4, 4.1-10, and 10+, positive core: 1, 2, 3, 4+, and maximum % of core: 50+ vs <50), rurality (rural/urban status), patient income quintiles, and provider characteristics (hospital type: academic, nonacademic, and regional cancer center; physician type: urologist, radiation oncologist, and others; physician and institution volume). Physician and institution volume (tertile) were based on the number of new low-grade PC patients seen by that physician or institution during the year at risk. We used Schoenfeld residuals to evaluate the PH assumption.[13] Multivariable survival analysis followed the methods and model building described by Austin.[14] Multicollinearity was assessed using tolerance and variance inflation factor scores.[15]

We performed a sensitivity analysis after constructing an ideal AS cohort (confirmatory biopsy within 1 year, PSA <10, positive cores ≤3, and maximum percentage of cores <50% at diagnosis) intended to represent patients who were most appropriate for AS and likely received higher quality of care. Additionally, an all-case analysis (full cohort without landmark approach) was conducted.

We repeated the analysis using a propensity-based approach. Propensity scores (PS) were created using logistic regression modeling of a patient's likelihood of receiving AS and the matching caliper was defined as 0.10 of the standard deviation of the logit of the PS (details in Supplemental Table 6, https://www.jurology.com). We used the missing-indicator approach for dealing with missing data. Cox PH modelling was then performed. We considered a $P$ value < .05 to be statistically significant, and all analyses were performed with SAS 9.4.

## RESULTS

Among the 21,282 men with low-grade PC in the landmark cohort, AS was started in n = 9,311 and initial treatment was provided in n = 11,971 (Supplemental Figure 2, https://www.jurology.com). Pathological characteristics (PSA, positive cores, and maximum % core) in the AS cohort were significantly more favorable than the initial treatment group (all $P$ < .05, Table 1). There was no evidence of

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**Table 1.** *Baseline Characteristics and Crude Events of Patients by Active Surveillance and Initial Treatment (Landmark Cohort)*

| Variables | AS N = 9,311 | | Initial treatment N = 11,971 | | *P* value[a] |
|---|---|---|---|---|---|
| Age, median (IQR), y | 64 | (59-69) | 62 | (57-67) | < .001 |
| Diagnosis year, No. (%) | | | | | |
| 2002-08 | 3,840 | (41) | 8,318 | (69) | < .001 |
| 2009-14 | 5,471 | (59) | 3,653 | (31) | |
| Comorbidity, median (IQR), ACG score | 8 | (3-17) | 9 | (3-17) | < .001 |
| Disease characteristics | | | | | |
| PSA at diagnosis, median (IQR)/No. available | 6 | (4-8)/5,606 | 6 | (5-8)/7,171 | .091 |
| No. positive cores at initial biopsy, median (IQR)/No. available | 1 | (1-3)/8,409 | 2 | (1-4)/9,963 | < .001 |
| Maximum % core at initial biopsy, median (IQR)/No. available | 8 | (5-20)/7,835 | 15 | (5-40)/9,150 | < .001 |
| Total No. cores taken at diagnosis biopsy, median (IQR)/No. available | 12 | (10-12)/8,324 | 10 | (8-12)/10,007 | .001 |
| No. biopsies (including diagnostic biopsy), median (IQR) | 2 | (2-3) | 2 | (1-2) | < .001 |
| Socioeconomic characteristics | | | | | |
| Rural, No. (%) | 992 | (11) | 1,695 | (14) | < .001 |
| Neighborhood income quintile, No. (%) | | | | | |
| 1st quintile (lowest) | 1,224 | (13) | 1,665 | (14) | .008 |
| 2nd quintile | 1,565 | (17) | 2,120 | (18) | |
| 3rd quintile | 1,788 | (19) | 2,333 | (20) | |
| 4th quintile | 2,044 | (22) | 2,654 | (22) | |
| 5th quintile | 2,670 | (29) | 3,168 | (27) | |
| Missing | 20 | | 31 | | |
| Provider-related characteristics, No. (%) | | | | | |
| Hospital type[b] | | | | | |
| Academic | 4,436 | (48) | 5,238 | (44) | < .001 |
| RCC | 1,013 | (11) | 1,905 | (16) | |
| Nonacademic | 3,862 | (41) | 4,828 | (40) | |
| Primary prostate cancer physician[c] | | | | | |
| Urologist | 7,578 | (81) | 8,440 | (70) | < .001 |
| Radiation oncologist | 1,692 | (18) | 3,513 | (29) | |
| Other[d] | 41 | (0.44) | 18 | (0.15) | |
| Physician volume[e] | | | | | |
| 1st tertile (lowest) | 166 | (1.8) | 198 | (1.7) | < .001 |
| 2nd tertile | 1,982 | (21) | 1,762 | (15) | |
| 3rd tertile | 7,124 | (77) | 10,000 | (84) | |
| Missing | 39 | | 11 | | |
| Institution volume[e] | | | | | |
| 1st tertile (lowest) | 369 | (3.9) | 208 | (1.7) | |
| 2nd tertile | 1,691 | (18) | 2,222 | (19) | |
| 3rd tertile | 7,207 | (78) | 9,528 | (79) | |
| Missing | 44 | | 13 | | < .001 |
| Crude events | | | | | |
| Treatment after initial AS, No. (%) | 5,287 | (57) | NA | | NA |
| Treatment type after initial AS, No. (%) | | | | | |
| RP alone | 2,083 | (39) | NA | | NA |
| RT alone | 2,515 | (48) | | | |
| HT alone | 163 | (3.1) | | | |
| RP+HT | 32 | (0.61) | | | |
| RP+RT | 191 | (3.6) | | | |
| RT+HT | 298 | (5.6) | | | |
| Metastasis, No. (%) | 361 | (3.9) | 591 | (4.9) | .001 |
| Metastasis-free survival time, median (IQR), mo | 77 | (50-111) | 110 | (78-137) | < .001 |
| Overall death, No. (%) | 702 | (7.5) | 1,083 | (9.0) | < .001 |
| Follow-up time for patients without death, median (IQR), mo | 102 | (75-136) | 136 | (104-162) | < .001 |
| Prostate cancer-related death, No. (%)[f] | 64 | (0.68) | 73 | (0.60) | .5 |

Abbreviations: ACG, Adjusted Clinical Groups; AS, active surveillance; HT, hormonal therapy; IQR, interquartile range; NA, not applicable; PSA, prostate-specific antigen; RCC, regional cancer center; RP, radical prostatectomy; RT, radiation therapy.

[a] To test for differences between the AS and initial treatment groups, Wilcoxon tests were used; continuous variables and $\chi^2$ tests were used for categorical variables.

[b] Hospital type was defined as academic hospital, which is affiliated with a university as a teaching hospital; RCC, which is a hospital that treats cancer patients and is recognized as a regional cancer center by Cancer Care Ontario (currently under Ontario Health); and nonacademic, which includes general hospitals.

[c] A contact was defined as any physician billing claim related to prostate cancer occurring after this time frame.

[d] "Other" category for type of primary physician includes family practitioner and general practice, and hematologist.

[e] Provider and institution volume based on the number of low-risk patients treated by the physician or institution during the entire study period.

[f] Cancer-specific mortality restricted on December 31, 2015.

collinearity among variables in the multivariable model (Supplemental Table 2, https://www.jurology.com). The Schoenfeld residuals were not correlated with time, upholding the PH assumption (data not shown).

### Metastasis (Landmark Analysis)

The 5-, 10- and 15-year MFS is shown in the Figure and Supplemental Table 3 (https://www.jurology.com; estimates from the landmark analysis approximate 7, 12 and 17 years post diagnosis). In adjusted

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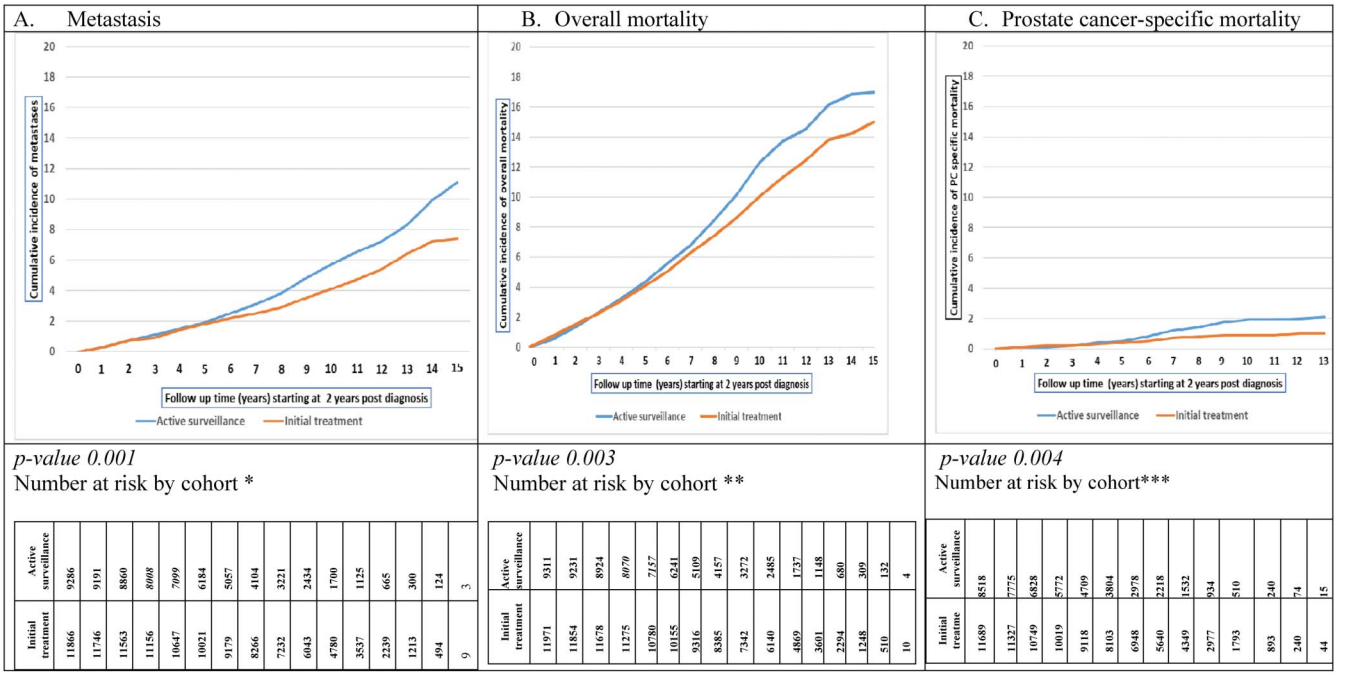


**Figure.** Cumulative incidence of metastases (A), overall mortality (B), and prostate cancer (PC)-specific mortality (C) for active surveillance and initial treatment from landmark analysis. *P* value comparing active surveillance and initial treatment using log-rank test. * For metastasis outcome in the primary analysis n = 180 patients (n = 37 on active surveillance and n = 143 on initial treatment) were excluded due to development of metastasis within 2-year landmark time. ** Survival time and event was censored on December 31, 2017. *** Cause-specific death data were available until December 31, 2015. Survival time and event for PC-specific mortality was restricted to December 31, 2015. As such, the number at risk differs between PC-specific mortality and overall mortality analyses.

Cox models, risk of metastasis was significantly higher with AS than initial treatment (HR 1.34, 95% CI 1.15-1.57, $P \leq .001$). Other predictors of metastatic disease were increasing age, higher comorbidity, lower income quintile, and being managed by a nonurologist physician (Table 2).

## Overall Mortality (Landmark Analysis)

The Figure and Supplemental Table 3 (https://www.jurology.com) show the OS estimates at 5, 10 and 15 years. In adjusted Cox models, risk of overall mortality was significantly higher with AS vs initial treatment (HR 1.12, 95%CI 1.01-1.24, $P = .038$). Predictors of overall mortality were increasing age, higher comorbidity, higher PSA, higher positive cores and maximum % of cores at diagnosis, lower income quintile, nonacademic hospital, and nonurologist physician (Table 3).

## PC-specific Mortality (Landmark Analysis)

There were 64 deaths from PC with AS and 73 with initial treatment during a median 10 years of follow-up. CSS at 5 and 10 years for AS was 99.4% and 98.1%, and for initial treatment it was 99.6% and 99.1%, respectively (see Figure and Supplemental Table 3, https://www.jurology.com). In multivariable analyses, factors associated with PC-specific mortality were use of AS (HR 1.66; 95%CI 1.15-2.39 vs initial treatment), older age, higher maximum % cores, and lower income quintile (Table 4).

## Discontinuation of AS

The discontinuation of AS (transition to definitive treatment) was 62.9% over a median follow-up of 10 years. The treatment-free survival rate at 5, 10, and 15 years was 50.2%, 38.7%, and 33.7%, respectively (Supplemental Table 3, https://www.jurology.com).

## Sensitivity Analyses

Overall, analyses for the ideal cohort and the full cohort (all cases) resulted in multivariable adjusted HRs for AS vs initial treatment that were similar in direction, and not dramatically different in magnitude, to the primary landmark analysis (Tables 2-4, and Supplemental Tables 4 and 8, https://www.jurology.com). The estimates of 5-, 10-, and 15-year survival rates were also broadly similar to the primary landmark analysis (Supplemental Tables 5 and 9, https://www.jurology.com). We note that CSS was lower in the ideal AS cohort (at 10 and 13 years), and the estimate of the adjusted HR for PC-specific mortality decreased from 1.66 in the primary analysis to 1.14 with the ideal AS cohort; however, the 95%CIs were wide (0.45 to 2.89).

There were no statistically significant associations of cancer-specific variables (PSA, number of positive cores, or maximum core percent) with PC-specific

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**Table 2.** *Cox Proportional Hazards Model of Time to Metastasis From Landmark Analysis*

| Variables | Multivariable HR (95%CI) | *P* value |
|---|---|---|
| AS vs initial treatment | 1.34 (1.15-1.57) | < .001 |
| Age, per decade increase | 1.64 (1.47-1.83) | < .001 |
| Diagnosis year | | |
| 2002-2008 | Reference | .4 |
| 2009-2014 | 0.93 (0.77-1.14) | |
| ACG comorbidity score, per 1-unit increase | 1.01 (1.00-1.02) | .007 |
| Disease characteristics | | |
| PSA category at diagnosis | | |
| 0-4 | Reference | |
| 4.1-10 | 0.91 (0.71-1.17) | .4 |
| 10.1+ | 1.18 (0.89-1.56) | .2 |
| Positive core at diagnosis | | |
| 1 | Reference | |
| 2 | 1.05 (0.85-1.25) | .6 |
| 3 | 1.14 (0.91-1.43) | .3 |
| 4+ | 1.22 (0.98-1.49) | .063 |
| Maximum % core at initial biopsy | | |
| (50+ vs <50) | 1.21 (0.95-1.53) | .12 |
| Socioeconomic characteristics | | |
| Rural (yes vs no) | 1.02 (0.81-1.29) | .8 |
| Neighborhood income quintile | | |
| 1st quintile (lowest) | Reference | |
| 2nd quintile | 0.83 (0.65-1.06) | .13 |
| 3rd quintile | 0.97 (0.77-1.22) | .7 |
| 4th quintile | 0.81 (0.64-1.03) | .081 |
| 5th quintile | 0.69 (0.54-0.87) | .002 |
| Provider-related characteristics | | |
| Hospital type[a] | | |
| Academic center | Reference | |
| RCC | 1.04 (0.81-1.33) | .8 |
| Nonacademic | 1.07 (0.87-1.32) | .5 |
| Primary physician | | |
| Urologist | Reference | |
| Radiation oncologist | 1.33 (1.10-1.62) | .003 |
| Others[b] | ND | > .9 |
| Physician tertile | | |
| 1st tertile (lowest) | 1.59 (0.98-2.61) | |
| 2nd tertile | 1.11 (0.92-1.36) | .057 |
| 3rd tertile | Reference | .3 |
| Institution tertile | | |
| 1st tertile (lowest) | 0.86 (0.51-1.42) | .5 |
| 2nd tertile | 0.93 (0.75-1.15) | .4 |
| 3rd tertile | Reference | |

Abbreviations: ACG, Adjusted Clinical Groups; AS, active surveillance; CI, confidence interval; HR, hazard ratio; ND, not determinable; PSA, prostate-specific antigen; RCC, regional cancer center.
Local Health Integration Network (14 crown agencies which were established by the Government of Ontario to plan, coordinate, integrate, and fund health services at a local level) variable adjusted as categorical variable, but data not shown.
Model building strategy: semi-parametric Cox proportional hazards model was used for multivariable analysis, variable with $P < .10$ (from univariable Cox proportional hazards model) included for multivariable model. Follow-up time (years) starting at 2 years post diagnosis.
[a] Hospital type was defined as the academic hospital, which is affiliated with the university as a teaching hospital; RCC, which is a hospital that treats cancer patients and is recognized as a regional cancer center by Cancer Care Ontario (currently under Ontario Health); and nonacademic, which includes general hospitals.
[b] "Others" category for type of primary physician includes family practitioner and general practice, and hematologist.

**Table 3.** *Cox Proportional Hazards Survival Model of Overall Mortality From Landmark Analysis*

| Variables | Multivariable HR (95%CI) | *P* value |
|---|---|---|
| AS vs initial treatment | 1.12 (1.01-1.24) | .038 |
| Age, per decade increase | 2.67 (2.48-2.88) | < .001 |
| Diagnosis year | | |
| 2002-08 | Reference | |
| 2009-14 | 0.64 (0.55-0.73) | .001 |
| ACG scores, per 1-unit increase | 1.03 (1.02-1.03) | < .001 |
| Disease characteristics | | |
| PSA category at diagnosis | | |
| 0-4 | Reference | |
| 4.1-10 | 1.04 (0.87-1.24) | .6 |
| 10.1+ | 1.19 (0.95-1.49) | .12 |
| Positive cores at diagnosis | | |
| 1 | Reference | |
| 2 | 1.09 (0.95-1.27) | .3 |
| 3 | 1.18 (1.00-1.38) | .048 |
| 4+ | 1.23 (1.06-1.44) | .007 |
| Maximum % core at initial biopsy | | |
| (50+ vs <50) | 1.12 (0.95-1.31) | .2 |
| Socioeconomic characteristics | | |
| Rural (yes vs no) | 1.04 (0.89-1.21) | .6 |
| Neighborhood income quintile | | |
| 1st quintile (lowest) | Reference | |
| 2nd quintile | 0.99 (0.85-1.16) | .9 |
| 3rd quintile | 0.96 (0.82-1.12) | .6 |
| 4th quintile | 0.78 (0.66-0.91) | .002 |
| 5th quintile | 0.67 (0.57-0.78) | <.001 |
| Provider-related characteristics | | |
| Hospital type[a] | | |
| Academic center | Reference | |
| RCC | 1.05 (0.89-1.24) | .6 |
| Nonacademic | 1.16 (1.01-1.34) | .036 |
| Primary prostate cancer physician | | |
| Urologist | Reference | |
| Radiation oncologist | 1.29 (1.14-1.47) | < .001 |
| Others[b] | ND | .9 |
| Physician tertile | | |
| 1st tertile (lowest) | 1.47 (1.08-2.02) | .015 |
| 2nd tertile | 1.00 (0.88-1.14) | .9 |
| 3rd tertile | Reference | |
| Institution tertile | | |
| 1st tertile (lowest) | 0.94 (0.68-1.30) | .7 |
| 2nd tertile | 0.92 (0.80-1.05) | .2 |
| 3rd tertile | Reference | |

Abbreviations: ACG, Adjusted Clinical Groups; AS, active surveillance; CI, confidence interval; HR, hazard ratio; ND, not determinable; PSA, prostate-specific antigen; RCC, regional cancer center.
Local Health Integration Network (14 crown agencies which were established by the Government of Ontario to plan, coordinate, integrate, and fund health services at a local level) variable adjusted as categorical variable, but data not shown.
Model building strategy: semi-parametric Cox proportional hazards model was used for multivariable analysis, variable with $P < .10$ (from univariable Cox proportional hazards model) included for multivariable model. Follow-up time (years) starting at 2 years post diagnosis.
[a] Hospital type was defined as the academic hospital, which is affiliated with the university as a teaching hospital; RCC, which is a hospital that treats cancer patients and is recognized as a regional cancer center by Cancer Care Ontario (currently under Ontario Health); and nonacademic, which includes general hospitals.
[b] "Others" category for type of primary physician includes family practitioner and general practice, and hematologist.

mortality or metastasis when assessed within the AS cohort only.

## PS Matching Analysis

After PS matching, the study population consisted of 7,525 men in each cohort. Before matching, large imbalances between cohorts were observed, and PS matching was effective in eliminating imbalances between cohorts (Supplemental Table 6, https://www.jurology.com). PS analysis confirmed the results from the main analysis (Supplemental Table 7, https://www.jurology.com).

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**Table 4.** *Cox Proportional Survival Model of Prostate Cancer-specific Mortality From Landmark Analysis*

| Variables | Multivariable HR (95%CI) | *P* value |
|---|---|---|
| AS vs initial treatment | 1.66 (1.15-2.39) | .007 |
| Age, per decade increase | 3.23 (2.44-4.28) | < .001 |
| Diagnosis year | | |
| 2002-08 | Reference | .001 |
| 2009-14 | 0.25 (0.11-0.58) | |
| ACG scores, per 1-unit increase | 1.01 (0.99-1.03) | .099 |
| Disease characteristics | | |
| PSA category at diagnosis | | |
| 0-4 | Reference | |
| 4.1-10 | 0.82 (0.39-1.69) | .5 |
| 10.1+ | 1.39 (0.67-2.86) | .4 |
| Positive cores at diagnosis | | |
| 1 | Reference | |
| 2 | 1.24 (0.72-2.13) | .4 |
| 3 | 1.00 (0.49-1.98) | .9 |
| 4+ | 1.57 (0.95-1.98) | .075 |
| Maximum % core at initial biopsy | | |
| (50+ vs <50) | 1.39 (0.82-2.35) | .2 |
| Socioeconomic characteristics | | |
| Rural (yes vs no) | 1.75 (1.14-2.69) | .011 |
| Neighborhood income quintile | | |
| 1st quintile (lowest) | Reference | |
| 2nd quintile | 0.74 (0.44-1.26) | .3 |
| 3rd quintile | 0.70 (0.42-1.19) | .2 |
| 4th quintile | 0.55 (0.32-0.96) | .035 |
| 5th quintile | 0.37 (0.21-0.67) | < .001 |
| Provider-related characteristics | | |
| Primary prostate cancer physician | | |
| Urologist | Reference | |
| Radiation oncologist | 1.04 (0.71-1.52) | .8 |
| Others[a] | ND | > .9 |

Abbreviations: ACG, Adjusted Clinical Groups; AS, active surveillance; CI, confidence interval; HR, hazard ratio; ND, not determinable; PSA, prostate-specific antigen. Survival time and event was censored on December 31, 2015 for prostate cancer–specific mortality.
Model building strategy: semi-parametric Cox proportional hazards model was used for multivariable analysis, variable with $P < .10$ (from univariable Cox proportional hazards model) included for multivariable model. Variables "Hospital type," "Institution volume," and "Physician volume" were excluded due to $P > .10$ in univariable Cox proportional hazards model. Follow-up time (years) starting at 2 years post diagnosis.
[a] "Others" category for type of primary physician includes family practitioner and general practice, and hematologist.

## DISCUSSION

In this large population-based study of low-grade PC from Ontario, Canada, we examined long-term oncological outcomes over a decade of follow-up and found similar rates of metastases and OS at 5, 10, and 15 years between AS and initial treatment. However, adjusted results showed worse metastasis, overall mortality, and PC-specific mortality in the AS cohort compared to initial treatment using a landmark approach. A propensity-based approach confirmed the results of our primary analysis.

Although outcomes on AS are excellent, these results do suggest that some men are misclassified or may miss an opportunity for cure. With the landmark approach, MFS on AS at 5-, 10-, and 15-year follow-up was 98.1%, 94.2%, and 88.9%, respectively. Prior single-institution studies on AS reported MFS ranging from 97.6% to 99.2% at 5 years, 97.3% to 99.9% at 10 years,[3,4,16-21] and 93.0% to 99.9% at 15 years.[3,16] However, the landmark approach, 5-, 10-, and 15-year timepoints more closely represent 7, 12, and 17 years post diagnosis. Using the full cohort (without landmark approach), we found similar 5- and 10-year (post-diagnosis) MFS in AS, but slightly lower 15-year MFS compared to reports from academic centers (Supplemental Table 9, https://www.jurology.com). This is likely due to relatively short median follow-up and few outcomes in published studies leading to imprecise estimates.

Our 5- and 10-year OS outcomes at a population level are comparable to published series from mostly single-academic centers,[3,4,16-23] which is reassuring (Supplemental Table 9, https://www.jurology.com). Although our 15-year results appear to be better than those of published studies, direct comparisons are difficult due to differences in patient populations and analysis strategy (landmark analysis) and only a few series having 15 years of follow-up.

In our landmark approach, CSS at 5- and 10-year follow-up was 99.4% and 98.1% for AS and 99.6% and 99.1% for initial treatment, respectively. These estimates are similar to published data from academic centers and reinforce that AS can be implemented at a population level with excellent long-term CSS.[3,4,16-25]

However, at 10-year follow-up, we found slightly lower CSS with AS (98.1% vs 99.1%, overall HR for PC-specific mortality was 1.66, 95%CI 1.15-2.39, for AS vs initial treatment). We also observed worse PC-specific mortality in lower socioeconomic groups and rural inhabitants. A Swedish population-based study also reported significantly higher PC death at 10 years after diagnosis among men with low-risk PC who received surveillance (including AS and WW) compared to initial treatment (2.4% vs 0.7%);[22] however, no statistically significant difference was observed in a UK-based randomized trial (approximately 1% irrespective of treatment—radical prostatectomy, radiation therapy, or AS).[20] Although the absolute difference we observed in CSS between AS and initial treatment was 1% at 10-year follow-up, these numbers need to be contextualized by the burdens of initial treatment. Our data suggest that 125 patients on AS would need to receive initial treatment to prevent 1 PC-specific death at 10 years, at a cost of the known side effects associated with standard treatments. The estimated rates for urinary, bowel, and sexual-related side effects are 11%-27%, 3%-17%, and 72%-83%, respectively.[26] In our sensitivity analyses of an ideal AS cohort, only 17/4,831 men died from PC over 10 years of follow-up (99.3% survival rate) and the difference between AS and initial treatment seen in the main analysis was reduced. While the reduced sample size and lower statistical power limit interpretation of the

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sensitivity analysis, the results suggest that PC-specific mortality may be slightly higher with AS in the real-world setting. The latter points to a need for a careful discussion between patient and clinician to balance treatment-related side effects and impact on quality of life vs the modest decrease in PC-specific mortality associated with intervention.

With regard to the need for intervention, just over one-third of patients remained treatment-free on AS after 10 years of follow-up. This is lower than in published academic series, which range from 44%-64% at 10-year follow-up.[3,4,20,27] The higher percentage in academic series may be due to more formalized settings and protocols, better counselling during initial AS uptake, active monitoring, or quality of care.

Our study has several limitations. Firstly, AS was inferred if there was no definitive treatment claim, as there is no specific physician billing claim code for AS. This may result in some degree of misclassification bias due to WW or advanced patients being incorrectly classified as AS, which may lead to worse estimates of MFS, CSS, and OS for AS. Nevertheless, our results for most of these outcomes agree with published data (Supplement Table 9, https://www.jurology.com). Secondly, we recognize that while patients with missing pathological data differed from the included patients, the available characteristics suggest that these patients were not appropriate for a low-risk cohort (Supplemental Table 10, https://www.jurology.com). In addition, several data on prognostic variables such as cancer staging (missing in 34% of AS patients) and PSA level that influence treatment choice and outcome were not complete. However, Gleason score, which is key to defining AS eligibility, was available and our outcomes agree with published data. Thirdly, coding for metastasis is not as accurate as other outcomes in our databases and may lead to under-reporting, although our estimates are similar to published studies. Also, cause of death data were not as current as OS since cause of death was available only until December 2015. Finally, most patients were diagnosed in the pre-MRI era using traditional biopsy techniques. Some jurisdictions have started using pre-biopsy multiparametric MRI for PC patients who intend to undergo AS to improve early identification of high-grade cancer;[28,29] however, MRI may not be readily available to all men with low-risk PC.[29] Other strategies to risk stratify patients, including biomarkers, advanced imaging techniques, and newer biopsy strategies (such as transperineal), are now becoming available and may better select patients for AS.[28,29] While mature data on outcomes will take many years,[30] these strategies will likely improve oncological outcomes for AS patients and reduce any differences compared to radical treatment.[29]

This study has several important strengths including the size of the cohort, length of follow-up, and use of population-based outcomes within the context of universal health care. Furthermore, we distinguished between AS and WW. The various analytical approaches used—landmark methods to avoid immortal time bias and propensity matching to reduce selection bias—are additional strengths. Single-center results lead to practice change, but outcomes after widespread adoption are important measures of the true resulting impact of change.

## CONCLUSIONS

In this large, real-world study of long-term outcomes in men with low-grade PC, AS is associated with excellent long-term MFS and OS. However, CSS was slightly inferior at 10 and 15 years compared to initial treatment. Slightly inferior CSS with AS must be weighed against known long-term sequelae of active treatment.

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## REFERENCES


1. Chen RC, Rumble RB, Loblaw DA, et al. Active surveillance for the management of localized prostate cancer (Cancer Care Ontario guideline): American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol*. 2016;34(18):2182-2190.
2. Bekelman JE, Rumble RB, Chen RC, et al. Clinically localized prostate cancer: ASCO clinical practice guideline endorsement of an American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology Guideline. *J Clin Oncol*. 2018;36(32):3251-3258.
3. Tosoian JJ, Mamawala M, Epstein JI, et al. Active surveillance of grade group 1 prostate cancer: long-term outcomes from a large prospective cohort. *Eur Urol*. 2020;77(6):675-682.
4. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol*. 2015;33(3):272-277.
5. Auffenberg GB, Lane BR, Linsell S, Cher ML, Miller DC. Practice- vs physician-level variation in use of active surveillance for men with low-risk prostate cancer: implications for collaborative quality improvement. *JAMA Surg*. 2017;152(10):978.
6. Earle CC. Ontario cancer data linkage project: "cd-link". *Healthc Q*. 2014;17(1):11-13.
7. Timilshina N, Komisarenko M, Martin LJ, et al. Factors associated with discontinuation of active surveillance among men with low-risk prostate cancer: a population-based study. *J Urol*. 2021;206(4):903-913.
8. Richard PO, Timilshina N, Komisarenko M, et al. The long-term outcomes of Gleason grade groups 2 and 3 prostate cancer managed by active surveillance: results from a large, population-based cohort. *Can Urol Assoc J*. 2020;14(6):174-181.
9. D'Amico AV. Active surveillance versus treatment of prostate cancer: should metastasis be the primary end point?. *J Clin Oncol*. 2017;35(15):1638-1640.
10. Xie W, Regan MM, Buyse M, et al. Metastasis-free survival is a strong surrogate of overall survival in localized prostate cancer. *J Clin Oncol*. 2017;35(27):3097-3104.
11. Krahn MD, Bremner KE, Luo J, Tomlinson G, Alibhai S. Long-term health care costs for prostate cancer patients on androgen deprivation therapy. *Curr Oncol*. 2016;23(5):e443-e453.
12. Agarwal P, Moshier E, Ru M, et al. Immortal time bias in observational studies of time-to-event outcomes: assessing effects of postmastectomy radiation therapy using the National Cancer Database. *Cancer Control*. 2018;25(1):107327481878935.
13. Sun Y, Li M, Gilbert PB. Goodness-of-fit test of the stratified mark-specific proportional hazards model with continuous mark. *Comput Stat Data Anal*. 2016;93:348-358.
14. Austin PC. A tutorial on multilevel survival analysis: methods, models and applications. *Int Stat Rev*. 2017;85(2):185-203.
15. O'Brien RM. A caution regarding rules of thumb for variance inflation factors. *Qual Quantity*. 2007;41(5):673-690.
16. Godtman RA, Holmberg E, Khatami A, Pihl CG, Stranne J, Hugosson J. Long-term results of active surveillance in the Goteborg randomized, population-based prostate cancer screening trial. *Eur Urol*. 2016;70(5):760-766.
17. Marenghi C, Alvisi MF, Palorini F, et al. Eleven-year management of prostate cancer patients on active surveillance: what have we learned? *Tumori*. 2017;103(5):464-474.
18. Bokhorst LP, Valdagni R, Rannikko A, et al. A decade of active surveillance in the PRIAS study: an update and evaluation of the criteria used to recommend a switch to active treatment. *Eur Urol*. 2016;70(6):954-960.
19. Preston MA, Feldman AS, Coen JJ, et al. Active surveillance for low-risk prostate cancer: need for intervention and survival at 10 years. *Urol Oncol*. 2015;33(9):383.e9-383.e16.
20. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375(15):1415-1424.
21. Selvadurai ED, Singhera M, Thomas K, et al. Medium-term outcomes of active surveillance for localised prostate cancer. *Eur Urol*. 2013;64(6):981-987.
22. Stattin P, Holmberg E, Johansson JE, Holmberg L, Adolfsson J, Hugosson J. Outcomes in localized prostate cancer: national Prostate Cancer Register of Sweden follow-up study. *J Natl Cancer Inst*. 2010;102(13):950-958.
23. 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(1):126-131.
24. Newcomb LF, Thompson IM Jr, Boyer HD, et al. Outcomes of active surveillance for clinically localized prostate cancer in the prospective, multi-institutional Canary PASS cohort. *J Urol*. 2016;195(2):313-320.
25. Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of prostatectomy versus observation for early prostate cancer. *N Engl J Med*. 2017;377(2):132-142.
26. Mazariego CG, Egger S, King MT, et al. Fifteen year quality of life outcomes in men with localised prostate cancer: population based Australian prospective study. *BMJ*. 2020;371:m3503.
27. Carlsson S, Benfante N, Alvim R, et al. Long-term outcomes of active surveillance for prostate cancer: the memorial Sloan Kettering Cancer Center experience. *J Urol*. 2032;203(6):1122-1127.
28. Lawrentschuk N. Sensible government decisions on funding for imaging can change practice and deliver better care for men with prostate cancer. *BJU Int*. 2022;130(S14):4.
29. Doan P, Graham P, Lahoud J, et al. A comparison of prostate cancer prediction models in men undergoing both magnetic resonance imaging and transperineal biopsy: are the models still relevant?. *BJU Int*. 2021;128(S336):36-44.
30. Emmett L, Buteau J, Papa N, et al. The additive diagnostic value of prostate-specific membrane antigen positron emission tomography computed tomography to multiparametric magnetic resonance imaging triage in the diagnosis of prostate cancer (primary): a prospective multicentre study. *Eur Urol*. 2021;80(6):682-689.


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