

Active Surveillance for low-risk Prostate Cancer Compared with Immediate Treatment: A Canadian cost comparison

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Abstract:	<p>Background: Active surveillance is an accepted management strategy for patients with low-risk prostate cancer (PCa). The financial benefits of active surveillance (AS) over immediate treatment (IT) have not been adequately studied in Canada or elsewhere. The study objective was to evaluate the direct costs associated with AS and IT in the Canadian context.</p> <p>Methods: A Markov model with Monte-Carlo microsimulations was developed to estimate the Canadian cost of PCa associated with IT and AS strategies. The patients on AS were assumed to receive delayed treatment at a rate of 8.35%, 4.17% and 2.1% per year for the first 2 years, years 3 to 5, and years 6 to 10 of follow-up, respectively. All costs were assigned in Canadian dollars (\$) and reflect Quebec's health system (RAMQ).</p> <p>Results: With AS, the average cost of PCa management over the first year and 5 years of follow-up was estimated at \$6,200 (95% confidence interval (CI): \$6,083 to \$6,317) per patient. The average cost corresponding to the IT strategy was estimated at \$13,735 (95%CI: \$13,615 to \$13,855) per patient. In addition, patients on AS having received a delayed treatment have incurred higher costs estimated at \$16,257 per patient.</p> <p>Interpretation: Our study demonstrates that AS could offer important economic benefits to the Canadian health system. We estimated that each annual cohort of incident prostate cancer managed with AS strategy allows cost savings of \$96.1 million. These benefits could be maintained after 10 years of follow-up.</p>

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2 **Active Surveillance for low-risk Prostate Cancer Compared with Immediate Treatment:**
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4 **A Canadian cost comparison**
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Background

Prostate cancer is the most common cancer and the 3rd leading cause of cancer mortality in Canadian men. The Canadian Cancer Statistics reported in 2011 an incidence rate of 122 per 100,000 persons-years, which is twice the incidence rate of lung or colorectal cancer, respectively the 2nd and 3rd leading causes of cancer (1). While the incidence of colorectal cancer was stable over the last 30 years, prostate cancer incidence has increased by 50%. Correspondingly, the economic burden of prostate cancer is also very high in Canada and elsewhere (2-6).

As revealed by several studies, the majority of cancers at diagnosis are low to intermediate risk. The natural history of prostate cancer is variable, but many cancers, especially the low-risk category, may be considered indolent and generally not require active treatment. Active surveillance (AS) (7) with delayed treatment is one of the accepted alternatives to active treatment for low risk cancers (8-10), especially since the introduction of prostate-specific antigen (PSA) testing has allowed the detection of localised low risk cancers. The AS strategy presents several advantages, especially for older men and/or for those with low life expectancy, but also for those with good life expectancy for whom the AS may allow the preservation of quality of life compared to active treatment (11-13). One study has shown that when quality of life associated with the clinical discomfort of initial treatment and psychological discomfort of living under AS were taken into consideration, the quality-adjusted life expectancy (QALE) was greater for AS (11.07 QALE) than for brachytherapy (10.57 QALE), for intensity-modulated radiation therapy (10.51 QALE), and for radical prostatectomy (10.23 QALE), respectively (14). In addition, a second study has shown that in a group of low-risk patients aged 70 years, the initial treatment with radiation therapy has an advantage of approximately 0.4 QALE, when compared to watchful waiting (15), but no benefit in the case of radical prostatectomy (9.4 QALE for both radical prostatectomy and watchful waiting). However, management of PCa with watchful waiting was used before the introduction of PSA testing and is corresponding with the decision of delaying the initial treatment, until evidence of clinically progressive tumour, with or without symptoms. In contrast, AS *“involves actively monitoring the course of the disease with the expectation to intervene with curative intent if the cancer progresses”*(7).

Despite published guideline recommendations (7, 16), overtreatment of prostate cancer is common in the US and elsewhere, with approximately 70% to 90% undergoing active treatments (17, 18). In Canada approximately 75% of patients with prostate cancer have received active treatment from 1995

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2 through 2002 (19). It is believed today that most of these patients did not require active treatment at the
3 time of diagnosis, but they incurred cost and morbidity (20, 21).
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6 The costs of AS with delayed treatment compared to the immediate treatment (IT) were recently
7 evaluated in the US healthcare system perspective by Keegan et al. (22). The corresponding estimates
8 in the Canadian universal healthcare context are unknown. Despite the fact that clinical practice of
9 prostate cancer is similar between US and Canada, the cost of healthcare services is likely to differ
10 between the two countries. In addition, the US model did not take into consideration mortality and PCa
11 recurrence, elements that could significantly impact the percentage of patients requiring treatment and
12 cost estimates, especially on a long term basis.
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19 The primary objective of this study was to develop a model to estimate the direct cost associated with
20 AS and IT for low-risk prostate cancer in Canada. This model accounted for the rate of progression
21 requiring delayed treatment, overall mortality, and disease recurrence requiring additional treatment, in
22 the context of the Quebec's public healthcare system. The second objective was to compare the
23 Canadian and US cost estimates.
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29 **Methods**

30 *Modeling assumptions*

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32 A Markov model with Monte-Carlo microsimulations was developed to simulate the management of
33 low-risk prostate cancer and cost over the first year, 5-year, and 10-year period of follow-up,
34 accounting for the rate of death and disease recurrence or progression. Two alternative management
35 strategies were modeled: AS with delayed treatment and IT strategies. The Markov model is a state
36 transition model with cycle length of one year; Figure 1 (A) shows the strategy of IT, whereas Figure 1
37 (B) presents the strategy where patients are initially on AS and can receive delayed treatment. The five
38 health states defined in relation to active treatment options are: radical prostatectomy (RP),
39 radiotherapy with intensity-modulated radiation therapy (IMRT), brachytherapy, androgen deprivation
40 therapy (ADT), and IMRT plus ADT for 6 months. The models' assumptions were derived from a
41 recent Canadian active surveillance cohort (9).
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52 *Cost assignments*

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54 All direct costs were assigned in Canadian dollars (\$) and estimated from the 2012 Quebec's public
55 healthcare system perspective. The cost of AS and treatments were categorized into: *initial cost*
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1 assigned in the first year, and *follow-up cost* assigned over the following 5-year and 10-year period,
2 respectively. The cost components, unit costs and sources are presented in Table 1. Cost of treatments
3 was based on specific protocols used at the McGill University Health Center; however, these protocols
4 are similar to those described in Keegan et al (22). The AS protocol was derived from Klotz et al. (9).
5 To reflect the time value of money, a standard discount rate of 5% was used (23).
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11 *Cost analyses*

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14 With more than 50% rate of low-risk prostate cancer at diagnosis and based on the 2011 Canadian
15 prostate cancer incidence (1), we estimated approximately 12,750 patients 65 years and older, as
16 potential candidates for AS. Consequently, the disease management and associated cost of 12,750
17 incident subjects of 65 years and older, initially on AS or assigned to IT, were simulated over the first
18 year and 5- and 10-years of follow-up by applying the corresponding Markov models (Figures 1 A) and
19 B)). The mean cost per patient is the average of individual cost estimations obtained with Monte-Carlo
20 microsimulations.
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27 *Sensitivity analysis*

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30 **First**, in order to compare our Canadian cost estimates with the US cost estimates, our Markov model
31 was changed to reflect assumptions derived from Keegan et al. (22). **Second**, a discount rate of 3%, and
32 10% respectively were considered. **Finally**, in order to estimate if the cost difference between AS and
33 IT strategy maintained on a longer horizon of time, a 15-year period of follow-up was modeled by
34 assuming a rate of mortality after the 10th year of follow-up of 8.16% per year. This rate corresponds to
35 the Statistics Canada estimate for general population aged 75 and older, which is the age category of
36 the simulated incident cases after 10 years of follow-up.
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43 **Results**

44 *Cost of AS and treatment*

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47 *Initial* and *5-year follow-up* costs specific to each treatment are presented in Table 2. Brachytherapy
48 and prostatectomy are the treatments with the lowest *initial* cost (\$7,428 and \$8,455, respectively),
49 while the IMRT+ADT is the intervention with the highest cost, estimated at \$14,444. In contrast, the
50 ADT was the treatment with the highest cost over the *5-year follow-up* period, estimated at \$23,202.
51 These estimates are all higher than the *initial* and *5-year follow-up* cost of AS, estimated at \$1,224, and
52 \$1,767, respectively.
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Treatment course and associated costs

At the end of 5 years of follow-up, the Markov model counted a number of 2,805 (22.0%) patients having received delayed treatment, 442 (3.5%) having received delayed treatment and died, 2,205 (17.3%) died on AS, and 7,298 (57.2%) of patients still on AS. The corresponding rates after the 10 years are as follows: 2,938 (23.1%) of patients having received delayed treatment, 984 (7.7%) having received delayed treatment and died, 3,454 (27.1%) died on AS, and 5,374 (42.1%) still on AS.

The cost per patient over the first year and 5 years of follow-up was estimated at \$13,735 (95%CI: \$13,615 to \$13,855) and \$6,200 (95%CI: \$6,083 to \$6,317) under IT, and AS strategy, respectively (Table 3). With a 5% discount rate, these figures are \$13,066 (95%CI: \$12,966 to \$13,165), and \$5,515 (95%CI: \$5,413 to \$5,619), respectively, corresponding to a relative reduction of 57.8%. The 10-year follow-up period shows that the absolute cost benefits observed in the previous period are maintained at the end of this period.

Patients remaining on AS over the 5-year period of follow-up have incurred an average cost of \$2,764 compared to \$16,257 in group of patients receiving delayed treatment. Depending on the type of treatment, this cost varies from \$12,821 (95%CI: \$12,452 to \$13,190) per patient having received surgery or \$14,512 (95%CI: \$14,046 to \$14,973) per patient having received brachytherapy, to \$20,377 (95%CI: \$19,826 to \$20,927) per patient having received IMRT plus ADT.

Furthermore, over the 10 years of follow-up, the lowest mean cost was still observed in group of patients having received surgery (\$20,935 (95%CI: \$20,117 to \$21,753)) or brachytherapy (\$23,401 (95%CI: \$22,421 to \$24,382)). However, highest cost was estimated for patients having received ADT (\$30,524 (95%CI: \$28,813 to \$32,236)).

Total cost estimation

At the Canadian level, the overall cost savings attributable to the AS strategy over the first year and 5 years of follow-up was estimated at \$96.1 million (Table 4). This value is explained by a total of \$104.4 million savings obtained by avoiding the treatment in 17.3% of cases who died before requiring treatment, and 57.2% of cases still on AS, and a supplementary cost of \$8.2 million for delaying treatment of 25.5% of cases, respectively. Similar values were observed over 10 years of follow-up, with an overall cost savings of \$99.5 million (Table 4).

Sensitivity analysis

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2 The results of the sensitivity analysis are presented in Table 5.
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5 **Interpretation**

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7 Our study demonstrates that for eligible patients, AS could offer not only the known clinical
8 advantages from the patient's perspective, but also economic benefits from the health care system
9 perspective. At the Canadian level, the overall cost savings of an annual cohort of incident prostate
10 cancers managed with AS over a first year and 5 years of follow-up was estimated at \$96.1 million.
11 This figure is explained by the low cost of AS in Quebec, by avoiding the high-cost of treatment for
12 approximately 74.5% of eligible patients, and a minimal additional cost related to delayed treatment for
13 25.5% of the patients, estimated at \$500 per patient per year. Furthermore, when we look to specific
14 treatments, delaying ADT will allow important savings over IT, estimated at \$4,000 per patient per
15 year. In addition, these cost benefits could be maintained over a longer time horizon of 10 to 15 years
16 of follow-up. At the end of the 15-year period there are 24% of patients still on AS, who will all be 80
17 years or older. Therefore, they will most likely cease AS or no longer be eligible for treatment.
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21 The US cost estimates (22) are higher than Canadian estimates but similar trends were observed for
22 specific treatments in relation to the number of years in AS, and treatment delay, respectively
23 (Electronic Appendix, Figure A1). While the mean cost of surgery, brachytherapy, IMRT and IMRT
24 plus ADT is slightly increased with each additional year of AS, the mean cost of ADT is considerably
25 decreased with the delay of treatment initiation. In addition, Keegan et al. (22) suggested that the
26 accrued cost of patients on AS undergoing delayed treatment are impressive, and have highlighted the
27 importance of rapidly identifying those patients likely to necessitate active treatment. Our results
28 confirm that a delayed treatment is associated with additional cost in patients requiring active
29 treatment, but this cost is minimal. The cost of treatments will increase between 3.3% and 6.7% per
30 year; however this increase will be entirely balanced by the 5% yearly discount rate of a delayed
31 expense. In addition, when no clinical additional benefits are expected with an early initiation of ADT,
32 the clinicians can be reassured on the fact that there is no economic reason to precipitate this initiation.
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36 Four other studies have evaluated the cost of AS and cost of active treatment (radical prostatectomy,
37 brachytherapy, IMRT) with all but one reflecting US costs, which are considerably higher than
38 Canadian costs (24-27). In addition, high variation has been observed across the US studies, mainly
39 observed for the initial cost of treatments. Therefore, these estimates are higher in Keegan et al. (22)
40 and correspond to 1.5 times the cost of brachytherapy and to 5.5 times the cost of AS revealed by
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2 Eldefrawy et al. (24). Moreover, the only non-US evaluation of AS cost was performed in Sweden and
3 was compared with the cost of radical prostatectomy (27). Their results show that during a median
4 follow-up of 12 years, the overall cost in radical prostatectomy group was 34% higher than in AS
5 group, corresponding to a difference of €6,123.
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10 Our study presents some limitations. First, this economic evaluation was mainly based on costs derived
11 from RAMQ lists. While the costs for medications, professional fees and laboratory costs are generally
12 similar across Canadian provinces, the medical fees and honoraria may be sometimes lower in Quebec;
13 however, we estimated that these differences might be minor and their proportionality allow us to
14 assume the transferability of our results to other Canadian provinces. Second, although our model
15 expands on the previous publication to account for risk of death and recurrence requiring additional
16 treatment, this model does not account for costs associated with side effects or complications related to
17 treatments. Third, treatment distribution was considered constant over time. Even if the probability of
18 receiving radiation therapy can increase with age, we believe the variation will be minimal in a
19 population of 65 years and older, and its impact on cost estimates will be non-significant. However, we
20 have evaluated the impact of AS cost savings in the case when only 10% of patients could receive RP
21 after 10 years of follow-up (41.6% IMRT, 16% IMRT plus ADT, 25% brachytherapy, and 7.4% ADT,
22 respectively). The corresponding cost benefits of AS were even more important, estimated at
23 approximately \$9,500 per patient (data not shown). The decrease of the percentage of patients receiving
24 both RP and IMRT (as primary treatment followed by salvage therapy, respectively) is likely to be the
25 main factor explaining this situation.
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39 In conclusion, 11 years after diagnosis of prostate cancer, AS with delayed treatment remains the
40 strategy with the lowest cost comparing with IT strategy. In the current situation where expenses of
41 health care systems are rapidly growing and where access to innovative medicines is limited or
42 restricted from public funding, finding ways to increase the efficiency of the system is desirable.
43 Furthermore, the management optimization of low-risk prostate cancer could potentially result in cost
44 reallocation and maximization of health care services offered to patients with prostate cancer. To the
45 best of our knowledge, this study is the first economic evaluation performed in the context of a
46 universal health care system, pooling together the most recent technologies such as IMRT or robot-
47 assisted radical prostatectomy and AS strategy. The results of our study add to the economic rationale
48 advocating AS for eligible men with low-risk prostate cancer and highlights cost savings estimates
49 specific to the Canadian public system.
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2 **Acknowledgment**
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Confidential

References

1. Statistics Canada. Canadian Cancer Statistics 2011. 2011.
2. US National Institutes of Health. Costs of Cancer Care. Cancer Trends Progress Report - 2010-2011 Updates. In: National Cancer Institute, editor. 2006.
3. Fourcade RO, Benedict A, Black LK, Stokes ME, Alcaraz A, Castro R. Treatment costs of prostate cancer in the first year after diagnosis: a short-term cost of illness study for France, Germany, Italy, Spain and the UK. *BJU Int.* 2010;105(1):49-56. Epub 2010/02/06.
4. Roehrborn CG, Black LK. The economic burden of prostate cancer. *BJU Int.* 2011;108(6):806-13. Epub 2011/09/03.
5. Grover SA, Coupal L, Zowall H, Rajan R, Trachtenberg J, Elhilali M, et al. The economic burden of prostate cancer in Canada: forecasts from the Montreal Prostate Cancer Model. *CMAJ.* 2000;162(7):987-92. Epub 2000/04/14.
6. Health Canada. Economic Burden of Illness in Canada, 1998. Ottawa: Health Canada; 2002.
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. 2011.
8. Wu JN, Dall'Era MA. Active surveillance for localized prostate cancer--current practices and recommendations. *ScientificWorldJournal.* 2010;10:2352-61. Epub 2010/12/21.
9. 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):126-31. Epub 2009/11/18.
10. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med.* 2012;366(11):981-90. Epub 2012/03/16.
11. Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, Stranne J, et al. The excess burden of side-effects from treatment in men allocated to screening for prostate cancer. The Goteborg randomised population-based prostate cancer screening trial. *Eur J Cancer.* 2011;47(4):545-53. Epub 2010/11/20.
12. Johansson E, Bill-Axelsson A, Holmberg L, Onelov E, Johansson JE, Steineck G. Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: the Randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) clinical trial. *Eur Urol.* 2009;55(2):422-30. Epub 2008/09/12.
13. Thong MS, Mols F, Kil PJ, Korfage IJ, van de Poll-Franse LV. Prostate cancer survivors who would be eligible for active surveillance but were either treated with radiotherapy or managed expectantly: comparisons on long-term quality of life and symptom burden. *BJU Int.* 2010;105(5):652-8. Epub 2009/09/15.
14. Hayes JH, Ollendorf DA, Pearson SD, Barry MJ, Kantoff PW, Stewart ST, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. *JAMA.* 2010;304(21):2373-80. Epub 2010/12/02.
15. Sommers BD, Beard CJ, D'Amico AV, Dahl D, Kaplan I, Richie JP, et al. Decision analysis using individual patient preferences to determine optimal treatment for localized prostate cancer. *Cancer.* 2007;110(10):2210-7. Epub 2007/09/26.
16. National Institute for Health and Clinical Excellence. Prostate cancer: diagnosis and treatment. NICE clinical guideline 58. London2008.
17. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol.* 2010;28(7):1117-23. Epub 2010/02/04.

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18. Crawford ED, Black L, Eaddy M, Kruep EJ. A retrospective analysis illustrating the substantial clinical and economic burden of prostate cancer. *Prostate Cancer Prostatic Dis.* 2010;13(2):162-7. Epub 2010/02/04.
 19. Krahn MD, Zagorski B, Laporte A, Alibhai SM, Bremner KE, Tomlinson G, et al. Healthcare costs associated with prostate cancer: estimates from a population-based study. *BJU Int.* 2010;105(3):338-46. Epub 2009/07/15.
 20. van Leeuwen PJ, Connolly D, Gavin A, Roobol MJ, Black A, Bangma CH, et al. Prostate cancer mortality in screen and clinically detected prostate cancer: estimating the screening benefit. *Eur J Cancer.* 2010;46(2):377-83. Epub 2009/10/07.
 21. Andriole GL, Crawford ED, Grubb RL, 3rd, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med.* 2009;360(13):1310-9. Epub 2009/03/20.
 22. Keegan KA, Dall'Era MA, Durbin-Johnson B, Evans CP. Active surveillance for prostate cancer compared with immediate treatment: an economic analysis. *Cancer.* 2012;118(14):3512-8. Epub 2011/12/20.
 23. Drummond M. SMJ, Torrance G.W., O'Brien B.J. Stoddart G.L.,. *Methods for the Economic Evaluation of Health Care Programmes.* third ed. New York: Oxford University Press; 2005.
 24. Eldefrawy A, Katkoori D, Abramowitz M, Soloway MS, Manoharan M. Active surveillance vs. treatment for low-risk prostate cancer: A cost comparison. *Urol Oncol.* 2011. Epub 2011/05/28.
 25. Corcoran AT, Peele PB, Benoit RM. Cost comparison between watchful waiting with active surveillance and active treatment of clinically localized prostate cancer. *Urology.* 2010;76(3):703-7. Epub 2010/04/13.
 26. Wilson LS, Tesoro R, Elkin EP, Sadetsky N, Broering JM, Latini DM, et al. Cumulative cost pattern comparison of prostate cancer treatments. *Cancer.* 2007;109(3):518-27. Epub 2006/12/23.
 27. Andersson SO, Andren O, Lyth J, Stark JR, Henriksson M, Adami HO, et al. Managing localized prostate cancer by radical prostatectomy or watchful waiting: Cost analysis of a randomized trial (SPCG-4). *Scand J Urol Nephrol.* 2011;45(3):177-83. Epub 2011/01/27.
 28. Régie de l'Assurance Maladie du Québec. Manuel des médecins spécialistes. avril 2012.
 29. Régie de l'Assurance Maladie du Québec (RAMQ). Liste de médicaments assurés. 2012.
 30. Ministère de la Santé et des Services sociaux. Banque de données APR-DRG 2010-2011 et contour financier de santé physique. In: Service de l'allocation des ressources, editor. 2010-2011.
 31. Conseil d'évaluation des technologies de la santé du Québec. Brachytherapy and Prostate Cancer. January 2000.
 32. Canadian Institute of Health Information. Canadian Patient Cost Database. In: <http://www.cihi.ca/cihi-ext-portal/internet/en/document/spending+and+health+workforce/spending/spending+by+category/cpcd>, editor. 2010-2011.

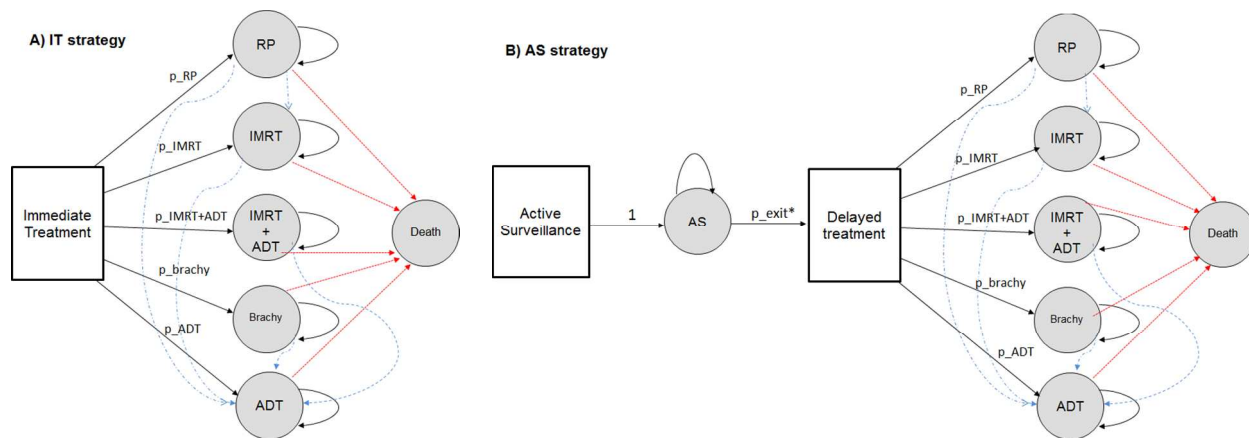


Figure 1: Markov models with transition to Death (red lines) and recurrence requiring additional treatment (blue lines) for: A) IT strategy and B) AS strategy.

* p_{exit} = yearly rate of switch to active treatment, 0.0835 (year 1 and 2 of follow-up), 0.0417 (year 3 to 5 of follow-up) and 0.021 (year 6 to 10 of follow-up); (9)

RP = radical prostatectomy; IMRT = intensity-modulated radiation therapy; ADT = androgen deprivation therapy; brachy = brachytherapy.

p_{RP} = probability of receiving radical prostatectomy; p_{IMRT} = probability of receiving IMRT; $p_{\text{IMRT+ADT}}$ = probability of receiving IMRT+ADT; p_{Brachy} = probability of receiving brachytherapy; p_{ADT} = probability of receiving ADT; $p_{\text{RP}}=0.26$, $p_{\text{IMRT}}=0.34$; $p_{\text{IMRT+ADT}}=0.13$; $p_{\text{Brachy}}=0.20$; $p_{\text{ADT}}=0.074$; (9)

1-year probability of death=0.038; 1-year probability of recurrence requiring additional treatment=0.139, for AS strategy and 0.0257, for IT strategy (9).

Table 1: Cost components and unit costs related to prostate cancer management (2012 Canadian \$):

	Cost per unit	Source
Initial office consultation - urology	\$77	RAMQ* list (28)
Initial office consultation - radiation oncology	\$133	RAMQ* list (28)
Urologist reimbursement for prostate biopsy	\$78	RAMQ* list (28)
Prostate biopsy (based on 12 sample needle core)		
pathology	\$158	MUHC internal estimates
professional and technical fees	\$183	MUHC internal estimates
Prostate analysis after surgery (prostatectomy with Obturator Lymph Nodes)		
pathology	\$204	MUHC internal estimates
professional and technical fees	\$640	MUHC internal estimates
PSA test	\$11	MUHC internal estimates
Office visits - urology	\$59	RAMQ* list (28)
Office visits - radiation oncology	\$44	RAMQ* list (28)
Urologist reimbursement for radical prostatectomy	\$922	RAMQ* list (28)
Radio-oncologist reimbursement for radiation therapy		
computed tomography planning + IGRT plan IMRT radiation session (includes office visit, image fusion and checking)	\$1,010	RAMQ* list (28)
dose planning +ultrasound guidance + interstitial implant (brachytherapy)	\$81	RAMQ* list (28)
	\$735	RAMQ* list (28)
Medication costs (Zoladex implant each 3 months)	\$1,088	RAMQ* list (29)
Nursing (average salary/month)	\$6,667	MUHC internal estimates
Surgical procedure*	\$4,547	Quebec Ministry of Health and Social Services (30)
Brachytherapy procedure (Pd-103) including seeds cost*	\$6,700	CETS 2000 (31); Canadian Patient Cost Database (32)
IMRT procedure&	\$7,402	MUHC internal estimates
Anesthesia for surgery	\$650	MUHC internal estimates
Anesthesia for brachytherapy	\$250	MUHC internal estimates

**Régie de l'Assurance Maladie du Québec*, the administrator of the public and universal healthcare insurance program in the province of Québec, Canada; The costs of medical procedures related to treatments and medical visit costs were based on the RAMQ's billing manual (28), and the costs of medications were based on the RAMQ's list of medications approved for public reimbursement (29).

**This amount includes intervention, nursing care, diagnosis and therapeutic services;

& Includes cost of dosimetry (radiation therapist, planning system, information system), physics quality assurance (physicist, physics associates, specialised quality assurance equipment, planning system, information system) and treatment preparation & delivery (radiation therapy, linear accelerator, nurse, information system) equivalent of 38 fractions. This value does not include overheads.

Table 2: Initial and 5-year cost of treatments and active surveillance (2012 Canadian \$)

Treatment type	Initial	5-year period of follow-up
Active surveillance	\$1,224	\$1,767
Radical prostatectomy	\$7,428	\$929
IMRT	\$12,261	\$618
IMRT + ADT*	\$14,444	\$618
Brachytherapy	\$8,455	\$618
Primary ADT	\$5,136	\$23,202

IMRT = intensity-modulated radiation therapy; ADT = androgen deprivation therapy.

* ADT for 6 months

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Table 3: Cost estimates under AS and IT strategies over the first year and 5 to 10 years of follow-up:

	Mortality rate*	Recurrence rate*	Discount rate*	Mean cost (95% CI) [§] (per patient)	Cost difference (IT versus AS)	
					absolute	relative
<i>First year and 5 years of follow-up</i>						
Active surveillance	3.8%	13.9%	-	\$6,200 (\$6,083 to \$6,317)	\$7,535	54.9%
	3.8%	13.9%	5%	\$5,515 (\$5,413 to \$5,619)	\$7,551	57.8%
Immediate Treatment	3.8%	2.57%	-	\$13,735 (\$13,615 to \$13,855)		
	3.8%	2.57%	5%	\$13,166 (\$12,966 to \$13,165)		
<i>First year and 10 years of follow-up</i>						
Active surveillance	3.8%	13.9%	-	\$10,600 (\$10,377 to \$10,822)	\$7,808	42.4%
	3.8%	13.9%	5%	\$8,484 (\$8,313 to \$8,654)	\$7,755	47.8%
Immediate Treatment	3.8%	2.57%	-	\$18,408 (\$18,162 to \$18,653)		
	3.8%	2.57%	5%	\$16,239 (\$16,060 to \$16,418)		

*Yearly rate;

§ The 95% confidence interval (95%CI) of the mean cost was obtained by the simulation of 1,000 samples of equal sample size of 12,750 subjects.

Table 4: Total cost under AS and IT strategies and possible cost savings corresponding to an annual cohort of 12,750 patients with prostate cancer stratified by patients' treatment status:

Treatment status	%	N	Mean cost per patient		Total cost		Cost difference per patient AS versus IT	Total cost difference
			AS strategy	IT strategy	AS strategy	IT Strategy		
<i>First year and 5 years of follow-up</i>								
Patients requiring treatment	25.5%	3,247	\$16,257	\$13,735	\$52,786,479	\$44,597,545	\$2,522	\$8,188,934*
Patients not requiring treatment	74.5%	9,503	\$2,753	\$13,735	\$26,161,759	\$130,523,705	-\$10,982	-\$104,361,946**
Total	100.0%	12,750	\$6,200	\$13,735	\$79,050,000	\$175,121,250	-\$7,535	-\$96,071,250 [§]
<i>First year and 10 years of follow-up</i>								
Patients requiring treatment	30.8%	3,922	\$25,552	\$18,407	\$100,214,944	\$72,192,254	\$7,145	\$28,022,690*
Patients not requiring treatment	69.2%	8,828	\$3,959	\$18,407	\$34,950,052	\$162,496,996	-\$14,448	-\$127,546,944**
Total	100.0%	12,750	\$10,600	\$18,407	\$135,150,000	\$234,689,250	-\$7,807	-\$99,539,250 [§]

* Additional cost attributable to delayed treatment; ** Cost savings attributable to AS strategy; [§] Total cost savings obtained with the AS strategy.

Table 5: Sensitivity analysis:

	Mortality rate*	Recurrence rate*	Discount rate*	Mean cost (95% CI) [§] (per patient)	Cost difference (IT versus AS) absolute	relative
1) Model integrating assumptions derived from Keegan et al. (22)**						
First year and 5 years of follow-up						
Active surveillance	0%	0%	-	\$5,855 (\$5,780 to \$5,930)	\$6,416	52.3%
	0%	0%	5%	\$5,474 (\$5,408 to \$5,539)	\$6,237	53.3%
Immediate Treatment	0%	0%	-	\$12,271 (\$12,161 to \$12,381)		
	0%	0%	5%	\$11,711 (\$11,625 to \$11,798)		
First year and 10 years of follow-up						
Active surveillance	0%	0%	-	\$9,201 (\$9,069 to \$9,334)	\$5,843	38.8%
	0%	0%	5%	\$7,673 (\$7,584 to \$7,763)	\$6,165	44.6%
Immediate Treatment	0%	0%	-	\$15,044 (\$14,806 to \$15,282)		
	0%	0%	5%	\$13,838 (\$13,679 to \$13,997)		
2) Model with discount rates of 3% and 10%						
First year and 5 years of follow-up						
Active surveillance	3.8%	13.9%	3%	\$5,810 (\$5,701 to \$5,920)	\$7,496	56.3%
	3.8%	13.9%	10%	\$5,134 (\$5,039 to \$5,230)	\$7,367	58.9%
Immediate Treatment	3.8%	2.57%	3%	\$13,306 (\$13,199 to \$13,413)		
	3.8%	2.57%	10%	\$12,501 (\$12,417 to \$12,586)		
First year and 10 years of follow-up						
Active surveillance	3.8%	13.9%	3%	\$9,438 (\$9,246 to \$9,629)	\$7,601	44.6%
	3.8%	13.9%	10%	\$7,357 (\$7,214 to \$7,499)	\$7,239	49.6%
Immediate Treatment	3.8%	2.57%	3%	\$17,039 (\$16,836 to \$17,242)		
	3.8%	2.57%	10%	\$14,596 (\$14,461 to \$14,731)		
3) Model with 15 years period of follow-up						
Active surveillance	3.8% [†] ; 8.16% [‡]	13.9%	-	\$14,806 (\$14,480 to \$15,132)	\$8,063	35.3%
	3.8% [†] ; 8.16% [‡]	13.9%	5%	\$11,082 (\$10,853 to \$11,311)	\$7,013	38.8%
Immediate Treatment	3.8% [†] ; 8.16% [‡]	2.57%	-	\$22,869 (\$22,511 to \$23,227)		
	3.8% [†] ; 8.16% [‡]	2.57%	5%	\$18,095 (\$17,864 to \$18,324)		

*Yearly rate;

**The assumptions are: 1) 2 additional biopsies in the first 5-year period of follow-up; 2) rate of death and rate of recurrence, both set to 0; 3) probability of receiving each specific treatment assumed to be 0.4 for RP, 0.25 for IMRT, 0.1 for IMRT plus ADT, 0.15 for brachytherapy and 0.1 for ADT; and 4) probability of receiving delayed treatment of 7% per year, in the first 5-years of follow-up, and 4.5% per year in the following 5-year period.;

§ The 95% confidence interval (95%CI) of the mean cost was obtained by the simulation of 1,000 samples of equal sample size of 12,750 subjects.

† Years 1 to 10; ‡ Years 11 to 15.

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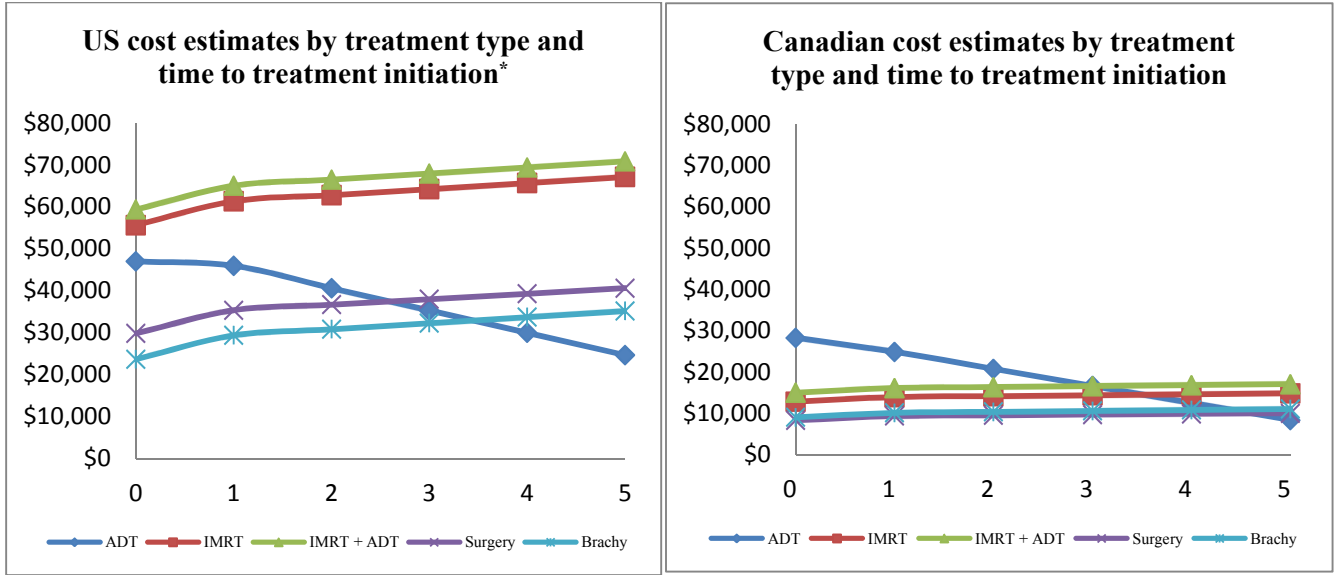


Figure A1: Mean cost estimates over a first year and 5-year period of follow-up after diagnosis of prostate cancer by specific treatment and time to treatment initiation; US and Canadian cost estimates.

*in US dollars; ** in Canadian dollars; Exchange rate: 1 CAD = 0.974 US (Bank of Canada, March 11th, 2013); Values are obtained from the model integrating assumptions derived from Keegan et al. (22) (Table 5)