The uptake of active surveillance for the management of prostate cancer: A population-based analysis

Patrick O. Richard, MD;[1,2] Shabbir M.H. Alibhai, MD;[3] Tony Panzarella, MD;[4] Laurence Klotz, MD;[5] Maria Komisarenko, MD;[1] Neil E. Fleshner, MD;[1] David Urbach, MD;[6] Antonio Finelli, MD[1]

[1]Division of Urology, Departments of Surgery and Surgical Oncology, Princess Margaret Cancer Centre, University Health Network and the University of Toronto; [2]Division of Urology, Department of Surgery, Centre Hospitalier Universitaire de Sherbrooke and the University of Sherbrooke, Sherbrooke, QC, Canada; [3]Department of Medicine, University Health Network and the University of Toronto; [4]Biostatistics Department, Princess Margaret Hospital, University Health Network and the University of Toronto; [5]Division of Urology, Sunnybrook Health Sciences Centre and the University of Toronto; [6]Department of Surgery, University Health Network and the University of Toronto; Toronto, ON, Canada

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Abstract

Introduction: Active surveillance (AS) is a strategy for the management of low-risk prostate cancer (PCa). However, few studies have assessed the uptake of AS at a population level and none of these were based on a Canadian population. Therefore, our objectives were to estimate the proportion of men being managed by AS in Ontario and to assess the factors associated with its uptake.

Methods: This was a retrospective, population-based study using administrative databases from the province of Ontario to identify men ≤75 years diagnosed with localized PCa between 2002 and 2010. Descriptive statistics were used to estimate the proportion of men managed by AS, whereas mixed models were used to assess the factors associated with the uptake of AS.

Results: 45 691 men met our inclusion criteria. Of these, 18% were managed by AS. Over time, the rates of AS increased significantly from 11% to 21% ($p<0.001$). Older age, residing in an urban centre, being diagnosed in the later years of the study period, having a neighborhood income in the highest quintile, and being managed by urologists were all associated with greater odds of receiving AS.

Conclusions: There has been a steady increase in the uptake of AS between 2002 and 2010. However, only 18% of men diagnosed with localized PCa were managed by AS during the study period. The decisions to adopt AS were influenced by several individual and physician characteristics. The data suggest that there is significant opportunity for more widespread adoption of AS.

Introduction

Since the introduction of prostate-specific antigen (PSA)-based screening, there has been an increase in the incidence of prostate cancer (PCa).[1,2] However, this increase is mostly driven by an increase in the diagnosis of clinically insignificant cancers.[3] Thus, the management of PCa has been associated with considerable overtreatment. Active surveillance (AS) has been proposed as a strategy to decrease overtreatment[4-10] and is now recognized as a management option by a number of evidence-based guidelines.[11-13]

Although several prospective series have reported on its safety,[4-10] few studies have reported on the uptake of AS at a population level.[14-23] No previous population-based study has evaluated the proportion of men being managed by AS in Canada. In other areas of PCa management, there are significant differences between Canada and other countries. Although a recent single-institution series from the University of Ottawa has examined the treatment patterns of men diagnosed with low-risk PCa,[24] there remains a need to better understand the rates of AS use and the factors related to its adoption, outside of single-institution series. We hypothesized that the rates of AS increased throughout the study period.

Methods

Participants

This was an institutional review board-approved, population-based, retrospective study that identified, using administrative databases, men aged 18–75 years who were diagnosed with adenocarcinoma of the prostate between January 1, 2002 and December 31, 2010 in Ontario. We excluded men whose diagnostic procedure was not a transrectal ultrasound-guided biopsy (TRUSB) or a transurethral resection of the prostate (TURP). Men who died or who received primary medical or surgical castration and/or palliative radiotherapy within the first year after diagnosis were also excluded.

All medical procedures in Ontario are reimbursed by a single payer system (Ontario Health Insurance Plan [OHIP]). All OHIP fee codes used are listed in Appendix 1 (available at *www.cuaj.ca*). We linked these OHIP codes to the Ontario Cancer Registry, the Registered Persons Database, and the Ontario Drug Database to identify the management

of subjects diagnosed with PCa (data cutoff December 31, 2013). As there are no codes to differentiate between radiotherapy given with curative or palliative intent, we defined the latter as therapy given within one month or ≥6 months after castration. All localized PCa were included in this study, regardless of the risk-group stratification.[25]

Treatment groups

Subjects were allocated to one of four groups. The ones who received definitive therapies (i.e., surgery, external beam radiotherapy, or brachytherapy) within the first year following diagnosis without a second TRUSB beforehand were allocated to the definitive treatment group. The remaining men were considered to be in the expectant/observation group that was then subdivided into AS, watchful waiting (WW), and delayed treatments.

The AS group was composed of individuals who had undergone a second TRUSB (confirmatory biopsy) following diagnosis, before any definitive treatments were instituted or before castration. The remaining patients were allocated to the WW/delayed treatment group, which consisted of men who had no subsequent repeat TRUSB or treatments other than castration or palliative radiotherapy (WW) and of men who received definitive therapies >12 months after diagnosis (delayed treatment).

Variables

Using the databases, we determined individual-, physician- and institution-level characteristics. The individual-level characteristics included age at diagnosis, year of diagnosis, neighbourhood income quintile (hereinafter referred to as simply income quintile), and the area of residency. The Aggregated Diagnosis Groups (ADG) score, derived from the Johns Hopkins University Adjusted Clinical Groups Case-Mix system, was used to measure comorbidity.[26]

Physician- and institution-level characteristics included the treating physician' speciality and his/her annual new PCa-related case volume, as well as the type of treating centre and its annual new PCa-related case volume. The treating physician was defined as the physician who claimed the most PCa-related visits for each individual during the first year after diagnosis, while the treating institution was defined as the institution where the patient received the majority of his PCa care during the same timeframe.

Outcomes

The primary outcome was to determine the proportion of men with localized PCa managed by AS during the study period. Secondary outcomes were to estimate the uptake of AS over time and to estimate the characteristics associated with the uptake of AS.

Statistical analysis

Descriptive statistics were used to describe the cohort. Medians and interquartile range (IQR) were reported for continuous variables, while proportions were used to report categorical variables. Medians were compared using Wilcoxon or the Kruskal-Wallis sum of rank tests, where appropriate. Chi-squared analyses were used to compare categorical variables, while the Chi-square test for trend was used to estimate whether there was a significant increase in the adoption of AS over time.

Baseline characteristics associated with the adoption of AS were evaluated using a non-linear mixed model adjusted for a priori defined covariates based on previous studies (Appendix 2 at *www.cuaj.ca*) and adjusted for physician- and institution-level clusters assuming cross-classified data (i.e., physicians could work in more than one institution).[27] Estimates in the multivariable models are reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Physician- and institution-attributable intra-class correlations were obtained by calculating the ratio of the between-cluster variance to the total variance.[28] Five models specified for each of the outcomes were constructed to account for explained and unexplained variances.

Sensitivity analyses were also performed using three different definitions to identify men managed by AS (Appendix 3 at *www.cuaj.ca*). All statistical analyses were performed using SAS 9.4 and R version 3.1.3 statistical software. All analyses were two-sided, and p values less than 0.05 were considered statistically significant, with the exception of when multiple comparisons were required, at which time a Bonferroni correction was used.[29]

Results

A total of 79 498 men diagnosed with PCa between 2002 and 2010 were identified, of which 33 807 were excluded for various reasons (Appendix 4 at *www.cuaj.ca*). The final cohort was composed of 45 691 men. The characteristics of these men and their treating physicians (n=424) and institutions (n=215) are listed in Table 1.

Of the men included in this study, 70% (n=31 819) opted for upfront definitive therapies, whereas the remaining patients (n=13 872) were managed, at least initially, expectantly. Of these, 58% (n=8079), 33% (n=4570), and 9% (n=1223) were managed by AS, WW, and delayed definitive treatment, respectively. The proportion of men managed by AS represented 18% of the total cohort (Table 2). Over time, the proportion of men managed expectantly increased significantly (p<0.001; Appendix 5 at *www.cuaj.ca*). This increase was mainly driven by an increase in the number of men managed by AS, which increased from 11% in 2002 to 21% in 2010 (p<0.001).

Table 1. Individual-, physician- and institution-level characteristics according to treatment groups[a]

Variables	Total (n=45 691) n (%)	Expectant therapy (n=13 872)			Definitive treatment (n=31 819) n (%)
		Active surveillance (n=8079) n (%)	Watchful waiting (n=4570) n (%)	Delayed treatment (n=1223) n(%)	
Individual-level characteristics					
Year of diagnosis					
2002–2004	12 554 (28)	1637 (28)	1204 (26)	396 (32)	9713 (29.3)
2005–2007	15 937 (25)	2917 (33)	1497 (33)	430 (35)	11 093 (34.9)
2008–2010	17200 (38)	3525 (39)	1869 (41)	397 (33)	11 409 (35.9)
Age group (years old)					
Less or equal to 55	6148 (14)	948 (12)	343 (8)	120 (10)	4737 (14.9)
56–65	19 430 (43)	3369 (42)	1337 (29)	472 (39)	14 252 (44.8)
66–75	20 113 (44)	3762 (47)	2890 (63)	631 (52)	12 830 (40.3)
Diagnostic procedure					
Biopsy	43 670 (96)	7975 (99)	3232 (71)	1084 (89)	31 379 (71.9)
TURP	2021 (4)	104 (1)	1338 (29)	139 (11)	440 (21.8)
ADG score, median (IQR)	16 (7–22)	16 (7–23)	17 (9–26)	17 (8–23)	15 (7–22)
Survival status					
Alive	42 592 (93)	7746 (96)	3982 (87)	1127 (92)	29 737 (94)
Died	3099 (7)	333 (4)	588 (13)	96 (8)	2082 (7)
Prostate cancer death	396 (0.9)	13 (0.2)	45 (1)	15 (1)	323 (1)
Income quintile					
First (lowest)	6428 (14)	1061 (13)	778 (17)	189 (16)	4400 (14)
Second	8408 (18)	1442 (18)	923 (20)	238 (20)	5805 (18)
Third	8974 (20)	1485 (18)	893 (20)	244 (20)	6352 (20)
Fourth	9937 (22)	1734 (22)	928 (20)	247 (20)	7028 (22)
Fifth (highest)	11 791 (26)	2327 (29)	1025 (22)	302 (25)	8137 (26)
Rural					
Yes	6653 (15)	817 (10)	709 (16)	211 (17)	4916 (16)
No	39 003 (85)	7257 (90)	3857 (84)	1012 (83)	26 877 (85)
Physician-level characteristics					
Type of primary physician					
Urologist	30 552 (67)	5323 (66)	3866 (85)	1030 (84)	20 333 (64)
Radiation oncologist	14 986 (33)	2705 (34)	627 (14)	190 (16)	11 464 (36)
Physician volume per year					
1st quartile (lowest)	11 278 (25)	1799 (22)	1724 (38)	450 (37)	7305 (23)
2nd quartile	11 327 (25)	1794 (22)	1323 (29)	358 (30)	7852 (25)
3rd quartile	11 152 (24)	1807 (22)	813 (18)	215 (18)	8317 (26)
4th quartile (highest)	11 781 (26)	2628 (33)	633 (14)	197 (16)	8323 (26)
Institution-level characteristics					
Institution volume per year					
1st quartile (lowest)	10 954 (24)	1522 (19)	1389 (30)	380 (31)	7663 (24)
2nd quartile	10 824 (24)	1676 (21)	1390 (30)	297 (24)	7561 (24)
3rd quartile	11 315 (25)	1490 (18)	892 (20)	285 (23)	8648 (27)
4th quartile (highest)	11 497 (25)	2952 (37)	503 (11)	192 (16)	7850 (25)
Type of centre					
Non-cancer centre	19 444 (43)	3147 (39)	2340 (51)	636 (52)	13 321 (42)
Cancer centre	25 151 (55)	4493 (56)	1735 (38)	518 (42)	18 405 (58)

[a]All adjusted p values were significant (p<0.001) when the active surveillance group was compared to the watchful waiting group, to the delayed treatment group, and to the definitive treatment group, with the exception of the type of centre variable comparison between the AS group and the definitive treatment group (p=0.2). ADG: Aggregated Diagnosis Groups; IQR: interquartile range; TURP: transurethral resection of the prostate.

In multivariable analysis, older age, residing in an urban centre, being diagnosed in the later years of the study period, having an average neighbourhood income in the highest quintile, and being primarily managed by an urologist were all associated with greater odds of receiving AS. A forest plot summary of the effects of each covariate included in the full model (Model 5) is presented in Fig. 1.

Despite adding all individual-, physician-, and institution-level characteristics (Model 5; Appendix 6 at *www.cuaj.ca*), there remained significant variance between physicians

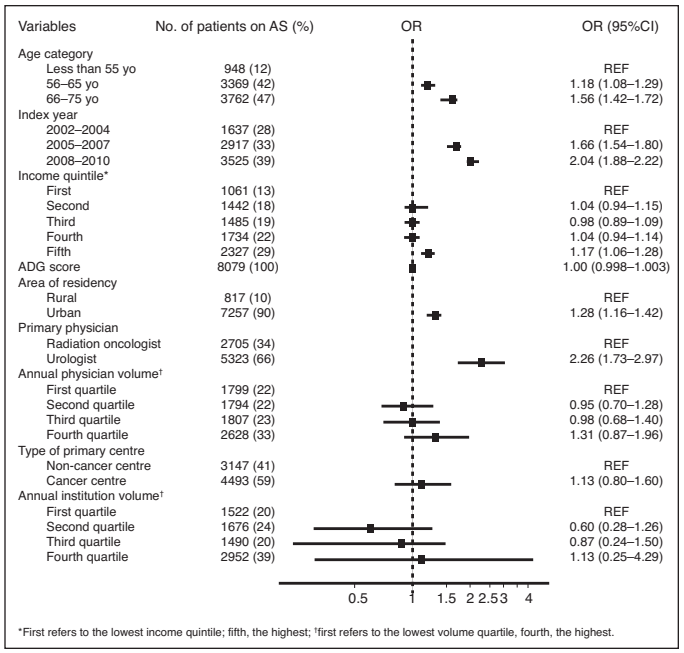

Fig. 1. Forest plot of the odds ratio (OD) for each covariate included in the multivariable analysis – uptake of active surveillance. ADG: Aggregated Diagnosis Groups; AS: active surveillance.

(14%) and institutions (36%). All three sensitivity analyses yielded similar results, with the exception of higher comorbidity, which was associated with lower odds of adopting AS using the most liberal definition of AS (Appendix 7 at *www.cuaj.ca*). There was marked heterogeneity between physicians with regard to the annual proportion of new patients managed by AS. Such heterogeneity was also observed, but to a lesser degree, among the treating institutions (Fig. 2).

Discussion

In this first Canadian population-based study on AS, 18% of men diagnosed with localized PCa between 2002 and 2010 were managed by this approach. Since 2002, the use of AS has increased by approximately 1% per year to reach a rate of 21% in 2010. This supports the fact that there is a growing acceptance of AS and likely represents an underestimation of the true proportion of men managed by AS, as the study was not restricted to low-risk PCa.[18,20,23] Assuming that 50% of subject had low-risk disease[15] and that the majority of patients included in our AS group were indeed low-risk, one could postulate that approximately 36% of patients with low-risk disease were treated by this approach during the study period. These rates were similar to those in other population-based studies, which varied from 10–38%[11,16-18,20-22] and in line with the recent single-institution series by Cristea et al.[24] Differences in study methodology (any-risk cohort vs. low-risk cohort; pooling AS and WW together vs. presenting them separately) and the countries' healthcare systems could explain the divergent rates. Given the similarities of our single-payer healthcare system with that of Sweden, we expected our rates to more closely resemble theirs.[19,20] In the Swedish study, which excluded men with high-risk diseases, 38% of Swedish men were managed expectantly between 1998 and 2011.[19] Rates of AS for the period covering 2007 and 2011 were 59% and 41% for the very-low and low- and intermediate-risk groups, respectively. Although a direct comparison with our study is difficult because our cohort included men with high-risk PCa and restricted the age to ≤75 years (the Swedish trial included 10% of men >75 years of age), our rates were comparable.

The factors associated with the uptake of AS in this study were similar to those previously identified.[14,18,19] Increasing age was strongly associated with a greater likelihood of being managed by AS. This may reflect a degree of discomfort either from physicians, patients, or both, with AS as a safe option for younger and healthier men. Contrary to previous findings, we identified that men living in an urban area and men with the highest income quintile were more likely to receive AS.[14,30] This may be explained by the universal

Table 2. Type of management according to year of diagnosis (n=45 691)

Year of diagnosis	Active surveillance n (%)	Watchful waiting n (%)	Delayed treatment n (%)	Definitive treatment n (%)	Total per year n (%)
2002	436 (11)	397 (10)	135 (3)	3044 (76)	4012 (9)
2003	545 (14)	388 (10)	124 (3)	2952 (74)	4009 (9)
2004	656 (15)	419 (9)	137 (3)	3321 (73)	4533 (10)
2005	801 (17)	433 (9)	148 (3)	3403 (71)	4785 (11)
2006	998 (19)	519 (10)	133 (3)	3716 (69)	5366 (12)
2007	1118 (19)	545 (9)	149 (3)	3974 (69)	5786 (13)
2008	1104 (20)	567 (10)	145 (3)	3773 (68)	5589 (12)
2009	1215 (21)	640 (11)	156 (3)	3835 (66)	5846 (13)
2010	1206 (21)	662 (12)	96 (2)	3701 (66)	5765 (13)
Total	**8079 (18)**	**4570 (10)**	**1223 (3)**	**31 819 (70)**	**45 691 (100)**

Cochrane-Armitage test for trend p value <0.001.

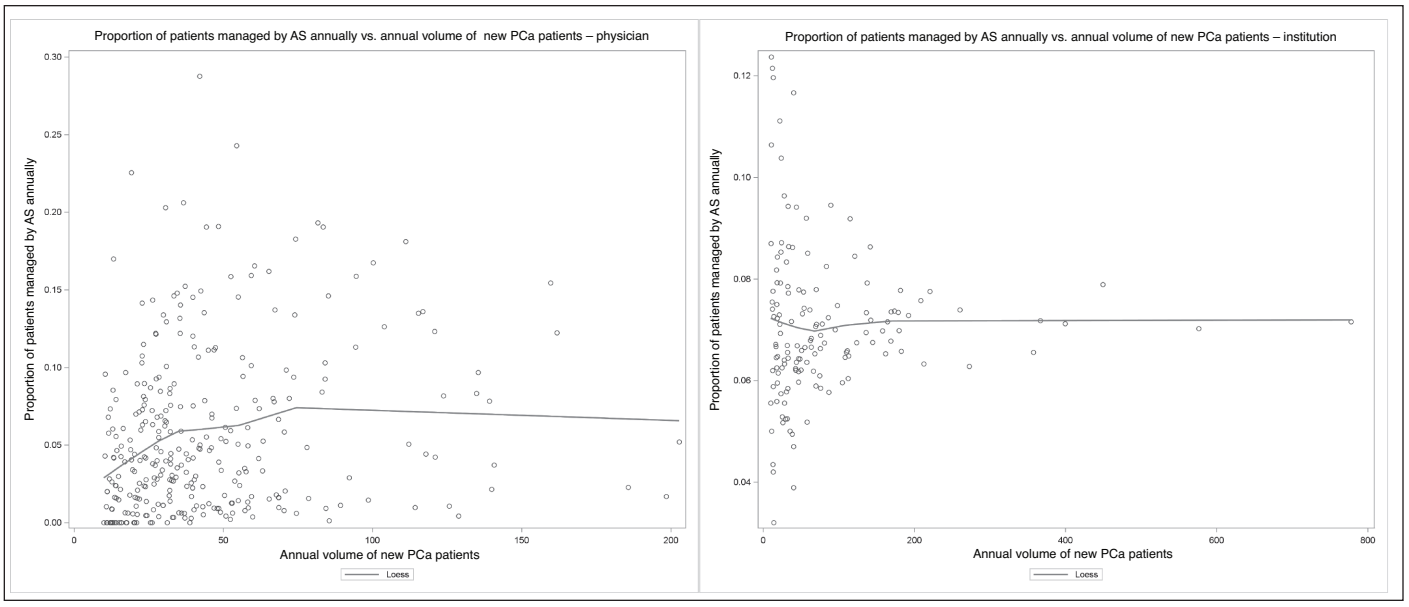

Fig. 2. Scatter plot of the proportion of patients managed by active surveillance annually vs. the annual volume of new prostate cancer patients ***(A)*** for each physician (minimum of 10 new case/year); ***(B)*** for each institution (minimum of 10 new case /year). AS: active surveillance; PCa: prostate cancer.

access to healthcare as opposed to a system in which care is more accessible to higher socio-economic groups. The lack of financial incentive to treat a patient with radical therapies in Canada could also be a plausible explanation as to why men treated in urban centres were more likely to undergo AS. Physicians working in designated cancer centres, which are usually located in urban centres, may have also adopted AS earlier than their other colleagues. Although plausible, this factor was not found to be significantly associated with the uptake of AS in our study.

A major strength of our study is that we used administrative data that encompasses the care of the entire Ontario population. Thus, whereas a study based on Surveillance, Epidemiology, and End Results (SEER) only included Medicare patients ≥65 years of age, our study included all men ≤75 years of age. This study also has several limitations. First, a repeat biopsy was used as a surrogate to identify patients who were managed by AS. Although patients should undergo a confirmatory biopsy (generally within the first year), some refuse.[25] To partially account for this, we used a minimum look-forward window of three years to identify a repeat biopsy. In addition, we also used several sensitivity analyses to validate our findings. Furthermore, the fact that we could not adjust for risk-group classification represents a significant limitation, as high-risk PCa and, for the most part, intermediate-risk PCa men are not generally considered candidates for AS. Thus, our estimate of the rate of AS is likely conservative and our interpretation of the identified factors associated with the uptake is limited by this confounder.

In spite of these limitations, the study is the first one that attempts to estimate the proportion of men managed with AS in Canada. It supports a greater acceptance of AS as a management option during the study period, but highlights the need for more widespread adoption. In this era of personalized medicine and concerns regarding overtreatment, this study provides a starting point for further studies that should aim toward estimating the ideal proportion of patients (benchmark) with low-risk PCa that should be managed by AS.

Conclusion

Between 2002 and 2010, 18% of men diagnosed with localized PCa in Ontario were managed by AS. Over the years, there has been a steady increase in the uptake of AS, which attests to the growing acceptance of this management option. The decision to adopt AS was influenced by several individual and physician characteristics. Further research is underway to better understand the forces influencing care and the rigour with which AS is being provided. The data suggest that there is significant opportunity for more widespread adoption of AS in Ontario.

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Correspondence: Dr. Antonio Finelli, Division of Urology, Departments of Surgery and Surgical Oncology, Princess Margaret Cancer Centre, University Health Network and the University of Toronto, Toronto, ON, Canada; antonio.finelli@uhn.ca