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Active treatment in low-risk prostate cancer: a population-based study

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ABSTRACT

Background Active surveillance instead of active treatment (AT) is preferred for patients with low-risk prostate cancer (LR-PCa), but practice varies widely. We conducted a population-based study to assess the proportion of patients who underwent AT between January 2011 and December 2014, and to evaluate factors associated with AT.

Methods The provincial cancer registry was linked to administrative health datasets to identify patients with LR-PCa and to acquire demographic, tumour, and treatment data. The primary outcome was receipt of AT during the first 12 months after diagnosis, defined as any receipt of external-beam radiotherapy, brachytherapy, radical prostatectomy, cryotherapy, or androgen deprivation. Univariate and multivariate logistic regression were used to analyze the correlation between patient and tumour factors and AT.

Results Of 1565 patients with LR-PCa, 554 (35.4%) underwent AT within 12 months of diagnosis. Radical prostatectomy was the most common treatment (58%), followed by brachytherapy (29.6%). Younger age [odds ratio (OR) 0.92; 95% confidence interval (CI): 0.91 to 0.94], lower score (≥3) on the Charlson comorbidity index (OR: 0.36; 95% CI: 0.19 to 0.68), T2 stage (OR: 3.05; 95% CI: 2.03 to 4.58), higher prostate-specific antigen (PSA) at diagnosis (OR: 1.13; 95% CI: 1.06 to 1.21), radiation oncologist consultation (OR: 3.35; 95% CI: 2.55 to 4.39), and earlier diagnosis year (2012 OR: 0.46; 95% CI: 0.34 to 0.63; 2013 OR: 0.45; 95% CI: 0.32 to 0.63; 2014 OR: 0.33; 95% CI: 0.23 to 0.47) were associated with a higher probability of AT.

Conclusions This contemporary population-based study demonstrates that approximately one third of patients with LR-PCa undergo AT. Patients of younger age, with less comorbidity, a higher tumour stage, higher PSA, earlier year of diagnosis, and radiation oncologist consultation were more likely to undergo AT. Further investigation is needed to identify strategies that could minimize overtreatment.

Key Words Prostate cancer, low-risk; active surveillance; active treatment; radiotherapy; brachytherapy; radical prostatectomy

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INTRODUCTION

Prostate cancer (PCa) is a relatively indolent malignancy, with a lifetime risk of cancer-specific death of approximately 2.5%[1]. In this era of prostate-specific antigen (PSA) testing, most patients are diagnosed with low-risk PCa (LR-PCa)[2,3]. If left untreated, LR-PCa is unlikely to cause harm[4,5].

The difference in outcomes for patients with LR-PCa who receive immediate treatment compared with active surveillance (AS) does not appear to be significant. In the ProtecT trial, 1643 men were randomized to active monitoring, prostatectomy, or radiotherapy. After a median 10 years, PCa-specific deaths were not significantly different between the groups[6]. Long-term outcomes from a number of AS cohorts have also been favourable[7–9]. Stattin *et al.*[10], in a large national cancer registry study, reported an overall PCa-specific mortality rate of less than 3% for men with LR-PCa managed initially with AS. The absolute difference in PCa-specific mortality at 10 years for those managed with surveillance compared with surgery was approximately 2%. That result is comparable to the 5% absolute difference in the Scandinavian

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Prostate Cancer Group Study 4 that compared no treatment with surgery[11].

Upfront treatment of PCa puts patients at risk for significant morbidities, including rectal bleeding, urinary incontinence, and sexual dysfunction, with an accompanying deterioration in health-related quality of life[12]. International and Canadian guidelines[13–16] recommend that patients with LR-PCa should be counselled about AS and about how upfront treatment can cause significant morbidity with little benefit. Despite such guidelines, a 2015 report from the Canadian Partnership Against Cancer noted large interprovincial variations in the treatment of patients with LR-PCa[17]. Other contemporary literature shows a significant discrepancy in the use of AS for patients with LR-PCa[18,19]. We therefore undertook a population-based study to evaluate the use of upfront active treatment (AT) in patients with LR-PCa and to explore the factors associated with AT instead of AS.

METHODS

This retrospective provincial population–based study enrolled all patients 18 years of age and older diagnosed with prostate adenocarcinoma between 1 January 2011 and 31 December 2014. Patients were included if their disease was low-risk, defined per the Genitourinary Radiation Oncologists of Canada risk stratification system[20] as meeting all of these criteria: clinical stage T1–2a, biopsy Gleason sum score of 6 or less, and PSA 10 ng/mL or less. Patients were excluded if they did not have provincial health care coverage for the 12 months before diagnosis.

The primary outcome was receipt of AT, defined as treatment with external-beam radiotherapy, brachytherapy, radical prostatectomy, cryotherapy, or androgen deprivation therapy during the first 12 months after diagnosis. Androgen deprivation therapy included any of the luteinizing hormone–releasing hormone agonists or antagonists, or the antiandrogens.

The Alberta Cancer Registry (ACR) was used to identify patients who met the eligibility criteria. The ACR covers the province's population, which was 3.6 million in 2011, and meets the Gold Standard for Registry Certification by the North American Association of Central Cancer Registries, indicating complete, accurate, and timely data collection. All cancers in the province are mandatorily reported to the ACR. Treatment data for external-beam radiotherapy, brachytherapy, and androgen deprivation therapy were obtained from the ACR. Physician claims data were used to identify treatment with radical prostatectomy and cryotherapy.

Research ethics approval for the study was obtained from the Health Research Ethics Board of Alberta–Cancer Committee.

Statistics

The primary objectives of this study were to estimate the proportion of patients diagnosed with LR-PCa who received AT and to evaluate factors associated with the use of AT. The use of AT was stratified by provincial health services zone.

We explored the association between AT and age at diagnosis, comorbidity (Charlson comorbidity index), health services zone, year of diagnosis, clinical tumour stage, PSA at diagnosis, and consultation with a radiation oncologist within 12 months of diagnosis. Because the number of positive biopsy cores was available for only 394 patients, that factor was not included in the multivariable model. Chi-square and Fisher exact tests were used to compare categorical characteristics between patients who received AT and those who did not. Continuous variables were assumed to be normal per the central limit theorem, and *t*-tests were used to compare patients receiving and not receiving AT. Univariate and multivariable logistic regression were used to evaluate the correlation of clinico-demographic and tumour factors with AT. Tests of significance were 2-sided, with p values less than 0.05 denoting statistical significance. Significant predictive factors identified in the univariate analysis were included in the multivariable analysis. Odds ratios (ORs) are reported as point estimates, with 95% confidence intervals (CIs). All analyses were conducted using the IBM SPSS Statistics software application (version 25: IBM, Armonk, NY, U.S.A.).

RESULTS

Table I summarizes patient characteristics for the 1565 patients with LR-PCa identified from the ACR. Significant differences between patients who underwent AT and those who did not were observed. Patients undergoing AT were significantly younger and had fewer comorbidities and a higher serum PSA at diagnosis. A higher proportion of them were clinically staged as T2, had more than 3 positive cores in biopsy, and had a consultation with a radiation oncologist within 12 months of diagnosis.

Of the 1565 patients, 554 (35.4%) underwent AT within 12 months of diagnosis. Figure 1 shows the proportion of patients undergoing AT by year. Significant variation between the health services zones was evident, with the proportion of patients undergoing AT by 12 months ranging from 26% to 55% (Table II). Of all treatment modalities used, the most common were radical prostatectomy (58%) and brachytherapy (29.6%). Figure 2 summarizes the AT modalities stratified by health services zone.

On univariate analysis, delivery of AT was associated with age at diagnosis, score on the Charlson comorbidity index, health services zone, year of diagnosis, clinical tumour stage, serum PSA at diagnosis, number of involved biopsy cores, and radiation oncologist consultation within 12 months of diagnosis (Table III).

Using multivariable logistic regression, younger age (OR: 0.92; 95% CI: 0.91 to 0.94; $p < 0.001$), lower score on the Charlson comorbidity index (1–2 OR: 0.96; 95% CI: 0.70 to 1.30; $p = 0.77$; ≥3 OR: 0.36; 95% CI: 0.19 to 0.68; $p = 0.002$), clinical stage T2 (OR: 3.05; 95% CI: 2.03 to 4.58; $p < 0.001$), higher serum PSA at diagnosis (OR: 1.13; 95% CI: 1.06 to 1.21; $p < 0.001$), earlier year of diagnosis (2012 OR: 0.46; 95% CI: 0.34 to 0.63; $p < 0.001$; 2013 OR: 0.45; 95% CI: 0.32 to 0.63; $p = 0.001$; 2014 OR: 0.33; 95% CI: 0.23 to 0.47; $p < 0.001$), and consultation with a radiation oncologist within 12 months of diagnosis (OR: 3.35; 95% CI: 2.55 to 4.39; $p < 0.001$) were all associated with a higher likelihood of AT. A difference in the proportion of patients receiving AT at the two largest urban centres, Calgary and Edmonton, was also evident

TABLE I Patient characteristics

Characteristic	Active treatment		*p* Value
	No	Yes	
Patients *(n)*	1011	554	
Mean age at Dx (years)	63.5±8.5	59.9±7.3	<0.001
Age category at Dx [*n* (%)]			
<70 Years	820 (81.1)	515 (93.0)	<0.001
≥70 Years	191 (18.9)	39 (7.0)	
Score on the CCI [*n* (%)]			
0	678 (70.6)	423 (76.5)	<0.001
1–2	210 (21.9)	114 (20.6)	
≥3	73 (7.6)	16 (2.9)	
Unknown or missing	50 (4.9)	1 (0.2)	
Health services zone *(n)*			
Calgary	592	208	<0.001
Edmonton	141	174	
Central	106	67	
South	115	58	
North	56	46	
Dx year [*n* (%)]			
2011	229 (22.7)	233 (42.1)	<0.001
2012	273 (27.0)	144 (26.0)	
2013	230 (22.7)	100 (18.1)	
2014	279 (27.6)	77 (13.9)	
T Stage [*n* (%)]			
T1 (T1a–c, T1nos)	959 (94.9)	440 (79.4)	<0.001
T2	52 (5.1)	114 (20.6)	
Mean serum PSA at Dx (ng/mL)	5.6 (2.3)	5.8 (1.9)	0.02
PSA group [*n* (%)]			
0 to 2.5 ng/mL	126 (12.5)	21 (3.8)	<0.001
>2.5 ng/mL to 5 ng/mL	259 (25.6)	174 (31.4)	
>5 ng/mL to 10 ng/mL	625 (61.9)	359 (64.8)	
Positive biopsy cores [*n* (%)]			
1–2	125 (71.8)	86 (39.1)	<0.001
3–6	45 (25.9)	108 (49.1)	
≥7	4 (2.3)	26 (11.8)	
Unknown or missing	837 (82.8)	334 (60.3)	
Radiation oncologist consultation [*n* (%)]			
No	840 (83.1)	263 (47.5)	<0.001
Yes	171 (16.9)	291 (52.5)	

Dx = diagnosis; CCI = Charlson comorbidity index; PSA = prostate-specific antigen.

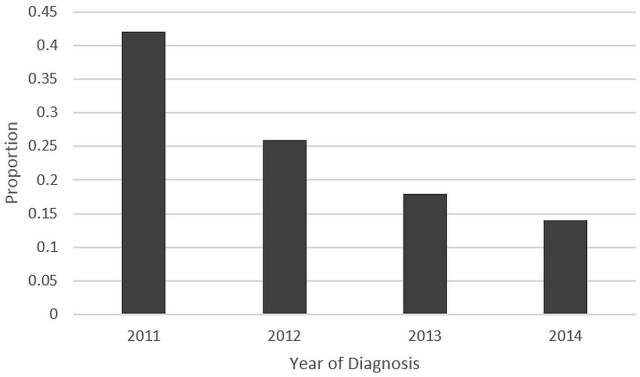

FIGURE 1 Proportion of patients with low-risk prostate cancer who underwent active treatment, stratified by year of diagnosis.

TABLE II Patients with low-risk prostate cancer who received active treatment, by health services zone

Health services zone	Patients				*p* Value
	Overall *(N)*	Received active treatment			
		(n)	Proportion	95% CI	
Calgary	800	208	0.26	0.23 to 0.29	Reference
Edmonton	315	174	0.55	0.50 to 0.61	<0.001
Central	173	67	0.39	0.32 to 0.46	0.001
South	173	58	0.34	0.27 to 0.41	0.044
North	102	46	0.45	0.35 to 0.55	<0.001
Unknown zone	2	1	—	—	—
TOTAL	1565	554	0.35	0.33 to 0.38	

CI = confidence interval.

(OR: 2.19; 95% CI: 1.58 to 3.04; p < 0.001). Table IV shows the results of the multivariate logistic regression.

DISCUSSION

This population-based study illustrates contemporary patterns of practice for patients with LR-PCa. Although approximately one third of patients underwent AT during the 4 year period of the study, the fact that that proportion declined over time is reassuring. Patients of younger age, and those with fewer comorbidities, T2 tumours, higher serum PSA at diagnosis, earlier year of diagnosis, and radiation oncologist consultation had a higher probability of undergoing AT.

We observed significant variation in the treatment of patients with LR-PCa by health services zone, which is congruent with several other reports. A study by Auffenberg *et al.*[21] demonstrated significant variation in AS (30%–73%) between 124 urologists who managed 2643 cases of LR-PCa in 13 different practices. Cooperberg *et al.*[7], in the CAPSURE registry-based study, also found significant differences in the primary treatment of localized PCa. Loeb *et al.*[22] reported that geographic region correlated with treatment

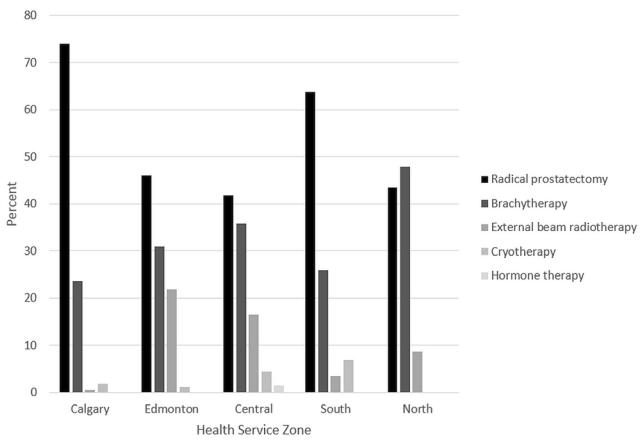

FIGURE 2 Active treatment modalities stratified by health service zone.

for patients with LR-PCa in a 10-year U.S. Veterans Affairs system–based study. In a population-based study of patients in Michigan, 49% of men initially underwent AS, but use of surveillance depended strongly on geographic location of treatment, with use of AS ranging from 27% to 80% depending on the practice ($p = 0.005$)[23]. That zonal variation might be explained by several factors, including disparities in access to specialists, availability of treatment facilities, and preferences of patients and the health care team.

With AS becoming more widely accepted as a standard approach for patients with LR-PCa, its use has increased. The results of the present study reflect the associated decline in AT during 2011–2014, similar to findings in another contemporary Canadian study by Tran *et al.*[19]. Comparable results have also been observed in studies from other countries. Loeb *et al.*[22] showed that, in 125,083 patients with LR-PCa, use of AS was increased in the men less than 65 years of age (4% in 2005 vs. 39% in 2015) and in those 65 years of age and older (3% in 2005 vs. 41% in 2015). Cooperberg and Carroll[24] showed an approximate 34% increase in the use of AS for patients with LR-PCa during the 2010–2013 period compared with the 1990–2009 period. Similar temporal trends during 2008–2012 were reported in an Australian study by Weerakoon *et al.*[25]. A U.S. Surveillance, Epidemiology, and End Results program study by Filson *et al.*[26] also demonstrated an increase in AS over time to 15.3% in 2007 from 9.7% in 2004, in agreement with our study.

Several guidelines have refined patient selection and management approach for AS[14,16,27,28]. Although the key eligibility criterion remains low-risk categorization, the Cancer Care Ontario guideline (endorsed by the American Society of Clinical Oncology) states that select patients with low-volume Gleason score 3+4 and low-volume Gleason pattern 4 PCa, or men older than 75 years of age (or both) can be offered AS[14]. In contrast, the European Association of Urology guideline does not recommend AS in Gleason score 3+4 PCa[16]. The guidelines all concur that extra caution should be practiced in the presence of high-volume disease, patient preference, African American ethnicity, high PSA density, strong family history of aggressive PCa, very extensive grade group 1 disease, or highly suspicious magnetic resonance imaging with a targeted biopsy showing no or only grade group 1 cancer, among other factors. Moreover, patients should also be made aware of the lack of prospective data concerning the outcome of AS beyond 15–20 years after diagnosis, which is pivotal in younger patients. That uncertainty with respect to the long-term outcomes of AS is reflected in our results, with younger patients being more likely to undergo AT.

We identified a number of factors associated with AT. Comorbidity burden was one such factor, which has also been reported in other studies[23]. Younger age and higher PSA at diagnosis were also identified as factors that correlate with AT, which is in agreement with several other studies[22,23,29,30]. We found that consultation with a radiation oncologist increased the odds of AT, which might be

TABLE III Univariable logistic regression of factors associated with active treatment

Factor	OR	95% CI	*p* Value
Age at Dx	0.95	0.93 to 0.96	<0.001
Score on the CCI			
0	1 (Reference)		
1–2	0.87	0.67 to 1.13	0.291
≥3	0.35	0.20 to 0.61	<0.001
Health services zone			
Calgary	1 (Reference)		
Edmonton	3.51	2.67 to 4.61	<0.001
Central	1.80	1.28 to 2.54	0.001
South	1.44	1.01 to 2.04	0.045
North	2.34	1.54 to 3.56	<0.001
Dx year			
2011	1 (Reference)		
2012	0.52	0.40 to 0.68	<0.001
2013	0.43	0.32 to 0.58	<0.001
2014	0.27	0.20 to 0.37	<0.001
T Stage			
T1	1 (Reference)		
T2	4.78	3.38 to 6.76	<0.001
Serum PSA at Dx	1.06	1.01 to 1.11	0.023
Positive biopsy cores			
1–2	1 (Reference)		
3–6	3.49	2.24 to 5.43	<0.001
≥7	9.45	3.18 to 28.04	<0.001
RO consultation within 12 months after Dx			
No	1 (Reference)		
Yes	5.44	4.30 to 6.87	<0.001

OR = odds ratio; CI = confidence interval; Dx = diagnosis; CCI = Charlson comorbidity index; PSA = prostate-specific antigen; RO = radiation oncologist.

TABLE IV Multivariable logistic regression of factors associated with active treatment

Factor	OR	95% CI	*p* Value
Age at Dx	0.92	0.91 to 0.94	<0.001
Score on the CCI			
0	1 (Reference)		
1–2	0.96	0.70 to 1.30	0.77
≥3	0.36	0.19 to 0.68	0.002
Health services zone			
Calgary	1 (Reference)		
Edmonton	2.19	1.58 to 3.04	<0.001
Central	1.50	0.99 to 2.27	0.057
South	1.43	0.97 to 2.11	0.074
North	1.53	0.92 to 2.53	0.099
Dx year			
2011	1 (Reference)		
2012	0.46	0.34 to 0.63	<0.001
2013	0.45	0.32 to 0.63	0.001
2014	0.33	0.23 to 0.47	<0.001
T stage			
T1	1 (Reference)		
T2	3.05	2.03 to 4.58	<0.001
Serum PSA at Dx	1.13	1.06 to 1.21	<0.001
RO consultation within 12 months after Dx			
No	1 (Reference)		
Yes	3.35	2.55 to 4.39	<0.001

OR = odds ratio; CI = confidence interval; Dx = diagnosis; CCI = Charlson comorbidity index; PSA = prostate-specific antigen; RO = radiation oncologist.

attributed to referral bias, whereby mainly patients with an inclination toward radiotherapy are subsequently referred to a radiation oncologist by their urologist. That hypothesis accords with the observation by Hoffman *et al.*[31], who conducted a U.S. Surveillance, Epidemiology, and End Results program–based study of 12,068 men with LR-PCa, that more than two thirds of men who underwent observation saw only a urologist and did not have a consultation with a radiation oncologist, emphasizing the important role of urologists in the decision-making for AS. In that study, men were more likely to undergo observation when seen only by a urologist than when seen by a radiation oncologist and a urologist (43.8% vs. 8.6%, $p < 0.001$). An alternative hypothesis for the latter finding is that radiation oncologists might not be recommending AS; however, our data do not permit further investigation in this area.

The strengths of our study include its population-based design and use of physician billing data to confirm treatment; however, the findings also have to be considered in the context of the its limitations. The study was retrospective in nature, and factors that might have had an effect on the decision for AT might not have been captured. However, administrative datasets, including the ACR and physician claims, were linked in an attempt to ensure complete and accurate data collection. Other factors such as patient or clinician preference, baseline psychological distress, anxiety, and health-related quality of life that might affect treatment choice were not captured in the study. The zone-wise stratification should be interpreted in light of the available treatment resources in the relevant zone. Not all treatment modalities were available in all zones, and patients would have been referred to other zones for treatment. Patients travelling out of province for treatment would not be captured in our data.

CONCLUSIONS

Our contemporary population-based study shows that approximately one third of patients with LR-PCa undergo AT within 12 months of diagnosis. Significant differences in the use of AT were evident between health services zones. The propensity to undergo AT was higher for patients of younger age and for those with fewer comorbidities, higher serum PSA at diagnosis, clinical T2 tumours, and radiation oncologist consultation. Further study is needed to identify strategies to optimize AS in patients with LR-PCa.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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