

# Long-term health care costs for prostate cancer patients on androgen deprivation therapy

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## ABSTRACT

**Background** Comparing relative costs for androgen deprivation therapy (ADT) protocols in prostate cancer (pca) requires an examination of all health care resources, not only those specific to pca. The objective of the present study was to use administrative data to estimate total health care costs in a population-based cohort of pca patients.

**Methods** Patients in Ontario with pca who started 90 days or more of ADT at age 66 years or older during 1995–2005 were selected from cancer registry and health care administrative databases. We classified patients ( $n = 21,818$ ) by regimen (medical castration, orchiectomy, anti-androgen monotherapy, medical castration with anti-androgen, orchiectomy with anti-androgen) and indication (neoadjuvant, adjuvant, metastatic disease, biochemical recurrence, primary nonmetastatic). Using nonparametric regression methods, with inverse probability weighting to adjust for censoring, and bootstrapping, we computed mean 1-year, 5-year, and 10-year longitudinal total direct medical costs (2009 Canadian dollars).

## Results

Mean first-year costs were highest for metastatic disease, ranging from \$24,400 for orchiectomy to \$32,120 for anti-androgen monotherapy. Mean first-year costs for all other indications were less than \$20,000. Mean 5-year and 10-year costs were lowest for neoadjuvant treatment: approximately \$43,000 and \$81,000 respectively, with differences of less than \$4,000 between regimens. Annual costs were highest in the first year of ADT. Orchiectomy was the least costly regimen for most time periods, but was limited to primary and metastatic indications. Out-patient drugs, including pharmacologic ADT, accounted for 17%–65% of total first-year costs.

**Conclusions** Compared with combined therapies, the ADT monotherapies, particularly orchiectomy when clinically feasible, are more economical. Our methods exemplified the use of algorithms to elucidate clinical information from administrative data. Our approach can be adapted for other cancers to expand the range of studies using Canadian administrative data.

**Key Words** Prostate neoplasms, androgen deprivation therapy, orchiectomy, costs, cost analyses

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## BACKGROUND

Androgen deprivation therapy (ADT) has been used to treat metastatic prostate cancer (pca) since the 1940s<sup>1</sup>. It is now also used as neoadjuvant and adjuvant therapy with surgery and radiotherapy and as primary therapy for nonmetastatic disease<sup>2–5</sup>. Luteinizing hormone-releasing hormone (LHRH) agonists and anti-androgens

are the most widely-used types of ADT, replacing bilateral orchiectomy and estrogen<sup>3,6,7</sup>.

The choice of ADT regimen depends on the indication for use<sup>4</sup> and patient factors, including preferences. Cost is another factor that is relevant to the health care system, patients, clinicians, and policymakers. Androgen deprivation therapy is one of the costliest treatments for pca<sup>8–10</sup>. In 2015 in Ontario, one 3-month depot

preparation of LHRH agonist cost approximately CA\$1000 to CA\$1500<sup>11</sup>.

Studies in the United States that estimated cumulative longitudinal costs for ADT have included only pCa-related costs<sup>9</sup> or included data only for the years that patients survived, thus excluding the high costs immediately before death<sup>10</sup>. Other studies compared the costs of various types of ADT and included only the costs of the ADT, assuming that the other health care costs would be similar<sup>12–14</sup>. A full understanding of the relative costs of various clinically-relevant ADT regimens and indications requires consideration of other pCa-related care, comorbid illness, treatment side effects<sup>15</sup>, and end-of-life care.

Administrative health care data are ideal for estimating long-term costs because they encompass a large number of patients—often an entire population—that can be followed for many years. The linked Surveillance, Epidemiology, and End Results–Medicare database<sup>16,17</sup> has been used for numerous cancer costing studies in the United States. It includes all claims, with their dates, payments, patient diagnosis codes, and procedure codes for all Medicare-covered patients and services. However, the Surveillance, Epidemiology, and End Results regions represent only approximately 14% of the U.S. population, and Medicare covers mainly patients 65 years of age and older<sup>18</sup>.

In Canada, universal health care insurance plans are managed by provincial and territorial governments and provide coverage for all permanent residents of all ages. Administrative records associated with those plans are an excellent source of utilization and costing data. Their lack of clinical detail can be overcome by developing algorithms that use information about diagnosis, drug prescriptions, surgical procedures, and other treatments.

The purpose of the present study was to estimate the total longitudinal health care cost for clinically relevant regimens related to common indications for ADT in the population of pCa patients in the province of Ontario who initiated ADT during 1995–2005. No other study has considered both regimen and indication when examining total costs for pCa patients treated with ADT. The present study exemplifies the use of administrative data and provides a methodology for future research.

## METHODS

### Ethics

Approval for the study was given by the Research Ethics Board of the University Health Network and the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Ontario. Individual patient consent was not possible and was waived because the study used administrative databases and because patient identifiers were removed for the analyses.

### Patients and Data

Using Canadian health care administrative databases, we selected patients in Ontario who began at least 90 consecutive days of LHRH agonist, estrogen, or anti-androgen, or who had a bilateral orchiectomy from 1 January 1995 to 31 December 2005 (Table 1). We specified a 90-day period because that is the recommended minimum therapeutic

duration of ADT for any indication<sup>19</sup>. Applying standard methods, we allowed up to 50% of the number of days of drug supplied for the patients to refill their prescriptions<sup>20,21</sup>. Thus, a patient had up to 45 days to refill a prescription for a 30-day supply or to obtain a new ADT prescription. We defined each patient's index date as the start of ADT.

We used the Ontario Health Insurance Program unique patient number to link the selected patients to the Ontario Cancer Registry<sup>22</sup>, retaining those with an initial diagnosis of pCa, but no other primary cancer, before or within 6 months after their ADT index date (thus allowing for delays in reporting to the cancer registry). Outpatient prescription drug coverage is available under the Ontario Drug Benefit program, but only for Ontario residents 65 years of age and older and those on social assistance. To assess prior ADT, we excluded patients younger than 66 years at index date.

Using unique encoded identifiers, the resulting cohort of patients was linked to other health care administrative databases; to data about radiation therapy obtained from the Radiation Oncology Research Unit at Queen's University in Kingston, Ontario; and to chemotherapy data obtained from Cancer Care Ontario. The linked data were analyzed at the Institute for Clinical Evaluative Sciences in Toronto, Ontario. Patients were followed from their index date until death or 31 December 2007.

### ADT Regimens and Indications

We classified each patient according to the ADT regimen received in the first 90 days after his index date: medical castration, orchiectomy, anti-androgen monotherapy, combined androgen blockade (CAB)—medical, and CAB—surgical. Based on the literature, clinical practice guidelines<sup>8,9,23,24</sup>, consultation with clinical experts, and the data described in Table 1, we initially identified 6 mutually-exclusive indications for ADT (Table 2): neoadjuvant therapy, adjuvant therapy, metastatic disease, biochemical recurrence, localized disease, and other. For the years covered by the study, the Ontario Cancer Registry contains limited staging information. We applied a previously used algorithm to identify patients with probable metastatic disease<sup>25</sup>.

For the analyses, we excluded patients who received ADT for “other” indications, and we selected patients treated with clinically relevant protocols only. Treatment with orchiectomy has declined in recent years<sup>3,6</sup>, and the indications for which it is relevant are few. We therefore included only patients who received orchiectomy for metastatic disease or as primary therapy, and those who received CAB—surgical for metastatic disease. We excluded patients who received ADT outside of the relevant indications.

### Data and Costing

Almost all medically necessary health care for permanent residents of Ontario is covered under the Ontario Health Insurance Plan, managed by the Ontario Ministry of Health and Long-Term Care (<http://www.health.gov.on.ca/en/public/programs/ohip>). The exceptions are outpatient prescription drugs, covered only for residents 65 years of age and older and for those on social assistance, and most

**TABLE I** Data sources

Variable	Database	Code
LHRH agonist,estrogen, anti-androgen	Ontario Drug Benefit Plan	Selected drug identification number (Canada)
Orchiectomy	Discharge Abstract Database	CCP 74.31 (removal of both testes in same operative episode) or 74.32 (removal of remaining testis) or CCI 1.QM.89 (excision total testis) or 1.QM.91 (excision radical testis)
	OHIP Claims History	OHIP fee code S589 (orchiectomy, unilateral) or S598 (radical orchiectomy for malignancy, unilateral; twice in one day for the same patient)
Radical prostatectomy	Discharge Abstract Database	CCP 72.4 or CCI 1.QT.91
	OHIP Claims History	OHIP fee code S645 (perineal prostatectomy), S651 (retropubic radical), or S653 (laparoscopic)
Radiation therapy	Radiation Oncology Research Unit Data	Curative intent = "C" Palliative intent = "P"
Palliative care	Discharge Abstract Database	Main patient service = 58 (palliative care unit)
	OHIP Claims History	OHIP fee codes A945, C945, C882, C982, K023, W882, W872, W972, W982
Narcotic medication	Ontario Drug Benefit Plan	Selected drug identification number (Canada) for narcotic medications
Metastases	Discharge Abstract Database	ICD-9 196.x, 197.x, 198.x, 199.x, or ICD-10 C77.x, C78.x, C79.x, C80.x
Pathologic fracture	Discharge Abstract Database	ICD-9 733.1, 733.10–733.19, or ICD-10 M8440–M8449
Chemotherapy	Discharge Abstract Database	CCP 13.55, CCI 1.ZZ.35; ICD-9 V66.2, V67.2; ICD-10 Z511, Z542
	OHIP Claims History	OHIP fee codes G381, G281, G339, G345, G359, G075, G382, G390 associated with prostate cancer (ICD 185)
Nephrostomy tube insertion	Discharge Abstract Database	CCP 67.02, 67.03; CCI 1.PE.52.HH

LHRH = luteinizing hormone–releasing hormone; CCP = Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; CCI = Canadian Classification of Health Interventions; OHIP = Ontario Health Insurance Plan; ICD = *International Classification of Diseases* (revision 9 or 10).

allied health services in community clinics. Patients have no co-payments or deductibles for most services that are covered by the Ontario Health Insurance Plan. Therefore, almost all the costs of health-related resources used by patients in the present study were covered by the public payer.

We used standard costing methods for administrative data in Ontario<sup>26</sup>. Table III describes the health care resources, data, and costing methods. Hospital admissions were obtained using the Discharge Abstract Database, and emergency room visits, ambulatory procedures, and chemotherapy were obtained from the National Ambulatory Care Reporting System—both maintained by the Canadian Institute for Health Information. All records in both databases are assigned a resource intensity weight<sup>28</sup>, which we multiplied by the cost per weighted case in Ontario for the year of use to estimate costs. We included cancer drugs recorded in the New Drug Funding Program data obtained from Cancer Care Ontario. That program (<https://www.cancercare.on.ca/toolbox/drugs/ndfp>) reimburses

cancer centres and hospitals for expensive chemotherapy approved for use in specific cancers. Costs for pharmacologic ADT and other outpatient prescription medications were identified from the database of the Ontario Drug Benefit program.

We used the Claims History Database of the Ontario Health Insurance Plan to identify costs for inpatient and outpatient physician services and outpatient diagnostic tests. Data from the Radiation Oncology Research Unit database, housed at Queen's University, Kingston, Ontario, were used to identify radiation therapy and its intent (curative or palliative). In Ontario, many radiation oncologists receive some of their income through alternative funding plans<sup>29</sup>. We estimated the income provided to radiation oncologists through alternative funding plans from responses to the 2004 and 2007 National Physician Surveys (<http://nationalphysiciansurvey.ca/>).

We identified home care services using the Home Care Database and the Ontario Home Care Administrative

**TABLE II** Androgen deprivation therapy (ADT) regimens and indications

Procedure type	Criteria
<i>Regimens</i>	
Orchiectomy	Orchiectomy, with or without estrogen or LHRH agonist, with no (or <90 days) anti-androgen
Medical castration	≥90 Days estrogen or LHRH agonist (buserelin, goserelin, leuprolide, triptorelin), or both, with no (or <90 days) anti-androgen
Anti-androgen monotherapy	≥90 Days steroidal anti-androgen (cyproterone) or nonsteroidal anti-androgen (bicalutamide, flutamide, nilutamide), with no castration. A patient who uses both ≥90 days steroidal and nonsteroidal anti-androgen is classified as steroidal.
Combined androgen blockade	
Surgical	Both orchiectomy and ≥90 days any anti-androgen. Date of orchiectomy can be within the first 90 days of anti-androgen, or the start of anti-androgen can be within 90 days after the date of orchiectomy. In the case of concurrent use of castration types, orchiectomy overrides medical castration.
Medical	LHRH agonist or estrogen, but no orchiectomy, and any anti-androgen at the same time for ≥90 days. Start of LHRH agonist or estrogen can be within the first 90 days of anti-androgen, or start of anti-androgen can be within 90 days after start of LHRH agonist or estrogen.
<i>Indications</i>	
Neoadjuvant therapy	ADT beginning ≤8 months before primary curative treatment (date of radical prostatectomy, or start of curative radiation therapy), and ending within 6 months after the start of curative treatment.
Adjuvant therapy	ADT beginning ≤8 months before primary curative treatment, or during or ≤6 months after curative treatment, and continuing for >6 months after the start of curative treatment.
Symptomatic metastatic (stage M1) disease	Any one of the events that follow after a prostate cancer diagnosis and before or within 6 months after the index date: <ul style="list-style-type: none"> <li>■ Palliative radiation therapy</li> <li>■ Admission to a palliative care facility</li> <li>■ Physician billings (&gt;2) for palliative care</li> <li>■ Prescriptions (≥2) for narcotic medication within a 6-month period for &gt;30 consecutive days</li> <li>■ Diagnosis of metastases or secondary malignancy</li> <li>■ Pathologic fracture</li> <li>■ Chemotherapy visit or follow-up after chemotherapy</li> <li>■ Physician billings (≥3) for chemotherapy for prostate cancer</li> <li>■ Nephrostomy tube insertion</li> </ul>
Biochemical recurrence after curative therapy	ADT beginning >6 months after radical prostatectomy or the start of curative radiation therapy
Primary therapy	ADT beginning ≤6 months before or ≤6 months after the initial prostate cancer diagnosis
Other	Not fulfilling criteria for any of the foregoing indications

System database. The average per-service cost was obtained from Community Care Access Centres in Toronto.

We included stays at complex continuing care facilities in Ontario. Each stay is assigned a case-mix index, indicating intensity of the required care. We multiplied that index value by the length of stay and by the provincial average cost per weighted chronic day for the year of the stay.

All costs were adjusted to 2009 Canadian dollars using the Consumer Price Index for health<sup>26,30,31</sup>. We summed all resource costs for each patient to estimate total health care costs.

### Clinical and Demographic Characteristics

We described comorbid illness by categorizing all *International Classification of Diseases* diagnostic codes

(revisions 9, 9 Clinical Modification, and 10) found for each patient in hospital records and physician billing data from 1 year before his index date into one of nearly 90 adjusted clinical groups, a population–patient case-mix adjustment system<sup>32</sup>. We were interested in the burden of comorbidity, and so we grouped the total number of adjusted clinical groups for each patient (comorbidity 0–3: low; 4–6: moderate; 7–9: high; and ≥10 very high)<sup>32</sup>.

We used the Statistics Canada Postal Code Conversion file and data from the 2001 Canadian Census to assign each patient's postal code to a standard geographic area, for which data on neighbourhood-level median household income (measured in quintiles) and rurality were obtained. Communities with a population less than 10,000 were defined as rural.

**TABLE III** Costing methodology

Resource	Data source	Costing methods
Emergency room visits	≥1 April 2002: NACRS	Resource intensity weight × cost per weighted case
	<1 April 2002: OHIP physician claims	Apply mean cost per visit April 2002–2003 to all emergency room visits identified in OHIP data
Inpatient hospital	CIHI-DAD	Resource intensity weight × cost per weighted case
Infusional chemotherapy (outpatient)	≥April 2003: NACRS	VFC code 7134066610, 713506605, 723406610, 723506605, 733406610, 733506605, or main problem = Z511. Cost = resource intensity weight × cost per weighted case
	<April 2003: OHIP physician claims	Fee codes G281, G339, G345, G359, G381 to identify chemotherapy visits. Cost = mean cost per visit April 2002–2003
	OHIP physician claims (all years)	Physician administration cost = fee codes G281, G339, G345, G359, G381, G075, G382, G390
	NDFP	Cost = dose cost
Radiation therapy (outpatient)	Radiation Oncology Research Unit database	Curative radiation: \$5484.10 per 35-fraction course Palliative radiation: \$831 per 5-fraction course <sup>27</sup>
	OHIP physician claims	Cost = claims for radiation oncologist (specialty) plus estimated salary based on National Physician Survey <sup>a</sup>
Outpatient diagnostic tests (laboratory tests, imaging, radiography, etc.)	OHIP claims	Cost = technical fee + professional fee
Ambulatory procedures	Same-day surgery data	Resource intensity weight × cost per weighted case
Physician services (licensed physicians/ medical doctors)	OHIP physician claims	Costs = all claims, but excluding costs included in diagnostic tests, radiation therapy, and chemotherapy
Home health	<April 2005: OHCAS	Service costs from Community Care Access Centre, Toronto (\$82–\$117 per visit).
	≥April 2005: Home Care Reporting System	
Complex continuing care	Continuing Care Reporting System	Case-mix index multiplied by length of stay and provincial average cost per weighted chronic day.

<sup>a</sup> Fee-for-service was estimated to constitute 47% of a radiation oncologist's income from January 2001 to 31 October 2002 and 63% thereafter. NACRS = National Ambulatory Care Reporting System; OHIP = Ontario Health Insurance Plan; CIHI-DAD = Canadian Institute for Health Information, Discharge Abstract Database; VFC = visit functional centre; NDFP = New Drug Funding Program (administered by Cancer Care Ontario); OHCAS = Ontario Home Care Administrative Services.

### Statistical Analysis

We would ideally have liked to follow all patients from start of ADT until death. However, as with most analyses of longitudinal cost data, many patients are still alive at the end of the observation period, and other patients have short periods of observation because they enter the study too late to be followed for the maximum time. Such patients are censored, and without adjustment, their inclusion will bias the estimates of mean total cost<sup>33</sup>.

Methods to account for censoring have been proposed. In the Kaplan–Meier sample average estimate from Lin *et al.*<sup>33</sup>, uncensored costs are weighted by survival probability. The entire study duration is partitioned, and for each time interval  $j$ , the mean cost for all patients  $\hat{E}_j$  observed at the start of the interval is multiplied by their probability

of survival  $\hat{S}_j$ . The mean total cost is then estimated by summing costs for all time intervals:

$$\hat{\mu}_{KMSA} = \sum_{j=1}^{K+1} \hat{S}_j \hat{E}_j.$$

When censoring occurs at interval boundaries, this approach provides consistent, asymptotically normal estimators of the mean total cost<sup>34</sup>.

Bang and Tsiatis account for censoring by weighting uncensored costs by the inverse probability of inclusion<sup>35,36</sup>. The study period is partitioned, and the total interval costs  $M_{ij}$  are divided by the probability of not being censored  $\hat{K}_j$  at the beginning of the interval. The results are summed across all intervals and divided by the sample



size  $n$  to yield the mean cost estimate. When partition boundaries occur at the censoring times, this estimator is equivalent to the Kaplan–Meier sample average estimator<sup>37</sup>. The Bang and Tsiatis partitioned estimator is defined by

$$\mu_{Bang} = \frac{1}{n} \sum_{i=1}^n \sum_{j=1}^K \frac{\Delta_i^j M_{ij}}{\hat{K}_j},$$

where  $\Delta_i^j = 1$  if patient  $i$  is not censored at the beginning of interval  $j$ .

We applied the foregoing methods to adjust for censoring in our data. For each indication and regimen combination, we divided the observation time for the patients into censored time intervals defined as the time between one loss of 1 or more patients because of censoring and the next loss of 1 or more patients. Total health care costs were computed for each censored time interval until no patients remained. The number of patients who died in each interval was also computed. We produced 1000 bootstrapped samples for each indication–regimen. We ran the Bang–Tsiatis and the Lin mean cost estimation procedures in each of the 1000 bootstrapped samples to calculate mean 1-year, 5-year, and 10-year costs, with their 95% confidence intervals (CIs) for each indication–regimen combination.

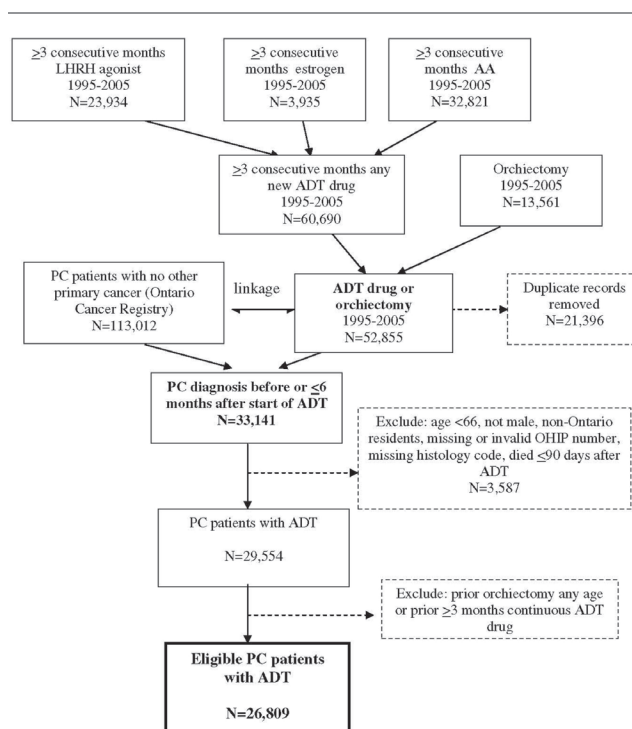
Analyses were performed using the SAS software application (version 9.1 for Unix and version 9.2 for Windows; SAS Institute, Cary, NC, U.S.A.) and the R software application (The R Foundation, Vienna, Austria).

## RESULTS

### Patients

Figure 1 shows the cohort selection process. After selecting 26,809 pCa patients who initiated ADT during 1995–2005, we excluded 4991 patients whose regimens or indications were not clinically relevant, leaving 21,818 patients for the analyses. Mean age in this cohort was 75 years, and year of pCa diagnosis ranged from 1965 to 2005. Only 0.2% of all patients were diagnosed before 1980; 55% were diagnosed during 1980–1999; and 45%, during 2000–2005. However, 87% of patients with recurrence and 61% of patients with metastatic disease were diagnosed during 1980–1999. Approximately 82% resided in urban areas. Patients were fairly evenly distributed among the middle-range neighbourhood income quintiles; only 17.6% were in the lowest quintile, and 22% in the highest. Patients receiving ADT for metastatic disease or as primary therapy for nonmetastatic disease were the oldest, and those with metastatic disease had the most comorbidity. Differences in age, comorbidity, and status on 31 December 2007 were larger between the ADT indications than between the regimens within indication groups (Table iv).

Likewise, length of survival after ADT initiation differed between the indications. Patients who received ADT as adjuvant or neoadjuvant treatment experienced similar survival (approximately 94% and 90% at 5 years, and 81% at 10 years). Patients who received ADT for recurrence had 5-year and 10-year survival rates of 71% and 58% respectively, and rates for patients who received primary ADT were 59% and 43% at 5 and 10 years respectively. The patients



**FIGURE 1** Cohort selection. LHRH = luteinizing hormone–releasing hormone; AA = anti-androgen; ADT = androgen deprivation therapy; pCa = prostate cancer.

with metastatic disease had the shortest survival, with only 30% surviving to 5 years, and 23% surviving to 10 years.

### Costs

Overall, variations in costs for each time period for patients who received different regimens within an indication were small compared with variations in costs between indications (Figure 2). Mean first-year costs were highest for the patients with metastases (Figure 2), ranging from \$24,400 for orchiectomy (95% CI: \$20,790 to \$27,330) to \$32,120 for anti-androgen monotherapy (95% CI: \$27,750 to \$35,660). Mean first-year costs for all other indications were less than \$20,000. The lowest first-year cost, \$14,240 (95% CI: \$11,990 to \$16,190), was for patients who underwent orchiectomy as primary treatment.

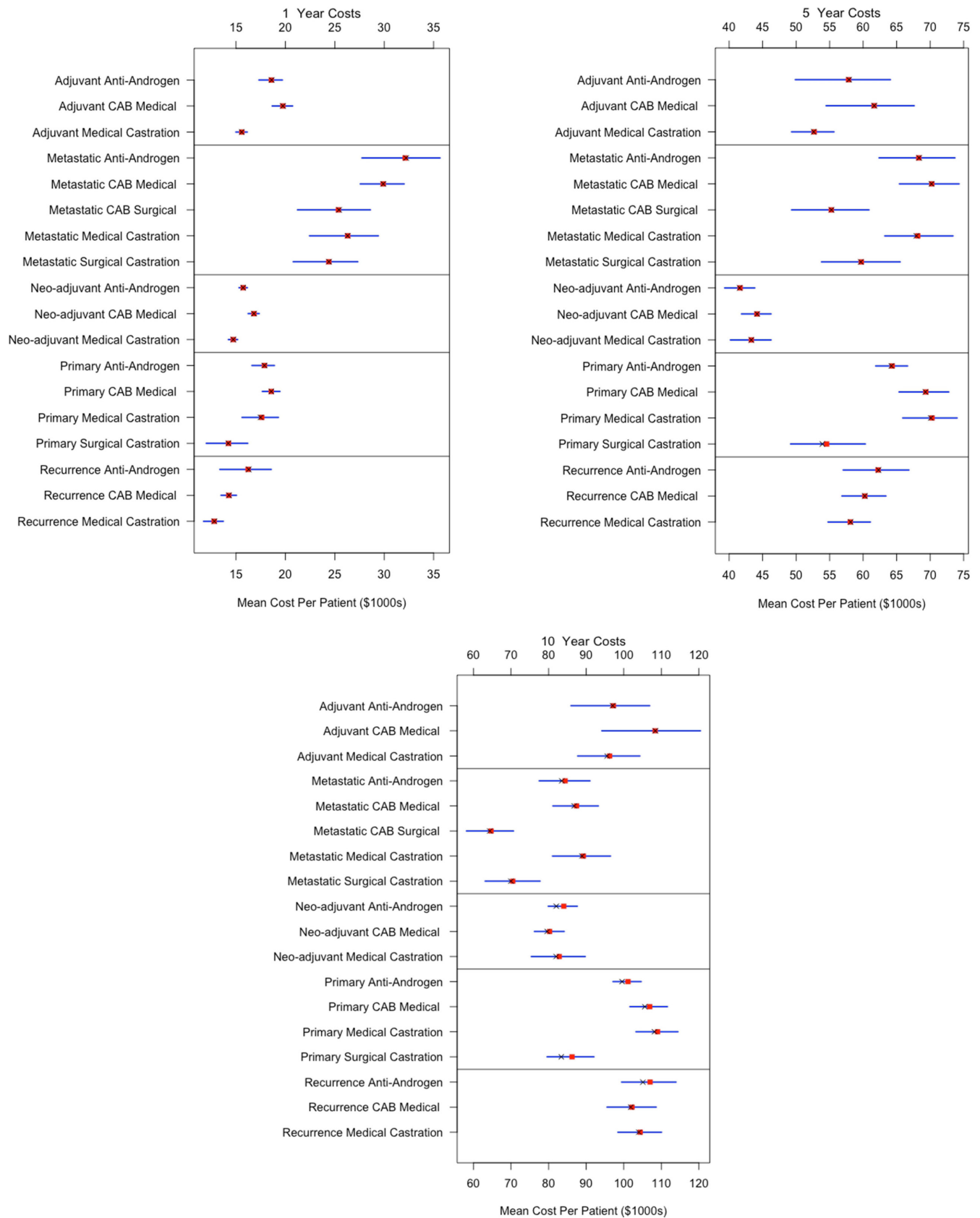
Mean 5-year costs were also highest for metastatic and primary indications. For both indications, the highest costs were for the CAB–medical and medical castration regimens, which ranged from \$68,160 (95% CI: \$63,230 to \$73,420) to \$70,290 (95% CI: \$65,910 to \$74,030). The CAB–medical regimen was, for most indications, associated with the highest cost at 5 years (Figure 2). The lowest mean 5-year costs were for the neoadjuvant regimens and ranged from \$41,650 for anti-androgens (95% CI: \$39,340 to \$43,830) to \$44,150 for CAB–medical (95% CI: \$41,850 to \$46,260).

Most of the mean 10-year costs fell into the range of approximately \$65,000–\$109,000 (Figure 2). Many of the trends already observed persisted. For example, mean costs for CAB–medical were as high as \$108,360 (95% CI: \$94,180 to \$120,410), among the highest of all the regimens.

TABLE IV Patient characteristics by androgen deprivation therapy indication and regimen

Patient group	Pts (n)	Mean age (years)	Adjusted clinical groups [n (%)]				Residence: urban vs. rural [n (%)]	Diagnosis era [n (%)]			Status at 31 Dec 2007: alive vs. dead [n (%)]
			0-3	4-6	7-9	≥10		1960-1979	1980-1999	2000-2005	
All patients	21,818	74.9±5.9	1,016 (4.7)	5,480 (25.1)	7,701 (35.3)	7,621 (34.9)	17,800 (81.6)	49 (0.2)	11,919 (54.6)	9,850 (45.1)	11,861 (54.4)
Neoadjuvant											
AA monotherapy	2,132	71.3±3.8	738 (4.9)	634 (29.7)	819 (38.4)	575 (27.0)	1,697 (79.6)	≤10 (<0.5)	1,229 (57.6)	897 (42.1)	1,689 (79.2)
CAB (medical)	1,534	71.7±3.9	77 (5.0)	420 (27.4)	607 (39.6)	430 (28.0)	1,216 (79.3)	≤10 (<0.7)	814 (53.1)	717 (46.7)	1,196 (78.0)
Medical castration	1,168	72.2±4.1	48 (4.1)	333 (28.5)	447 (38.3)	340 (29.1)	954 (81.7)	≤5 (<0.5)	≤425 (~36)	740 (63.8)	971 (83.1)
Adjuvant											
AA monotherapy	345	72.0±4.3	14 (4.1)	94 (27.2)	125 (36.2)	112 (32.5)	287 (83.2)	0	124 (35.9)	221 (64.1)	253 (73.3)
CAB (medical)	301	72.3±4.2	18 (6.0)	81 (26.9)	113 (37.5)	89 (29.6)	252 (83.7)	≤5	≤95 (~31)	206 (68.4)	226 (75.1)
Medical castration	1,310	71.8±4.0	49 (3.7)	387 (29.5)	498 (38.0)	376 (28.7)	1,077 (82.2)	≤5	≤314 (~24)	994 (75.9)	1,121 (85.6)
Primary											
AA monotherapy	3,663	77.2±6.0	181 (4.9)	872 (23.8)	1,266 (34.6)	1,344 (36.7)	2,961 (80.8)	0	1,961 (53.5)	1,702 (46.5)	1,560 (42.6)
CAB (medical)	1,936	75.8±6.0	103 (5.3)	518 (26.8)	678 (35.0)	637 (32.9)	1,556 (80.4)	0	941 (48.6)	995 (51.4)	904 (46.7)
Medical castration	1,951	77.2±5.7	86 (4.4)	494 (25.3)	720 (36.9)	651 (33.4)	1,671 (85.6)	0	523 (26.8)	1,428 (73.2)	1,065 (54.6)
Orchiectomy	1,057	78.3±5.7	32 (3.0)	239 (22.6)	369 (34.0)	417 (39.5)	849 (80.3)	0	811 (76.7)	246 (23.2)	327 (30.9)
Recurrence											
AA monotherapy	916	74.9±5.7	57 (6.2)	245 (26.7)	275 (30.0)	339 (37.0)	739 (80.7)	≤10 (~1)	832 (90.8)	≤81 (~9)	469 (51.2)
CAB (medical)	607	73.9±5.1	29 (4.8)	177 (29.1)	214 (35.3)	187 (30.8)	510 (84.0)	≤10 (~1.5)	566 (93.2)	≤36 (~6.0)	306 (50.4)
Medical castration	1,453	74.2±5.3	103 (7.1)	389 (26.8)	503 (34.6)	458 (31.5)	1,226 (84.4)	≤5 (~0.5)	1,187 (81.7)	≤262 (~18)	1,017 (70.0)
Metastatic											
AA monotherapy	1,129	77.3±6.8	38 (3.4)	181 (16.0)	320 (28.3)	590 (52.3)	918 (81.3)	6 (0.5)	687 (60.8)	436 (38.6)	242 (21.4)
CAB (medical)	717	76.1±6.5	25 (3.5)	117 (16.3)	233 (32.5)	342 (47.7)	594 (82.8)	≤5 (~0.7)	371 (51.7)	≤344 (~48)	153 (21.3)
CAB (surgical)	328	75.1±5.8	18 (5.5)	77 (23.5)	100 (30.5)	133 (40.5)	262 (79.9)	≤5 (~1.5)	274 (83.5)	≤50 (~15)	25 (7.6)
Medical castration	820	76.5±6.5	19 (2.3)	143 (17.4)	264 (32.2)	394 (48.0)	674 (82.2)	8 (1.0)	413 (50.4)	399 (48.7)	277 (33.8)
Orchiectomy	451	76.8±5.9	15 (3.3)	79 (17.5)	150 (33.3)	207 (45.9)	357 (79.2)	≤5 (~1)	353 (78.3)	≤96 (~21)	60 (13.1)

Pts = patients; AA = anti-androgen; CAB = combined androgen blockade.



**FIGURE 2** Mean longitudinal costs at 1, 5, and 10 years for androgen deprivation therapy indications and regimens. × = observed means; squares = bootstrapped corrected means; CAB = combined androgen blockade.



Orchiectomy and CAB–surgical were associated with the lowest costs for all time periods, but were used only for primary and metastatic treatment. Medical castration and CAB–medical, both of which include LHRH agonists, were usually the most costly regimens.

We estimated the percentage of total costs spent on outpatient drug prescriptions, including pharmacologic ADT, for each regimen. Those percentages were highest in the first year of ADT, when most patients would be receiving the most intense ADT. Because of high costs for other resources, outpatient prescriptions represented only 23%–24% of the total costs for patients with metastatic disease. Outpatient prescription drugs represented a higher percentage of the total cost for patients with recurrence: for example, 38%–65% in the first year. Neoadjuvant ADT is generally given for a short period before and after another primary treatment, and thus drug costs for patients on neoadjuvant regimens represented 27%–35% of the total cost in the first year and slightly less thereafter.

## DISCUSSION AND CONCLUSIONS

Our study used administrative data to estimate total longitudinal health care costs for a population-based sample of patients who initiated clinically relevant types of ADT for 5 common indications over an 11-year period in a large province in Canada. One consistent finding was lower overall health care costs for the surgical regimens (orchiectomy and CAB–surgical).

The average difference in the mean first-year costs for those regimens compared with their medical equivalents was \$3,277. From the point of view of overall cost, and assuming similar patients, if the 2771 patients in our cohort who received medical castration as primary treatment ( $n = 1951$ ) or for metastases ( $n = 820$ ) had received an orchiectomy, the first-year cost savings would be \$8,160,580. Another 717 patients received CAB–medical treatment for metastatic disease. Substituting a CAB–surgical regimen would potentially save \$3,255,180 in the first year. Overall, the exclusive use of orchiectomy would represent a savings of \$11,415,760 for 3488 patients in the first year after initiation of ADT. Those cost differences extend into later years, and the differences in cost between surgical and medical castration regimens at 10 years would total more than \$75 million.

Our cost estimates include costs for all health care and might be conservative in terms of savings based on ADT only. Survival rates were actually lower for patients who received surgical castration than for those who received medical castration; thus, high end-of-life costs are included in their total costs<sup>25</sup>. Previous studies that examined cost differences between medical and surgical castration estimated the annual savings to be approximately \$5,000<sup>12,14,38</sup> (converted to 2009 Canadian dollars).

Medical castration, either alone or with anti-androgen (CAB–medical), was the most costly regimen for most indications and time periods. However, anti-androgen monotherapy was associated with surprisingly high costs given the relatively low cost for those drugs in Ontario. We classified patients by their initial type of ADT, and it is possible that patients remained on anti-androgen monotherapy for

a longer period than they remained on LHRH agonists. Also, some patients using medical castration might have been on intermittent LHRH therapy, although most studies showing noninferiority of intermittent compared with continuous ADT were published after 2005<sup>39</sup>.

Patients who received ADT as neoadjuvant or adjuvant treatment were younger than the patients who received it for other indications. That difference probably accounts for their lower overall health costs. They received ADT for a short time in conjunction with either radiation therapy or radical prostatectomy, and hence their first-year costs were high compared with the first-year costs for primary ADT and recurrence, but their 5-year and 10-year costs were lower. The patients with metastasis were older and had a greater comorbidity score than most of the patients who received ADT for other indications; many of their high health costs were therefore undoubtedly not directly associated with ADT. However, our study represents the true clinical picture, in which patients who receive ADT for localized disease differ from those who receive it for advanced and metastatic disease. Patients were similar within indications, and we were most interested in comparing costs for regimens within indications.

Our 5-year costs for the various regimens and indications ranged from \$41,650 to \$70,260 (2009 Canadian dollars). A study that used the CAPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) database<sup>40</sup> and included only PCA-related costs estimated that mean cumulative 5-year costs for patients initially treated with ADT were \$69,244 (2004 U.S. dollars)<sup>9</sup>, higher than our estimates for most regimens. Another study using Surveillance, Epidemiology, and End Results–Medicare data and a matched control group to calculate net PCA-related costs estimated 5-year costs of hormonal therapy to be only \$26,896 (2007 U.S. dollars), but it considered data from only the years during which the patients survived, thus excluding the high costs immediately before death<sup>10</sup>. Neither study described the ADT regimens or their indications.

The methods used in the present study provide a model for similar economic evaluations for other pharmacologic or surgical therapies for cancers and other diseases. We used a rich selection of health care administrative data to estimate costs, and we applied algorithms and decision rules to classify patients by ADT regimen and indication. We present estimates of real-world longitudinal costs for a large population-based cohort of PCA patients who received ADT, for use in economic analyses and models. Total health care costs reflect not only variations in ADT indication and regimen, but also realistic differences in tumour factors, patient comorbidity, age, general health, and patient preference. Ideally, those factors—and not only cost—should be considered when determining the optimal type of ADT for a patient or group of patients.

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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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