Using real-world, population-level data to assess the uptake of active surveillance for low-grade prostate cancer before and after the release of clinical guidelines

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ABSTRACT

Introduction: Clinical guidelines recommend active surveillance (AS) as the preferred strategy for men with localized grade group (GG) 1 prostate cancer (PCa). We determined if the percentage of GG1 PCa patients in Ontario, Canada, managed by AS changed after the introduction of AS clinical guidelines and assessed adherence to the recommended followup protocol.

KEY MESSAGES

- Developing and disseminating clinical practice guidelines is time-consuming and costly.
- This work shows that the publication of guidelines recommending active surveillance for grade group 1 prostate cancer was associated with increased use of AS in Ontario.
- It provides support for the continued development of clinical practice guidelines by specialist and regional organizations in Canada.

Methods: Using Ontario administrative databases, we conducted time series analysis (autoregressive integrated moving average [ARIMA] models) in a population-based cohort of men diagnosed with GG1 PCa (2010–2018). Men were classified as managed by AS if they had repeat (confirmatory) biopsy within two years. Sensitivity analyses (treatment classification variation) and secondary analyses (low-risk GG1 and GG2 PCa) were conducted.
Results: We identified 12 236 eligible GG1 PCa patients, of which 7749 (63.3%) were initially managed by AS. Percentage AS increased from 44% in 2010 to 82% in 2018. Interrupted time series analysis estimated an immediate step change of 6.2 percentage points (95% confidence interval [CI] 3.0, 9.4) and a difference in slope of -2.3 percentage points (95% CI -6.9, 2.3) per year. Findings were robust to sensitivity analyses and similar for low-risk PCa. Adherence to monitoring and AS uptake in GG2 patients were not associated with guideline publication. Limitations include lack of treatment intent information in administrative data.
Conclusions: The use of AS for low-grade PCa patients in Ontario increased from almost one in two patients in 2010 to four in five patients in 2017/2018. Adoption appeared to reflect the growing acceptance of AS prior to the guidelines, as well as an increase in response to the guideline introduction.

INTRODUCTION

Clinical practice guidelines aim to help practitioners and patients make healthcare decisions that optimize patient care and reduce variability in healthcare provision.[1-5] The magnitude of uptake of guideline recommendations and the degree of improvement in outcomes vary significantly.[6-9] Within uro-oncology, adherence to clinical practice guidelines for treatment and monitoring for prostate cancer (PCa) is reported to be low and/or variable.[5,10-13]

Active surveillance (AS) has been promoted for low-risk PCa to avoid the adverse effects of definitive treatment (surgery/radiation). Clinical guidelines were published by Ontario Health (then Cancer Care Ontario) in 2015[14] (and endorsed by the American Society of Clinical Oncology in 2016[15]) which recommended AS as the preferred management strategy for patients with low-risk (grade group (GG) 1) localized PCa. While the uptake of AS has increased over time in many jurisdictions,[16-19] there are no reports of the influence of CPG guidelines on this trend.

Our main objective was to determine if the percentage of men in with low-grade (GG1) PCa managed by AS in Ontario changed after the introduction of the 2015 AS clinical guidelines and to assess adherence to the recommended follow-up AS protocol. In addition, we examined the change in percentage of men managed by AS who had low-risk GG1 or GG2 PCa.

METHODS

We conducted a retrospective study using Ontario population-level health administrative databases housed at ICES (https://www.ices.on.ca/). The study was approved by the University

Health Network Research Ethics Board. We used the Ontario Cancer Registry database to identify men diagnosed with PCa topography code C61 (ICD-O-3: C61.9), histology 81403 as their first primary cancer between January 1, 2010 and December 31, 2018. GG, PSA, and clinical stage at time of diagnostic biopsy were obtained from the Ontario Cancer Registry Collaborative Staging data (see Supplemental Table 1 for codes). We included patients with GG1 (main analysis) or GG2 PCa, and a transrectal or transperineal biopsy within 30 days of diagnosis). To optimize classification of management, only patients who had ≥ 2 years of follow-up from the time of diagnosis were included.

Data on repeat prostate biopsies, pelvic MRI, PSA tests, and PCa treatments were obtained from the Ontario Health Insurance Plan database for the 2-year period after PCa diagnosis for each patient. A repeat biopsy or pelvic MRI in the 60 to 730 days post diagnosis was considered a confirmatory biopsy.

Classification of treatment groups (Supplementary Table 2)

Patients who had a confirmatory biopsy within 2 years after diagnosis without any prior PCa treatment (radical prostatectomy, radiation, ADT, or orchiectomy) were classified as active surveillance (AS). Patients who had definitive PCa treatment within 6 months after their PCa diagnosis without a repeat biopsy/pelvic MRI before treatment were classified as Initial Treatment. Patients who did not have repeat biopsy/pelvic MRI or any PCa treatment within 2 years after diagnosis and were ≥ 75 year of age at diagnosis were classified as Watchful Waiting (WW). On average, patients aged over 75 have a life expectancy <10 years and are unlikely to be candidates for definitive treatment. Patients who could not be classified into AS, Initial Treatment, or WW were excluded. This included patients who received delayed therapy (6 to 24 months post-diagnosis) and younger patients (< 75 years) who did not have a confirmatory biopsy, pelvic MRI or definitive treatment within 2 years.

Sensitivity analyses

For the first sensitivity analysis, the definition of WW was modified to include patients aged 70-74 years with ACG comorbidity score >16 (highest tertile). Empirically, we found these patients were unlikely to be candidates for definitive treatment (<2% had radical prostatectomy, a marker of localized definitive treatment) and had average life expectancy <10 years based on life tables. In a second sensitivity analysis, pelvic MRI was not considered as a confirmatory biopsy.

Outcome measures

The main outcome measure was the percentage of GG1 PCa initially managed by AS (denominator is total of all treatment groups) by year of diagnosis. Furthermore, we also assessed AS in patients with low-risk (GG1, PSA <= 10; clinical stage <= cT2a) and with GG2 PCa.

Additional outcome measures assessed compliance with recommended AS monitoring protocols, including the percentage of AS patients who had a confirmatory biopsy/pelvic MRI within 1 year of diagnosis and who had PSA measured every 3-6 months. Two PSA metrics were used: the percentage of AS patients with ≥ 4 PSA measurements, and the percentage with average time between PSA measurements of ≤ 6 months during the 2-year follow-up.

Other variables
Age at diagnosis (categorical), neighbourhood income quintile, ACG comorbidity index (The Johns Hopkins ACG® System Version 10, Aggregated Diagnosis Groups; ADGs, excluding malignancy), geographic location (rurality, Local Health Integration Network [LHIN]) and PSA values were obtained from the administrative data. During the study period, Ontario was divided in 14 LHINs which were responsible for regional administration of public healthcare services.

Statistical analysis
We used interrupted time series analysis (autoregressive integrated moving average (ARIMA) models) [20] to examine whether publication of the AS guidelines in 2015 was associated with a change in the percentage of men managed by AS or in compliance measures (biopsy within 1 year and frequency of PSA testing).

ARIMA modeling was performed using R ('astsa' and 'forecast' packages) with two-sided test and alpha=0.05 to define statistical significance. We evaluated stationarity visually using plots of the raw and differenced data and used an automated algorithm (auto.arima) in the forecast package for R[21] to identify potential ARIMA model terms. We postulated that introduction of the AS guidelines would result in an immediate increase in percentage of patients on AS (**step change,** difference between the observed value and the predicted value after the guideline publication) as well as a change in the slope between pre- and post-guideline periods (**ramp).** We evaluated model fit by examining residuals and formally tested for autocorrelation using the Ljung-Box test.

RESULTS
A total of 16,544 GG1 PCa patients met the inclusion criteria. Patients who could not be classified into the AS, treatment or WW groups (n=4,308) were excluded, leaving 12,236 patients (Figure 1). For the main analysis, 7,749 of patients (63.3%) were classified as AS, 3,694 (30.2%) as initial treatment, and 793 (6.5%) as WW.

Compared to AS, patients who received immediate treatment were slightly younger, had a lower income quintile and more frequently lived in rural areas, but had similar PSA levels and ACG score (Table 1). WW patients were older (by definition), had slightly lower income quintile, higher ACG score, and higher PSA compared to the AS and initial treatment groups. The percentage of PCa patients managed by AS ranged from 43% to 73% across health planning units (data not shown).

For the main analysis, the percentage of patients on AS increased over time from 44% in 2010 to a high of 82% in 2017 (Figure 2a). The results were similar for the sensitivity analyses. Figure 2b shows the observed and predicted percentage on AS based on linear trend prior to publication of AS guidelines for the main analysis. Interrupted time series analysis estimated a statistically significant step change of 6.2 percentage points (95% CI: 3.0, 9.4) and a not statistically significant ramp (difference in slope between pre- and post-guideline periods) of -2.3 percentage points (95% CI: -6.9, 2.3). These results suggest that the publication of guidelines in 2015 was associated with an immediate increase of 6.2 percentage points in percentage AS

followed by a decrease of 2.3 percentage points in the difference per year thereafter. In other words, percentage AS at the end of 2015 was estimated to be 3.9 percentage points higher (6.2-2.3) than predicted had the guidelines not been published. As indicated by the reduced slope (ramp) and in the observed values shown in Figure 2, the rate of increase in percentage AS slowed after guideline introduction and percentage AS appeared to plateau in 2017 at about 81%. Results of the time series analyses were virtually identical for the 2 sensitivity analyses (data not shown).

When the cohort was limited to low-risk PCa (GG1, PSA <=10; clinical stage <cT2), the total number was lower (n=7,138); however, the overall percentage of patients on AS (66.1%) and the trend over time was similar to the full cohort (Supplementary Figure 1). The interrupted time series results were similar to those for the full GG1 cohort with a step change of 6.8 percentage points (95%CI: 2.2.0, 11.5) and a ramp (slope) of -1.3 percentage points (95%CI: -7.9, 5.3).

For patients with GG2 (n=14,548), the percentage AS was substantially lower (14% overall) compared to the GG1 cohort. For the main definition analysis, the percentage of GG2 patients on AS increased from 13.2% in 2010 to 17.3% in 2018 (Figure 3). Results of time series analysis were not statistically significant (step change 0.23 (95%CI -2.43, 2.90); ramp 1.07 (95%CI -0.27, 2.40). The results were similar for the first sensitivity analysis; however, when pelvic MRI was not considered as a "confirmatory biopsy", the percentage AS was lower and did not change over time (Figure 3).

Compliance measures for those with GG1 PCa

Overall, 52% of AS patients had a confirmatory biopsy within 1 year with no consistent trend over time (Figure 4a). Almost half (49%) of patients had ≥ 4 PSA tests in the 2 years post-diagnosis and the average time between PSA measurements was ≤6 months for 67% patients (figure 4b). There was no consistent time trend for either PSA metric. Results of time series analysis for compliance measures were not statistically significant (data not shown).

Patients who met the biopsy and PSA criteria had slightly higher PSA than those that did not (Supplementary Table 3). Older patients less likely to have a repeat biopsy within 1 year; however, there was no association age and meeting the PSA frequency criteria. There was no association of ACG score with any of the compliance measure criteria.

DISCUSSION

Although absolute rates vary due to different methodology and/or AS definitions, data from several countries show an increase over time in the percentage of men with low risk/GG1 PCa initially managed with AS.[16,17,22] AS uptake had been increasing steadily in Ontario prior to the 2015 clinical guidelines; however, time series analysis indicated that there was a significantly greater increase in AS after 2015 relative to that predicted based on the trend before 2015. Earlier clinical practice guidelines included AS as a treatment option for men with low-risk PCa,[23,24] particularly in men with lower life expectancy; however, the 2015 Ontario guidelines clearly recommended AS for most of these patients. We know of no other reports on the

association of clinical practice guidelines with AS uptake. However, the Michigan Urological Surgery Improvement Collaborative (MUSIC) demonstrated that a 2014 initiative promoting AS was associated with a dramatic increase (from approximately 44 to 73% for low-risk PCa) AS rates compared to the gradual national increase.[25]

Although the optimal rate of AS for low risk PCa has not been defined, Cooperberg et al. suggest that it is likely greater than 80%.[22] While recent US data suggests about 60% of low risk PCa is managed initially by AS,[22] higher rates of about 70- 75% have been reported by the MUSIC collaborative and in Sweden.[25,26] In the present study, about 80% of patients with GG1 PCa, and 85% with low-risk GG1 PCa, were initially managed by AS in the most recent years (2018) and our results suggest a similar plateauing of AS uptake (ceiling effect).

AS for selected patients with early intermediate-risk prostate cancer appears to be safe over 15 years.[27] In agreement with our results, a small increase over time in the rate of AS in ≥GG2 or favourable intermediate risk PCa has been reported;[17,25] however, the overall rate in these higher risk groups (16 to 25%) remains substantially lower than for GG1. We did not observe any effect of guideline publication on these rates.

Unlike previous AS clinical guidelines, the 2015 CCO guidelines provided a recommended surveillance protocol. In our study, just over half of men had a repeat biopsy within 1 year of diagnosis or had 4 PSA measurements within 2 years. Although there is variation in monitoring protocols across difference centres, the literature also suggests that a large proportion of men on AS do not undergo recommended follow-up testing.[12,28-31] We found no evidence that compliance with monitoring improved by calendar year of diagnosis, or specifically in relation to the published guidelines.

The reasons for poor compliance with monitoring during AS are not known. Prostate biopsy is an invasive procedure and understandably, men might be reluctant to undergo this procedure on a repeated basis. As reported here and by others, older men are less likely to have repeat biopsies.[28,30,31] While this may suggest that age and life expectancy considerations influence monitoring intensity, we did not see an association of age with PSA monitoring, and comorbidity was not associated with repeat biopsy or PSA monitoring. Patients who met the monitoring criteria had statistically significantly higher PSA values at diagnosis; however, the clinical difference was very small (0.2 ng/ml).

Poor compliance with longer term surveillance on AS may result from provider or patient fatigue and/or complacency about risk of PCa progression. If patients are not monitored with appropriate frequency while on AS, they may face delays in detecting disease progression and risk missing the opportunity for curative treatment. Further study of the factors (patient, physician and health system-related) associated with monitoring compliance, as well as examination of the impact of intensity/deintensification of AS follow-up on cancer-specific outcomes and patient-reported outcomes, is needed.

A strength of our study is the use of interrupted time series analysis which accounts for pre-existing trends by longitudinally tracking the outcome before and after the intervention, rather than simply comparing before and after measures. There were no other national/provincial

level interventions targeting AS during this period, although we cannot rule out local level initiatives.

The use of population-based data is also a strength; however, administrative databases do not specifically record management strategy for PCa and the potential for misclassification exists. There was a number of patients who could not be classified into any management group. In particular, 19% of patients (<75 years old) did not appear to have a confirmatory biopsy or treatment within 2 years after diagnosis. Since it is unlikely that all of these patients were on WW, they were excluded from the study. Patients in the unclassified group may have been considered for AS; but were not adherent to the monitoring protocol (e.g. declined to have a confirmatory biopsy). While treatment classification issues may affect estimates of the absolute uptake of AS, these factors likely have little effect on trends over time, where the same decision rules to allocate patients are used at each time interval.

CONCLUSIONS

AS use for low-grade PCa patients in Ontario increased from almost 1-in-2 patients in 2010 to 4-in-5 patients in 2017/2018. Adoption appeared to reflect growing acceptance of AS prior to guideline introduction; however, the significant increase associated with guideline introduction indicates that a clinical practice guideline influenced uro-oncology practice and supports the production of future guidelines in Canada. Overall, AS adoption is high in Ontario; however, there could be important variation across practices and clinicians. Identifying and addressing such variation could lead to improvements in patient care. In contrast to overall AS adoption, compliance with AS monitoring was low and did not change in relation to guideline publication. Further exploration of adherence with monitoring, and its importance on outcomes, is warranted to ensure optimal care of patients on AS.

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FIGURES AND TABLES

Figure 1. Flow chart for grade group 1 cohort identification.

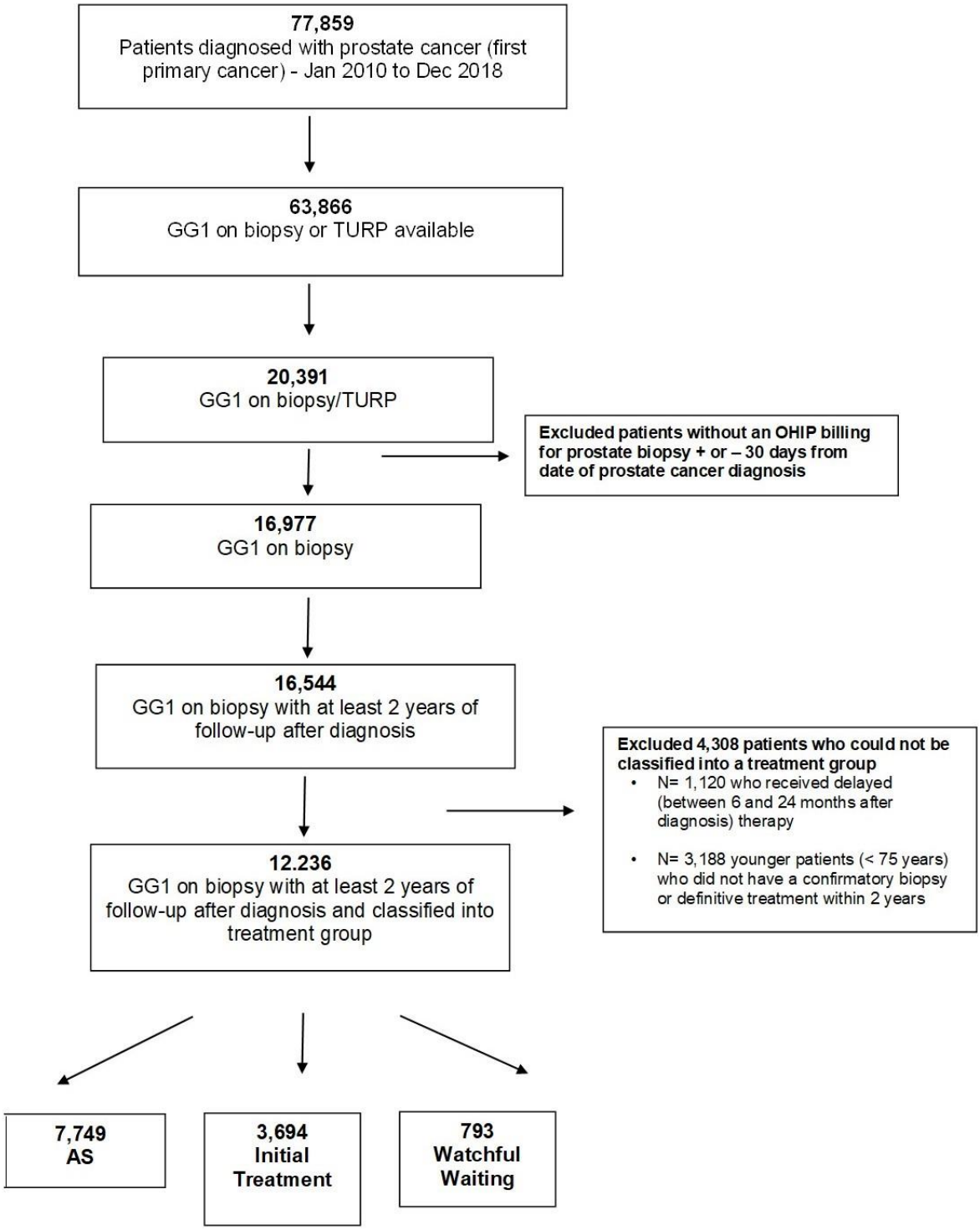
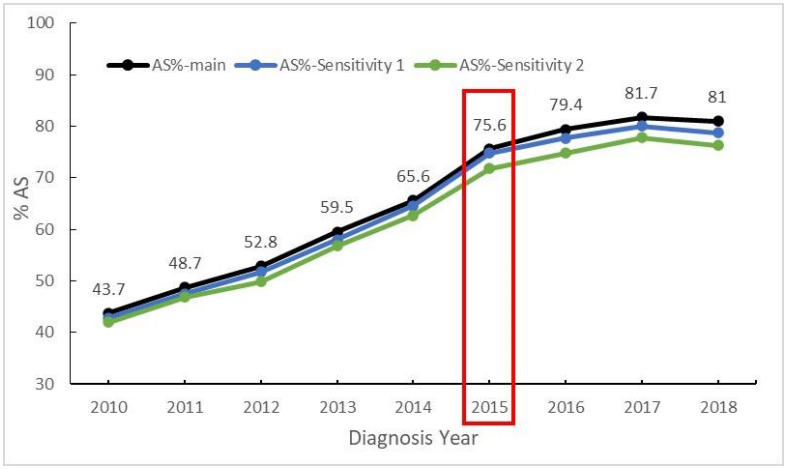


Figure 2. Percentage of active surveillance (AS) by year for men with grade group 1 prostate cancer. (A) Observed % AS results for main analyses (black line) and two sensitivity analyses (blue and green lines). % AS numbers on graph are for the main analysis. For sensitivity analysis 1, the definition of watchful waiting was modified to include patients who were aged 70–74 years with ACG comorbidity score >16 (highest tertile) at diagnosis. For sensitivity analysis 2, pelvic magnetic resonance imaging was not considered an alternative to confirmatory biopsy. (B) Observed % AS results for main analysis (black line) and associated forecasted % AS (red dashed line) predicted based on the linear trend prior to publication of the AS guidelines. Clinical guidelines for using AS to manage localized prostate cancer were published by Ontario Health (then Cancer Care Ontario) in 2015 (indicated by red rectangle on the figure).

A



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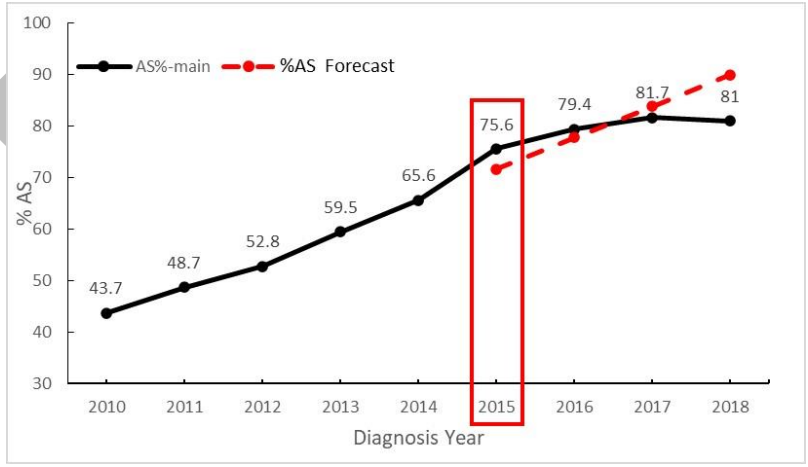


Figure 3. Percentage active surveillance (AS) by year for men with grade group 2 prostate cancer. Observed % AS results for main analyses (black line) and two sensitivity analyses (blue and green lines). Main and Sensitivity 1 results are similar and lines are overlaid on the graph. % AS numbers on graph are for the main analysis. For sensitivity analysis 1, the definition of watchful waiting was modified to include patients who were aged 70–74 years with ACG comorbidity score >16 (highest tertile) at diagnosis. For sensitivity analysis 2, pelvic magnetic resonance imaging was not considered an alternative to confirmatory biopsy. The forecasted % AS related to the main analysis (red dashed line) is predicted based on the linear trend prior to publication of the AS guidelines. Clinical guidelines for using AS to manage localized prostate cancer were published by Ontario Health (then Cancer Care Ontario) in 2015 (indicated by red rectangle on the figure).

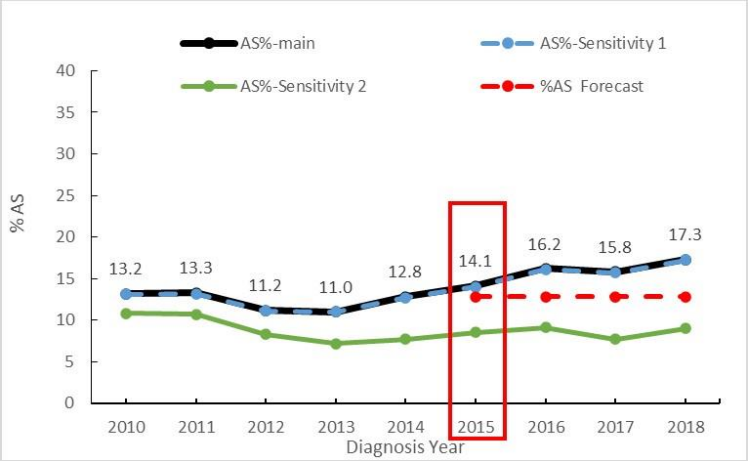
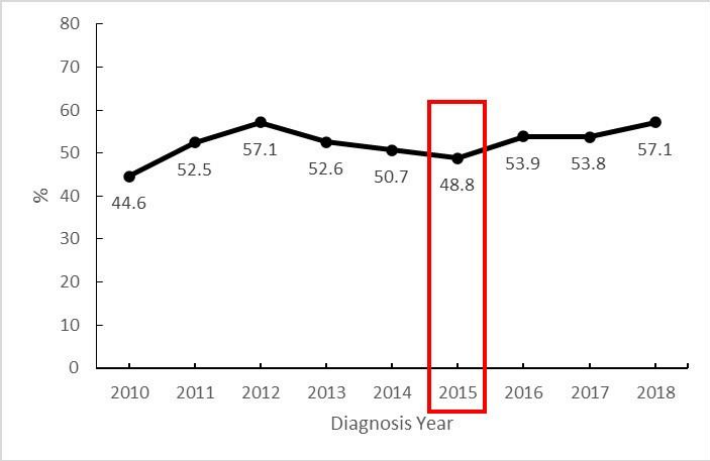


Figure 4. Percentage of men with grade group 1 prostate cancer on active surveillance (AS) who met compliance measures by year. (A) Percentage of men on AS who had a repeat biopsy within 2 years after prostate cancer diagnosis. (B) Percentage of men on AS who had ≥4 prostate-specific antigen (PSA) measures within 2 years after diagnosis (black line) or who had ≤6 months average between PSA measures within 2 years after diagnosis. Definition of AS based on the main analysis. Clinical guidelines for using AS to manage localized prostate cancer were published by Ontario Health (then Cancer Care Ontario) in 2015 (indicated by red rectangle on the figure).

A



B

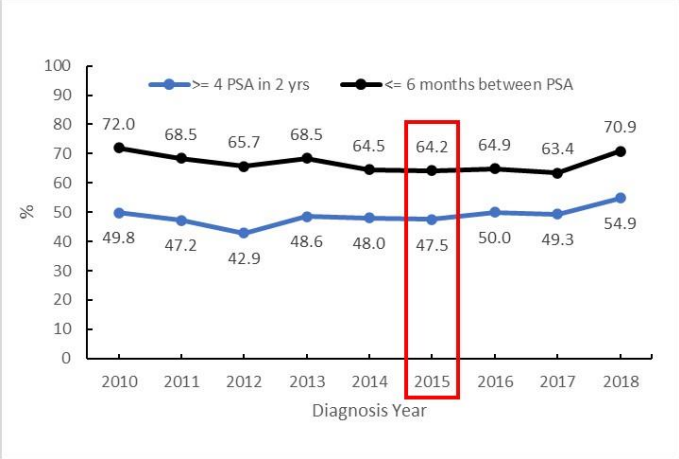


Table 1. Characteristics by management strategy (main analysis definition)			
	AS (n=7749)	**Initial treatment (n=3694)**	**WW (n=793)**
Age (years), n (%)			
<55	938 (12.1%)	618 (16.7%)	0
55–64	3276 (42.3%)	1605 (43.5%)	0
65–70	1945 (25.1%)	829 (22.4%)	0
70–74	1162 (15.0%)	411 (11.1%)	0
≥75	428 (5.5%)	231 (6.3%)	793 (100%)
Income quintile[1], n (%)			
1	917 (11.9%)	508 (13.8%)	126 (15.9%)
2	1339 (17.3%)	697 (18.9%)	165 (20.8%)
3	1494 (19.3%)	753 (20.4%)	169 (21.3%)
4	1685 (21.8%)	828 (22.5%)	155 (19.6%)
5	2289 (29.6%)	901 (24.4%)	178 (22.5%)
Missing	25	7	0
Rural, n (%)			
Yes	824 (10.7%)	545 (14.8%)	110 (13.9%)
Missing	12	3	0
ACG score[2], median (IQR)	7 (3, 15)	7 (3, 15)	14 (6, 21)
ACG score, n (%)			
< 7	3660 (47.2%)	1775 (48.1%)	215 (27.1%)
7–16	2435 (31.4%)	1135 (30.7%)	253 (31.9%)
>16	1654 (21.3%)	784 (21.2%)	325 (41.0%)
PSA (ng/ml), median (IQR)	6.2 (4.8, 8.3) (n=6979)	6.3 (4.8, 9.0) (n=3388)	8.1 (5.9, 11.0) (n=663)

[1]Neighborhood income quintile based on postal code and census data. [2] The Johns Hopkins ACG® System Aggregated Diagnosis Groups; ADGs, Version 10, excluding malignancy. ADG: aggregated diagnosis groups; AS: active surveillance; IQR: interquartile range; PSA: prostate-specific antigen; WW: watchful waiting.