# The burden of symptomatic skeletal events in castrate-resistant prostate cancer patients with bone metastases at three Canadian uro-oncology centres

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## Abstract

**Introduction:** Metastatic bone disease in castrate-resistant prostate cancer (CRPC) carries risks of significant morbidity, including symptomatic skeletal events. We estimated the healthcare resource costs of managing skeletal events.

**Methods:** A retrospective chart review was conducted for patients who died from or were treated palliatively for metastatic CRPC from 2006–2013 at Centre Hospitalier de l'Université de Montréal (Montreal), Princess Margaret Cancer Centre (Toronto), or Vancouver General Hospital (Vancouver).

**Results:** Of 393 patients, 275 (70%) experienced 833 events (85 per 100 patient-years), with a median time to first event of 17.6 months (95% confidence interval [CI] 15.3, 21.7). The mean metastatic bone disease-related healthcare resource use cost (2014 Canadian dollars) estimate for patients without symptomatic skeletal events was $9550 and between $22 101 (observed) and $34 615 (adjusted) for patients with at least one event. Fewer patients in Montreal (55%) experienced events compared to Toronto (79%) or Vancouver (76%). Median time to first event was longer in Montreal (25.0 months [18.5, 32.6]) than in Toronto (14.6 months [9.7, 16.8]) or Vancouver (17.3 months [14.8, 24.0]). More patients received bone-targeted therapy in Montreal (64%) and Toronto (60%) than in Vancouver (24%). Bone-targeted therapy was mostly administered every 3–4 weeks in Montreal and every 3–4 months in Toronto.

**Conclusions:** Metastatic bone disease-related healthcare resource use costs for Canadian CRPC patients are high. Symptomatic skeletal events occurred frequently, with the incremental cost of one or more events estimated between $12 641 and $25 120. Symptomatic skeletal event incidence and bone-targeted therapy use varied considerably between three Canadian uro-oncology centres. An important limitation is that only patients who died from prostate cancer were included, potentially overestimating costs.

## Introduction

Prostate cancer is the most common malignancy in men living in developed countries. In 2015, there were an estimated 24 000 new prostate cancer cases in Canada and 4100 prostate cancer deaths.[1] The majority of prostate cancer deaths are attributable to metastatic castrate-resistant prostate cancer (mCRPC),[2] with a historic median survival for this population of around two years. Bone is the primary site for prostate cancer metastases, with 90% of 1589 autopsied mCRPC patients exhibiting metastatic bone disease.[3]

CRPC patients with metastatic bone disease are at risk of significant morbidity, including skeletal-related events (SREs; palliative radiation, pathological fracture, surgery to bone, and spinal cord compression)[4] with consequential detriment to quality of life[5] and increased mortality.[6] Zoledronic acid (ZA) has been shown to delay SREs compared with placebo,[4,7] with denosumab further extending the time to first SRE compared to ZA.[8] International and local guidelines recommend bone-targeted therapy for prostate cancer patients with metastatic bone disease.[9,10]

Studies conducted in Europe and the U.S. describe the substantial healthcare resource use required for the management of metastatic bone disease and the treatment of SREs in patients with advanced cancer in general[11-14] and prostate cancer specifically.[6,15,16] While the trend of increased economic burden is clear, there is substantial geographical variation in absolute metastatic bone disease- and SRE-related healthcare resource use costs and a paucity of data specific to the Canadian healthcare system. Recent Canadian studies have explored drug costs in mCRPC,[17] SRE-related healthcare resource use in advanced cancer patients,[18] and metastatic bone disease-related healthcare resource use costs in prostate cancer patients from Quebec,[19] but no study has examined metastatic bone disease-related healthcare resource use costs in mCRPC

across the country or estimated the incremental costs of managing skeletal events.

This retrospective chart review estimated healthcare resource use costs attributable to metastatic bone disease and symptomatic skeletal events in mCRPC patients treated at three Canadian uro-oncology centres. This study also describes symptomatic skeletal event incidence and bone-targeted therapy use.

## Methods

### Study population

Charts were reviewed to identify all CRPC patients with metastatic bone disease who died from mCRPC or were admitted for palliative care between January 1, 2006 and January 31, 2013. Patients were identified based on International Classification of Diseases Ninth Revision (ICD-9) and/or Tenth Revision (ICD-10) codes for prostate cancer (ICD-9 code 185.xx, ICD-10 code C61) and metastatic bone disease diagnoses (ICD-9 code 198.5, ICD-10 code C79.5). CRPC status was confirmed by laboratory test results and comments in patient charts. Patients with a history of lung, kidney, or thyroid cancer or parathyroid disease at time of prostate cancer diagnosis were excluded, as were patients who died of traumatic events. Charts were obtained from three uro-oncology care centres, as these patients would have been identified as having experienced or being at high risk to experience a SRE. Patients were identified as having been referred to one of these centres, but may have died or gone on to receive palliative care elsewhere.

### Data and costs sources

Patients were identified from medical charts from Centre Hospitalier de l'Université de Montréal (CHUM), Princess Margaret Cancer Centre (PMCC), and Vancouver General Hospital (VGH).

Data were collected by abstractors trained at each study site. To minimize inconsistencies across the sites, a single data extraction sheet was used, which was validated at all sites. Data were reviewed centrally on an ongoing basis. Data collected included demographics, prostate cancer-related medical history, and metastatic bone disease-attributable resource use. Skeletal events identified through this retrospective approach were assumed to result from symptomatic presentation, reflecting standard clinical practice, and were considered symptomatic skeletal events (rather than skeletal-related events, a broader category including asymptomatic events captured through prospective study protocol-mandated proactive investigations).

Unit costs used to calculate healthcare resource use costs (2014 Canadian dollars) were derived from various Canadian sources.[20-25]

### Study endpoints

The primary objective of this study was to estimate costs attributable to metastatic bone disease management from diagnosis to death in patients who died from mCRPC or who were admitted for palliative care. Secondary objectives were to estimate the mean per-patient monthly cost of metastatic bone disease and to describe skeletal event incidence and bone-targeted therapy use.

### Statistical analysis

The cost estimate precision margin of error for a convenience sample of 463 patients was determined to be ±$4500 CAD. No power calculations were performed.

Metastatic bone disease-related healthcare resource use costs were calculated for resources used on or after the date of onset of metastatic bone disease (index date). Metastatic bone disease-attributable resources were categorized as symptomatic skeletal event- and non-symptomatic skeletal event-related and were tallied separately per patient based on observed data. A sensitivity analysis applying symptomatic skeletal event-related resource use reported by Habib and colleagues[18] was conducted post-hoc to provide adjusted costs for all symptomatic skeletal event types. Symptomatic skeletal event- and non-symptomatic skeletal event-related resources were multiplied by unit costs using observed and sensitivity estimates to obtain costs per patient. Total overall observed and adjusted metastatic bone disease-related healthcare resource use cost estimates are presented for patients with and without symptomatic skeletal events along with healthcare resource use costs by symptomatic skeletal event type.

Time to symptomatic skeletal event and time to death were estimated using the Kaplan-Meier method. The cumulative incidence of symptomatic skeletal events at years 2 and 5 includes death as a competing risk.[26] To address this potential confounder, symptomatic skeletal event rates were computed using patient-years of on-study followup from the index date to date of death or end of study.

When missing data could not be obtained, a variety of methods were used. When the start of treatment was missing, January 1 (if year known) or the index date was used; missing stop date information was imputed as December 31 (if year known) or the date of death. When the dose or frequency of treatment was missing, the standard oncology dose and frequency was used. Missing cost data were imputed using the average cost for patients with non-missing data.

## Results

### Population characteristics

Charts were reviewed for 393 patients. At onset of metastatic bone disease, patients had a mean age of 70.7 years (standard deviation [SD] 9.9) and median prostate-specific antigen (PSA) of 57.2 ng/mL (range 0, 8087) (Table 1). Seven percent of patients had visceral metastases, 11% had existing osteopenia/osteoporosis, and 28% had renal impairment. Population characteristics were similar between sites.

### Characterization of symptomatic skeletal events

Overall, 833 symptomatic skeletal events were recorded at a rate of 85 events per 100 patient-years, with a mean incidence of 2.12 (range 0, 17) symptomatic skeletal events per patient (Table 2). Palliative radiation was the most common symptomatic skeletal event (83%), followed by spinal cord compression (10%), pathological fracture (6%), and surgery to bone (1%). Patients treated at CHUM experienced fewer symptomatic skeletal events, both in terms of mean incidence (1.2 symptomatic skeletal events/patient) and symptomatic skeletal events per 100 patient-years (55.4) than patients treated at PMCC or VGH (2.4 and 2.8 symptomatic skeletal events/patient, and 105.3 and 90.3 symptomatic skeletal events/100 patient-years, respectively).

Two hundred and seventy-five (70%) patients experienced at least one symptomatic skeletal event (Table 2). Symptomatic skeletal events occurred in fewer patients at CHUM (55%) than at PMCC (79%) or VGH (76%). Overall, the median time to first symptomatic skeletal event was 17.6 month (95% confidence interval [CI] 15.3, 21.7), with a longer interval observed at CHUM (25.0 months [95% CI 18.5–32.6]) compared to PMCC (14.6 months [95% CI 9.7–16.8]) or VGH (17.3 months [95% CI 14.8–24.0]) (Fig. 1). The two- and five-year cumulative incidences of a symptomatic skeletal event calculated with death as a competing risk were 40% and 53% at CHUM, 65% and 78% at PMCC, and 54% and 70% at VGH.

The majority (67%) of patients who had a symptomatic skeletal event experienced multiple events (Fig. 2). More patients experienced multiple events at PMCC and VGH than at CHUM. Of patients with one or more symptomatic skeletal events, 90% required radiation therapy, 24% suffered at least one spinal cord compression, 14% experienced pathological fracture, and 1.5% underwent surgery to bone (Table 2).

### Health resource utilization costs

Resources attributed to metastatic bone disease management and each symptomatic skeletal event type are presented in Table 3. Mean symptomatic skeletal event-related healthcare resource use costs ranged from $2965 (SD $4534) for palliative radiotherapy to $21 289 (SD $16 660) for surgery to bone. Applying healthcare resource use reported by Habib et al,[18] adjusted costs ranged from $8506 (SD $6756) for palliative radiotherapy to $37 153 (SD $19 628) for spinal cord compression. Adjusted costs below are marked (*).

The mean estimated metastatic bone disease-related healthcare resource use cost was $9550 (SD $10 872) for patients with no symptomatic skeletal events and ranged from $22 101 (SD $23 611) to $34 615* (SD $30 282) for patients with symptomatic skeletal events. Mean monthly healthcare resource use cost estimates were $537 (SD $377) for patients without symptomatic skeletal events and between $946 (SD $1761) and $1474* (SD $1754) for patients with symptomatic skeletal events. Costs increased with multiple symptomatic skeletal events: mean metastatic bone disease-related healthcare resource use costs for a single symptomatic skeletal event were between $14 680 (SD $16 322) and $19 456* (SD $16 923), while for patients with five or more events, healthcare resource use costs ranged from $38 944 (SD $35 719) to $69 984* (SD $41 675).

### Use of bone-targeting therapy

Two-hundred and one (51%) patients received bone-targeting therapy, mostly ZA (Table 4). More patients received bone-targeting therapy at CHUM (64%) and PMCC (60%) than at VGH (24%). The scheduling of ZA differed substantially between sites: 77% patients at CHUM received ZA every 3–4 weeks, while 70% patients at PMCC received ZA every 3–4 months.

**Table 1. Patient demographics and baseline disease characteristics**

| | CHUM (n=130) | PMCC (n=154) | VGH (n=109) | Total (n=393) |
|---|---|---|---|---|
| Mean (SD) age, years | 72.2 (10.2) | 69.4 (9.9) | 70.7 (9.7) | 70.7 (9.9) |
| Median (range) PSA | 68.7 (0.0, 8087) | 45.8 (0.1, 5413) | 56.0 (0.7, 4157) | 57.2 (0, 8087) |
| Visceral metastases, n (%) | 8 (6) | 13 (8) | 6 (6) | 27 (7) |
| Osteopenia/osteoporosis, n (%) | 13 (10) | 19 (12) | 10 (9) | 42 (11) |
| Renal impairment*, n (%) | 32/117 (27) | 30/117 (26) | 22/71 (31) | 84/305 (28) |

*Renal impairment defined as an estimated glomerular filtration rate <60 mL/min/1.73 $m^2$; renal function data missing for 88 patients. CHUM: Centre Hospitalier de l'Université de Montréal; PMCC: Princess Margaret Cancer Centre; PSA: prostate-specific antigen; VGH: Vancouver General Hospital.

**Table 2. Incidence and type of symptomatic skeletal events by event and per patient**

| | CHUM (n=130) | PMCC (n=154) | VGH (n=109) | Total (n=393) |
|---|---|---|---|---|
| Total SSEs, n | 160 | 371 | 302 | 833 |
| Mean (range) SSEs per patient | 1.2 (0, 8) | 2.4 (0, 16) | 2.8 (0, 17) | 2.12 (0, 17) |
| Type of SSE, n (%) | | | | |
| Palliative radiation | 128 (80) | 307 (83) | 257 (85) | 692 (83) |
| Spinal cord compression | 24 (15) | 33 (9) | 29 (10) | 86 (10) |
| Pathological fracture | 6 (4) | 30 (8) | 15 (5) | 51 (6) |
| Surgery to bone | 2 (1) | 1 (0.3) | 1 (0.3) | 4 (1) |
| SSEs per 100 patient-years | 55.4 | 105.3 | 90.3 | 85.4 |
| Followup, years | 289 | 352 | 334 | 975 |
| SSEs per 100 patient-years by type, n | | | | |
| Palliative radiation | 44.3 | 87.1 | 76.9 | 70.9 |
| Spinal cord compression | 8.3 | 9.4 | 8.7 | 8.8 |
| Pathological fracture | 2.1 | 8.5 | 4.5 | 5.2 |
| Surgery to bone | 0.7 | 0.3 | 0.3 | 0.4 |
| Patients with ≥1 SSE, n (%) | 71 (55) | 121 (79) | 83 (76) | 275 (70) |
| Patients with 1 SSE, n (% patients with ≥1 SSE) | 36 (51) | 32 (26) | 22 (27) | 90 (33) |
| Patients with ≥2 SSEs | 35 (49) | 89 (74) | 61 (73) | 185 (67) |
| Mean (range) SSEs per patient with ≥1 SSE | 2.3 (1, 8) | 3.1 (1, 16) | 3.6 (1, 17) | 3.0 (1,17) |
| Type of SSE, n (% of patients with ≥1 SSE) | | | | |
| ≥1 palliative radiation | 60 (85) | 111 (91) | 77 (93) | 248 (90) |
| ≥1 spinal cord compression | 21 (30) | 27 (22) | 18 (22) | 66 (24) |
| ≥1 pathological fracture | 6 (9) | 24 (20) | 9 (11) | 39 (14) |
| ≥1 surgery to bone | 2 (3) | 1 (1) | 1 (1) | 4 (2) |

CHUM: Centre Hospitalier de l'Université de Montréal; PMCC: Princess Margaret Cancer Centre; SSE: symptomatic skeletal event; VGH: Vancouver General Hospital.

## Discussion

The estimated metastatic bone disease-related healthcare resource use cost for prostate cancer patients without skeletal complications was $9550. However, 70% patients experienced at least one symptomatic skeletal event, requiring additional resource consumption and elevating the healthcare resource use cost estimate to between $22 101 (observed) and $34 670 (adjusted), an increment of between $12 551 and $25 120 representing an approximately 2- to 3.5-fold increase.

The resource use observed in this study was lower than expected. For example, emergency room (ER) visits and hospitalizations were recorded for less than 20% of patients

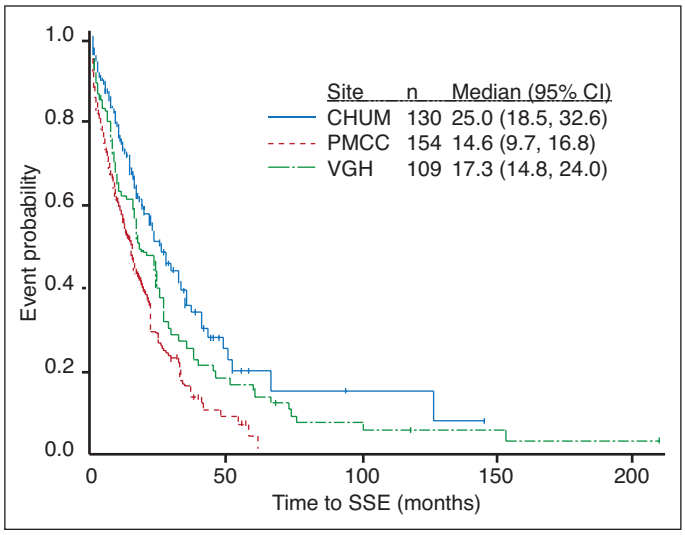


***Fig. 1.*** Time to first symptomatic skeletal event by site. CHUM: Centre Hospitalier de l'Université de Montréal; CI: confidence interval; PMCC: Princess Margaret Cancer Centre; SSE: symptomatic skeletal event; VGH: Vancouver General Hospital.

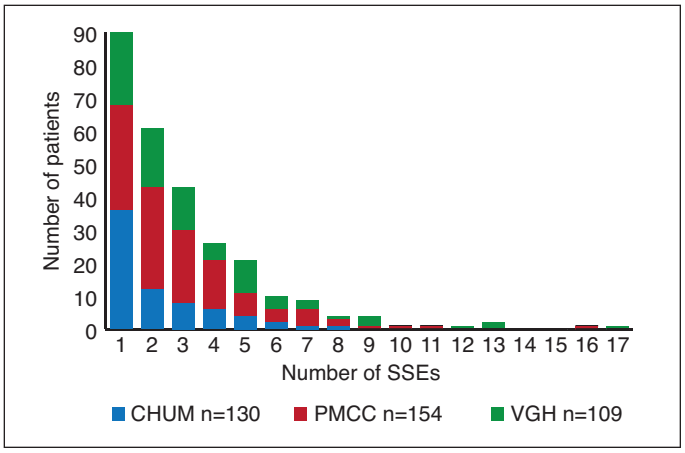


***Fig. 2.*** Distribution of symptomatic skeletal events by number per patient and by investigational site. CHUM: Centre Hospitalier de l'Université de Montréal; PMCC: Princess Margaret Cancer Centre; SSE: symptomatic skeletal event; VGH: Vancouver General Hospital.

**Table 3. Resource use, metastatic bone disease-, and symptomatic skeletal event-related healthcare resource use costs for patients with and without symptomatic skeletal events**

| | Patients with no SSE (n=118) | Patients with ≥1 SSE (n=275) | | | | Resource costs (CAD 2014)[20-25] |
|---|---|---|---|---|---|---|
| **General management of metastatic bone disease*** | | | | | | |
| Diagnostic investigations | 113 (96) | 268 (97) | | | | $182–582/exam[†] |
| Hormone therapy | 110 (93) | 272 (99) | | | | <$0.01–110/mg |
| Bone-targeted therapy | 50 (42) | 151 (55) | | | | <$0.01–90/mg |
| **Management of SSEs*** | | **Palliative radiotherapy (n=248)** | **Spinal cord compression (n=66)** | **Pathological fracture (n=39)** | **Surgical intervention (n=4)** | |
| Any SSE-related resource | | 248 (100) | 66 (100) | 37 (95) | 3 (75) | $182–582/exam |
| Diagnostic investigations | | 192 (77) | 61 (92) | 30 (77) | 3 (75) | <$0.01/mg |
| Other treatment | | 16 (7) | 9 (14) | 3 (8) | 0 | $5.35/mL[‡] |
| Emergency room visit | | 8 (3) | 10 (15) | 6 (15) | 1 (25) | $210/visit |
| Hospitalization/palliative care unit | | 9 (4) | 10 (15) | 6 (15) | 2 (50) | $1047/day |
| Rehabilitation | | 1 (0.4) | 12 (18) | 5 (13) | 0 | $951/day |
| Radiotherapy | | 248 (100) | 57 (86) | 16 (41) | 0 | $172/session |
| Bone surgery | | 0 | 1 (2) | 12 (31) | 3 (75) | $17 551/ procedure |
| Spinal decompression | | 0 | 12 (18) | 1 (3) | 0 | $14 334/ procedure |
| **Healthcare resource use cost by SSE type, mean (SD), CAD** | | | | | | |
| Observed | | $2965 ($4534) | $9565 ($15 386) | $10 777 ($16 640) | $21 289 ($16 660) | |
| Adjusted | | $8506 ($6756) | $37 153 ($19 628) | $15 955 ($10 472) | $32 450 ($0) | |
| **Metastatic bone disease-related healthcare resource use cost, mean (SD)** | | | | | | |
| Observed | $9550 ($10 872) | $22 101 ($23 611) | | | | - |
| Adjusted | - | $34 615 ($30 282) | | | | - |

*Unless noted otherwise, values represent n (%). [†]Diagnostic investigations: bone scan $350, X-ray $180, computed tomography $398, magnetic resonance imaging $582. [‡]Other treatment: Corticosteroids <$0.01–0.08/mg, IV hydration $5.35/mL. CAD: Canadian dollars; SD: standard deviation; SSE: symptomatic skeletal events.

experiencing spinal cord compressions, a clinically unlikely scenario. This low observed healthcare resource use may reflect some patient care occurring outside of study centres without subsequent transfer of relevant information to study centre charts. A recent study of Canadian SRE-related healthcare resource use in advanced cancer[18] reported higher resource use (for example, 54% patients with spinal cord compression visited the ER, and 85% were hospitalized), providing data for a post-hoc sensitivity analysis and adjustment of healthcare resource use costs.

Comparisons with other healthcare resource use cost studies are complicated by diverse methodologies, patient populations, and geographical variations in metastatic bone disease management, but these results are consistent with recent North American[6,12,16,19] and European[13-15] publications describing the economic burden of skeletal events.

The SRE rate for prostate cancer patients in the placebo arm of the pivotal ZA study was 49%.[4] SRE and symptomatic skeletal event rates for prostate cancer patients in a comparative study of denosumab and ZA were 36% and 41%,[8] and 25% and 30%,[27] respectively. Rates of spinal cord compression, the most morbid skeletal event,[5] were 3–7% in the overall populations of these studies[7,8] and 8–15% for patients with at least one SRE.

Here, we report that 70% patients experienced at least one symptomatic skeletal event, with 17% of the overall population suffering spinal cord compression. Of patients with at least one symptomatic skeletal event, 24% had spinal cord compression. These markedly higher event rates likely reflect both real-world data and examination of complete histories of patients with metastatic bone disease (rather than the limited observation periods used in the bone-targeting therapy studies), and may well provide a more comprehensive understanding of symptomatic skeletal event burden. Recent improvements in access to modern magnetic resonance (MR)-based imaging may also contribute to this

**Table 4. Frequency of administration of ZA by site**

| | CHUM (n=130) | PMCC (n=154) | VGH (n=109) | Total (n=393) |
|---|---|---|---|---|
| Patients receiving any bone-targeting therapy, n (%) | 83 (64) | 92 (60) | 26 (24) | 201 (51) |
| Patients receiving ZA, n | 77 | 87 | 26 | 190 |
| Less than once per month, n (%) | 59 (77) | 9 (10) | 10 (38) | 78 (41) |
| Greater or equal to once every 3 months, n (%) | 3 (4) | 61 (70) | 1 (4) | 65 (34) |
| Unknown frequency | 15 (19) | 17 (20) | 15 (58) | 47 (25) |

CHUM: Centre Hospitalier de l'Université de Montréal; PMCC: Princess Margaret Cancer Centre; VGH: Vancouver General Hospital; ZA: zoledronic acid.

observation, potentially uncovering subclinical spinal cord involvement that would not previously have been identified.

Post-hoc analysis revealed contrasting symptomatic skeletal event incidence and bone-targeting therapy use across study centres. CHUM reported over 20% fewer patients with symptomatic skeletal events than VGH or PMCC. The rate of events per 100 patient-years, around 40% lower at CHUM than at the other sites, is consistent with this observation and addresses potential confounding due to death as a competing risk. The difference appears to be driven by less frequent palliative radiation at CHUM (44.3 events/100 patient-years) than at PMCC (87.1) or VGH (76.9). Patients at CHUM experienced fewer multiple events (2.3 events/patient) compared to PMCC (3.1) and VGH (3.6). Forty-nine percent of patients at CHUM with a first symptomatic skeletal event experienced multiple events, compared to around 75% patients at PMCC and VGH.

A similar proportion of patients received bone-targeting therapy at CHUM (64%) and PMCC (60%), but with markedly different administration schedules; the majority of CHUM patients received ZA every 3–4 weeks, while most PMCC patients were treated every 3–4 months. Few (24%) patients at VGH received bone-targeting therapy.

While direct cause and effect cannot be determined for a study of this type, we note that the site reporting the fewest symptomatic skeletal events and lowest rate of multiple events also reported the highest proportion of patients treated with bone-targeting therapy administered every 3–4 weeks. These observations are generally supportive of the notion that bone-targeting therapy is integral to the appropriate care of patients with metastatic bone disease secondary to prostate cancer per local[9] and international guidelines[10] and provide a provocative real-world counterpoint to trials reporting non-inferiority for 12-weekly vs four-weekly administration of ZA.[1,20,28] Our results are also in accordance with those from a national claims database study by Hatoum et al, who reported that the rate of skeletal complications was correlated with the frequency of ZA usage: 0.16 complications per month with usage on the recommended schedule, 0.31 per month with non-recommended schedules, and 0.43 per month with no treatment.[29] However, we did not control for differences in treatment, baseline disease characteristics, or survival across the centres, which may also have affected rates of symptomatic skeletal events. For example, differing institutional thresholds for initiation of palliative radiation would influence the delivery of that particular symptomatic skeletal event component.

An important limitation of this study is its study design: because only patients who died from prostate cancer were included, exclusion of those dying from other causes may have led to an overestimation of costs. Furthermore, our ability to compare outcomes across the study centres is limited because we could not control for differences in treatment or disease characteristics in these centres. However, the rates of chemotherapy were consistent across the centres: 96%, 95%, and 91% for CHUM, PMCC, and VGH, respectively, suggesting treatment patterns were similar across the centres. Other limitations of this study include potential healthcare resource use underestimation due to incomplete patient charts, misassignment of healthcare resource use to symptomatic skeletal event type in the event of concurrent symptomatic skeletal events, and bias if interpretation of data abstraction instructions varied between centres. Some healthcare resource use elements had a high rate of imputation for missing data, risking reduced variability. Although the preplanned sample size was not achieved, the observed margin of error (±$2710) was smaller than expected. Time-to-event analyses incorporate confounding, as 99% of patients had death as an inclusion criterion. While this study included sites situated in three major Canadian provinces, the data are historic and may not be representative of national, provincial, or current practice.

## Conclusion

Symptomatic skeletal events were observed in 70% prostate cancer patients with metastatic bone disease treated at three Canadian uro-oncology centres. Metastatic bone disease and symptomatic skeletal events were associated with substantial healthcare resource use costs. The development of symptomatic skeletal events and patterns of bone-targeting therapy use varied considerably between centres.

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