RADIUM-223 TREATMENT IN PATIENTS WITH PROSTATE CANCER IN ONTARIO

CLINICAL AND LABORATORY CHARACTERISTICS THAT INFLUENCE PROGNOSIS OF MEN WITH METASTATIC CASTRATE RESISTANT PROSTATE CANCER TREATED WITH RADIUM-223

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TITLE: Clinicopathological Characteristics That Influence Prognosis of Men With Metastatic Castrate Resistant Prostate Cancer Treated With Radium-223

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LAY ABSTRACT

Prostate cancer is the leading cause of cancer in Canadian men, with a significant number of men experiencing spread of the disease to the bone. Radium-223 has been developed to treat prostate cancer in the bone and although effective, this treatment may not always work successfully. Although prior studies have attempted to elucidate which laboratory and clinical factors can help predict benefit from Radium-223, the data has been incomplete and too small to make any concrete conclusions. This study aims to investigate which of these factors can predict which patients will derive benefit and make Radium-223 more tolerable.

Between March 2014 and March 2023, a total of 1,588 patients with prostate cancer received Radium-223 treatment in Ontario, Canada. The timing of diagnosis varied, with about 20% diagnosed between 2002-2008, 50% between 2009-2015, and 30% between 2016-2022. Most patients who received treatment were diagnosed with prostate cancer at an advanced stage (45.8% at stage IV, 12.6% at stage III), and 23.8% at an early stage (I+II). Before starting Radium-223, 27.6% of patients had used androgen receptor-axis-targeted (ARAT) therapies, and 25.3% had used bone-modifying agents. The median overall survival from starting Radium-223 was 12.3 months. Higher hemoglobin and calcium levels were associated with longer survival, while higher neutrophils, alkaline phosphatase (ALP), and prostate-specific antigen (PSA) levels indicated shorter survival. Patient factors like older age and more advanced stage at diagnosis were linked to worse outcomes. Prior use of ARATs and chemotherapy was associated with poorer outcomes. Demographic factors showed that patients from rural areas were less likely to receive Radium-223 treatment, although this was not linked to worse survival. These findings help guide treatment decisions for patients with advanced prostate cancer.

ABSTRACT

Background: Radium-223 is an alpha-emitting radioactive calcium-mimetic nuclide preferentially distributed into high turnover bone affected by cancer cells after intravenous administration. It has been shown to reduce mortality in patients with boney metastases due to metastatic castration-resistant prostate cancer (mCRPC). However, which patients benefit most from radium-223 therapy remains an important unanswered question.

Methods: Patients diagnosed with prostate adenocarcinoma and treated at least once with radium-223 in the province of Ontario between March 3, 2014 and March 31, 2023 were identified by the Institute for Clinical Evaluative Sciences (IC/ES) database. Physician billing codes were used to identify radium-223, chemotherapy, radiation therapy and surgical interventions. Drug identification numbers (DIN) were used to identify patients who had been exposed to androgen receptor axis-targeted agents (ARAT) and bone modifying agents (denosumab or zoledronate). Laboratory data was extracted from the Ontario Laboratories Information System (OLIS) and included blood prostate-specific antigen (PSA), albumin, alkaline phosphatase (ALP), hemoglobin levels; and blood leukocyte, lymphocyte and neutrophil counts.

Results: A total of 1588 patients with prostate cancer received radium-223 treatment. Median age at treatment was 68 with approximately 20% (322) of patients diagnosed between 2002-2008, 50% (754) between 2009-2015 and 30% (512) between 2016-2022. Patients with metastatic disease at diagnosis comprised the majority of patients who received treatment (45.8% [728]), followed by 12.6% (200) with stage III and 23.8% (377) diagnosed at an early stage (I+II). Prior use of ARATs was seen in 27.6% (438) and 25.3% (401) of patients had prior use of a bone modifying agent. Median overall survival from diagnosis was 85.6 months while median overall survival from starting radium-223 was 12.3 months. In a multivariable model, higher pre-treatment hemoglobin (HR 0.82, 95% CI 0.78-0.85) and calcium (HR 0.21, 95% CI 0.14-0.32) levels were associated with longer survival and higher pre-treatment neutrophil count (HR 1.08, 95% CI 1.05-1.11), ALP (HR 1.08, 95% CI 1.06-1.11) and PSA levels (HR 1.02, 95% CI 1.01, 1.03) with shorter survival. Excluding laboratory values, older age (HR 1.02, 95% CI 1.02-1.03), prior use of ARATs (HR 1.24, 95% CI 1.06-1.45) and chemotherapy (HR 2.11, 95% CI 1.78, 2.51) were associated with worse survival while early stage at diagnosis (stage I [HR 0.41, 95% CI 0.23-0.74] and stage II [HR 0.73, 95%CI 0.61-0.88) were associated with longer survival. Analysis of demographic factors showed that rurality was associated with lower chance of receiving radium-223 but was not associated with worsening survival.

Conclusion: Survival after radium-223 treatment in patients with mCRPC was influenced by disease biology, burden, and patient age. Patients residing in rural areas were less likely to receive radium-223 treatment suggesting barriers to access.

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LIST OF ABBREVIATIONS AND SYMBOLS

ADT	Androgen Deprivation Therapy
ARAT	Androgen Receptor Axis-Targeted agents
SRE	Skeletal-Related Events
ALP	Alkaline Phosphatase Level
mCRPC	metastatic Castrate Resistant Prostate Cancer
ECOG	Eastern Cooperative Oncology Group
IC/ES	Institute for Clinical Evaluative Sciences
OHIP	Ontario Health Insurance Plan
LOINC	Logical Observation Identifiers Names and Codes
OLIS	Ontario Laboratories Information System
PARP	poly-ADP ribose polymerase
DIN	Drug Identification Number
ODB	Ontario Drug Benefit

DECLARATION OF ACADEMIC ACHIEVEMENT

I, Lorin Dodbiba, declare this thesis to be my own work. I am the sole author of this document. No part of this work has been published or submitted for publication or a higher degree at another institution.

To the best of my knowledge, the content of this document has not been reproduced elsewhere or infringes on copyright.

My supervisor, Dr. Gregory Pond, and the members of my supervisory committee, Dr. Kevin Zbuk and Dr. Sebastien Hotte, have provided guidance and support at all stages of this project.

INTRODUCTION

Prostate cancer is the most common potentially lethal cancer in Canadian men, with over twenty thousand patients being diagnosed yearly (Brenner et al., 2022). Although only 8% of patients will present with *de novo* metastatic prostate cancer (i.e. stage IV at diagnosis), approximately 10-20% of patients treated for localized disease will develop distant metastases (A. I. So et al., 2020). Another 25% of patients with localized disease may develop a biochemical recurrence which carries an additional risk of developing metastatic disease and mortality (Falagario et al., 2023). Once metastatic, androgen deprivation therapy (ADT) and androgen receptor axis-targeted (ARATs) agents are the backbone of treatment illustrating the importance of androgens in disease progression and mortality. Despite this, most incurable prostate cancers develop resistance to androgen deprivation and more aggressive treatments with chemotherapy (docetaxel, cabazitaxel) and radiation are required to slow disease progression and improve survival.

The natural history of the disease has shown that up to 90% of men with metastatic prostate cancer will develop bone metastases once early stage treatments fail (Scher et al., 2005; Tannock et al., 2004). Skeletal-related events (SREs) include pain necessitating radiation to bone, pathologic fracture, spinal cord compression, and/or surgery to bone increase treatment costs, decrease in quality of life, and increase risk of disability and death. In the absence of prophylaxis, about half of advanced prostate cancer patients with bone metastases will experience at least one SRE over a 2-year period (Saad et al., 2004; Simon Tchekmedyian et al., 2010). Once an SRE occurs, the chances of developing subsequent SREs increases dramatically, leading to a downward spiral of morbidity (Tchekmedyian et al., 2010). As the burden of bone metastases increases,

cancer cachexia, calcium derangement, and bone marrow failure occur, the latter limiting future treatments, increasing infection risk and the need for blood transfusion (Shamdas et al., 1993).

Bone modifying agents may reduce the risk of SREs and work by either binding calcium into the bone, reducing osteoclast function (bisphosphonates) or by inhibiting the RANK receptor which leads to osteoclastogenesis and subsequent bone resorption (So et al., 2012). The first agent to show significant reduction in SREs compared to placebo was zoledronic acid, with a reduction of approximately 10% in pathologic fractures (Saad et al., 2002, 2004). Denosumab showed an approximately 20% reduction in SREs in a comparison with zoledronic acid (Fizazi et al., 2011; Smith et al., 2012). Although there is compelling evidence for the use these agents, these studies did not show a survival benefit. Furthermore, both agents may have adverse effects including injection site reactions, hypocalcemia, osteonecrosis of the jaw and atypical fractures which can complicate patient outcomes.

Strontium-89 is a radioactive β-emitting isotope that mimics calcium and has been studied in metastatic prostate cancer involving bone. Although not conclusive, some studies have shown that compared to placebo, strontium-89 may help with pain control (Brundage et al., 1998). Compared to conventional radiotherapy, patients receiving strontium-89 were more likely to be free of pain and were more likely to have improved quality of life and increased time to further radiotherapy (Quilty et al., 1994). Although, strontium-89 may be useful in addressing multiple metastatic deposits where conventional radiation is not feasible, it has not been shown to reduce mortality.

Radium-223 is an α-emitting radioactive nucleotide which also mimics calcium and is preferentially distributed into high turnover bone affected by cancer cells. α particles can cause double stranded DNA breaks leading to cancer cell apoptosis and reduction of disease burden (Den et al., 2019). The efficacy of radium-223 was tested in the ALSYMPCA trial, a double-blind, placebo-controlled phase III trial comparing treatment with monthly radium-223 (up to a maximum of 6 cycles) vs placebo in patients with metastatic castration-resistant prostate cancer (mCRPC) (Parker et al., 2013). Radium-223 was the first bone targeting treatment to report a statistically significant reduction in mortality (Hazard Ratio (HR): 0.70; 95% Confidence Interval (CI): 0.58 to 0.83; P<0.001) and an improved time to first symptomatic SRE (HR: 0.66; 95% CI: 0.52 to 0.83; P<0.001). Additionally, laboratory-based outcomes such as the time to an increase in the total alkaline phosphatase level (ALP) (HR: 0.17; 95% CI: 0.13 to 0.22; P<0.001) and the time to an increase in the prostate-specific antigen (PSA) level (HR: 0.64; 95% CI: 0.54 to 0.77; P<0.001) were also significantly improved. A higher proportion of patients who received radium-223 also had a meaningful improvement in their health-related quality of life (evaluated by using the Functional Assessment of Cancer Therapy-Prostate questionnaire) (25% vs. 16%, P=0.02) (Parker et al., 2013).

Pancytopenia (odds ratio (OR): 4.83; 95% CI: 4.11-5.67) and anemia (OR: 2.89; 95% CI: 2.55-3.27) were the leading hematological side effects of radium-223 while bony pain (OR: 4.53; 95% CI: 3.67-5.59). Health deterioration (OR: 5.03; 95% CI: 4.23-5.98) can lead to early treatment termination (Huynh-Le et al., 2020). It is estimated that up to 15% of patients can experience substantial hematological side effects at the 6 month mark

which may be increased in patients previously treated with docetaxel chemotherapy (Higano et al., 2023). Although in the ALSYMPCA trial, patients were selected to be docetaxel ineligible at the time of radium-223 treatment, prior use of docetaxel chemotherapy was allowed. ARATs like abiraterone and enzalutamide were, however, not included and questions about their effects on the efficacy of raium-223 remain.

Given the potential adverse effects and that the absolute median overall survival benefit was only three months in the ALSYMPCA trial, real world data is needed to potentially identify factors influencing the effectiveness of radium-223. Retrospective studies report better survival with completing 4-6 cycles of Radium-223 (Cheng et al., 2019; Lavelli et al., 2019; Parikh et al., 2018). Clinical factors such as baseline Eastern Cooperative Oncology Group (ECOG) performance status, anemia, ALP, disease burden in bone, and visceral or lymphatic involvement may confound the number of cycles of therapy completed (Bhoil et al., 2022; Cheng et al., 2019; Lavelli et al., 2019; Liu et al., 2022; Parimi et al., 2017). Although useful, the results of these studies may be influenced by patient selection and are of limited statistical power. Cheng et al included 198 patients at four southern Ontario centres (Cheng et al., 2019). Although clinically important laboratory factors such as hemoglobin, PSA, ALP and neutrophils were included, up to 10% of patients had visceral metastases which is usually an exclusion criterion for treatment with radium-223. Other studies have correlated survival with baseline factors including lymphocyte-to-neutrophil ratio, number of bony metastases, albumin, PSA, ECOG and ALP. A scoring system has been developed based on these factors to help with patient selection (Al-Ezzi et al., 2021; Bauckneht et al., 2022; Frantellizzi et al., 2018). Frantellizzi et al identified baseline ECOG, hemoglobin (< 12 g/dl) and PSA (≥ 20 ng/ml)

for their scoring system but only used a sample size of 92 patients from one treatment centre. Al-Ezzi et al identified ECOG (0-1 vs 2-3), albumin (≥ 35 g/L vs < 35 g/L), baseline ALP (ALP ≤150 U/L vs ALP >150 U/L) and baseline PSA (≤ 80 µg/L vs > 80 µg/L) as the most important factors for a scoring system but only analyzed a total of six factors from one cancer centre. Bauckneht et al reported the largest cohort with 519 patients in multiple Italian cancer centres and focused mostly on inflammatory markers. They identified neutrophil-lymphocyte ratio (< 3.1 vs ≥ 3.1), ECOG (0–1 vs 2-3), number of bone metastases (< 6 vs 6-20 vs ≥ 20), baseline ALP (<220 vs ≥220) and baseline PSA (<44 vs ≥44) as predictors of survival.

None of these scoring systems analyzed how prior treatments (ARATs and/or chemotherapy) affected outcomes with radium-223 for these patients. Furthermore, certain factors such as quantification of the number of bony metastatic deposits are not always accurate and highly dependant on resources available. The optimal sequencing of systemic therapies is still uncertain for patients with CRPC, and may depend on individual patient factors as well as are sources in different jurisdictions. Only a small number of patients in the major population centres around Lake Ontario (with the vast majority in Toronto) have participated in clinical trials of systemic therapies for mCRPC. Similar to external beam radiation therapy, the delivery of radium-223 is typically centralized to centres with nuclear medicine departments that deliver radionucleotide treatments. This may challenge access to such therapies for patients residing in rural or more remote communities. The interaction between demographic, clinical and laboratory data might affect which patients will be optimally treated with radium-223.

Analyzing the effect of these factors can be quite difficult as most health institutions that contain laboratory and clinical data will lack data on socioeconomic or demographic factors, and will only cover patients from one geographic area. Canada's healthcare delivery relies on a single payer system where laboratory services, physician services and medical treatments are covered under provincial health plans. Each province collects this information through different administrative databases managed by different government agencies. In Ontario, Canada's most populous province, the Institute for Clinical Evaluative Sciences (IC/ES) is a non-profit organization which has access to patient-level, linkable health and demographic datasets, encompassing publicly funded health service records of Ontario residents eligible for the provincial health coverage. This unique method of data collection provides an opportunity to complete a more comprehensive analysis on the factors that identify the optimal patient for radium-223.

STUDY PURPOSE

Radium-223 has been shown to be an effective treatment for men with metastatic prostate cancer, but it does not always offer the desired benefit for an individual patient. Although some studies have identified pre-treatment factors that may affect the outcomes of patients treated with radium-223, they are limited by relatively small numbers of patients treated over a short period of time, and may ignore other important clinical factors which might affect outcomes. In this study we aim to better delineate the pre-treatment characteristics of patients treated with radium-223 in a large Ontario wide cohort, identify clinical and laboratory factors associated with outcomes, and analyze how treatment sequencing influences the efficacy of radium-223.

METHODS

Patient Selection

Using linked administrative health databases accessed through the Institute for Clinical Evaluative Sciences (IC/ES), we performed a population-based, retrospective cohort study of prostate cancer patients treated with radium-223 in Ontario, Canada, from 2014 (the year radium-223 was approved by Health Canda) to 2023. IC/ES is a not-for-profit research institute that has access to record-level, coded and linkable health data sets, encompassing publicly funded administrative health service records of Ontario residents eligible for universal health coverage. Ontario is the most populous province in Canada with a population of over 14 million people. All data utilized in this study were accessed through IC/ES, with a detailed list of individual databases provided in Appendix A.

Patients with a confirmed pathological diagnosis of prostate cancer between January 1, 2002, and December 31, 2022, were identified using the ICD-O-3 topography code C619 (malignancy originating from the prostate gland) and adenocarcinoma morphology codes (8140/3, 8550/3, 8000/3, 8010/3, 8552/3) in the Ontario Cancer Registry (OCR) database. Patients were included if they had pathologic diagnosis at least 30 or more days prior to radium-223 use. Data were collected from men aged 18 years or older who had received at least one cycle of radium-223, as identified by Ontario Health Insurance Plan (OHIP) billing codes X336 and X329, between March 3, 2014 (the date of Health Canada approval), and March 31, 2023. Patients with no laboratory data within 90 days of starting radium-223 treatment or those with elements of small cell, neuroendocrine or signet ring features on pathology were excluded.

Patient Demographics

Prostate cancer diagnosis date served as the index date from which the number of days to the first use of radium-223, the last follow-up, and death were directly provided by IC/ES and expressed in days. Age at diagnosis and year of diagnosis were extracted from the OCR database. Patients aged less than 45 years old and those aged more than 95 years were aggregated into respective groups to comply with IC/ES policy. Date of radium use was taken from the Cancer Care Ontario New Drug Funding Program (NDFP) database. All dates were de-identified as per IC/ES privacy policy and considered as the number of days before/after index date, where the index date was date of prostate cancer diagnosis. Age at radium-223 administration was estimated by assuming that the diagnosis occurred in the middle of the age year (i.e. day 182) and was calculated by adding age at diagnosis and days until use of radium-223. The year of radium-223 administration was similarly estimated using the year of diagnosis and adding days to radium-223 use. The Charlson Comorbidity Index was available for all patients who had at least one hospital admission in the 2 years prior to cancer diagnosis and was available from the Canadian Institute of Health Information Discharge Abstract Database (CIHI-DAD). Prior cancer diagnosis, stage at diagnosis and grade at diagnoses were all extracted from the OCR database. Grade at diagnosis represented low (1), medium (2) and high (3) grade of tumor differentiation. No Gleason score or International Society of Urological Pathology (ISUP) grading was captured through the IC/ES database.

Socioeconomic Status

Socioeconomic data were obtained from the Ontario Census Area Profiles (CENSUS) database which gathers data from each census metropolitan area (defined as an area a

total population of at least 100,000 people of which 50,000 or more must live in the core) or each census agglomeration (defined as a core population of at least 10,000 people). The Income quintile is derived from the nearest census-based neighbourhood income quintile within each area. “One” indicates the lowest quintile while “five” represents the highest. The Age and Labour Force quintile refers to the area-level proportion of people who do not have income from employment, including older adults (65 years or older), children (0 to 14 years old), adults whose work is not compensated and/or those unable to work due to disability (age 15 or over). “One” indicates the patient comes from an area with the lowest quintile of people fitting the age and labour force description while “five” represents the highest. The Racialized and Newcomer Populations quintile refers to the area-level proportion of the population who are recent immigrants (arrived in the past 5 years) or self-identify as a visible minority (persons, other than Aboriginal peoples, who are non-Caucasian in race or non-white in colour). “One” indicates the patient comes from an area with the lowest quintile of people fitting the racialized and newcomer population description while “five” represents the highest. The Households and Dwellings quintile refers to the area-level proportion of the population who are living alone, are not youth (defined as age 5-15), live in apartment buildings, are single/divorced/widowed, live in dwellings that are not owned or who have moved in the area during the past 5 years. “One” indicates the patient comes from an area with the lowest quintile of people fitting the household and dwellings description while “five” represents the highest. The Material Resources quintile refers to the proportion of the area-level population aged 25 to 64 who lack a high-school diploma, are lone parent families, are aged 15 or older and unemployed, considered low income (below poverty line), reside in dwellings that are in

need of major repair or are aged 15 and over and receive total income from government transfer payments. “One” indicates the patient comes from an area with the lowest quintile of people fitting the material resources description while “five” represents the highest. Rurality is defined as comprising a population size of less than 10, 000 people. The Rurality Index for Ontario (RIO) score is a measure of rurality which takes into account measure of community population/population density, travel time to nearest basic referral centre and travel time to nearest advanced referral centre (Kralj, 2000). It ranges from 0 (most urban) to 100 (most remote) and is based on 2008 census data. The Registered Persons Database (RPDB) provided the distance to nearest regional cancer centre (expressed in kilometres (km)) and whether diagnosis was made at teaching hospital.

Cancer Treatments

OHIP physician billing codes were used to determine use of chemotherapy, radiation therapy and orthopedic surgery (categorized by spinal decompression, arthroplasty, arthroscopy/denervation, excision and reduction procedures) (Appendix B). Pre- and post-treatment clinical data about use of ARATs, poly-ADP ribose polymerase (PARP) inhibitors and use of bone modifying agents (denosumab or zoledronate) was collected using drug identification numbers (DIN) (Appendix C). Data for ARATs and PARP inhibitors was only available for patients who were eligible for the Ontario Drug Benefit (ODB) which covers patients over the age of 65 or those using the plan as outlines in the database (Appendix A). SREs in this study are defined as receiving surgical intervention for spinal decompression, use of radiation therapy or undergoing another orthopedic procedure as defined above. Ontario Health Insurance Plan (OHIP) Claims Database was used to identify these procedures.

Laboratory Data

Baseline laboratory parameters from the Ontario Laboratories Information System (OLIS) database were utilized if they were recorded within 3 months (90 days) prior to the first dose of radium-223. Logical Observation Identifiers Names and Codes (LOINC) (Appendix D) were used to identify each parameter and included: PSA, testosterone, albumin, hemoglobin, platelets, neutrophils, lymphocytes, leukocytes, ALP, calcium, phosphate, and creatinine. Hemoglobin, leukocytes, platelets, neutrophils, and lymphocytes were selected for analysis because they serve as indicators of bone marrow production and are critical markers of myelosuppression, which can influence clinical outcomes. ALP, calcium, and phosphate were selected because they are markers of bone turnover, the physiological mechanism targeted by radium-223 therapy, and are important indicators in prostate cancer treatment. PSA levels generally reflect disease burden, which can influence survival outcomes, while testosterone levels were used as an internal control, given that only men with castrate levels of testosterone are eligible for radium-223 treatment. Albumin was selected as an indicator of overall nutrition and is a generic predictor of cancer survival, while creatinine was chosen because its relationship with other laboratory factors like calcium and its role as a marker of muscle mass, which reflects overall patient fitness.

Consent and Ethics

IC/ES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA) and is authorized to collect personal health information, without consent, for the purpose of analysis or compiling statistical information. Data access and use through IC/ES was approved through the McMaster University Research Ethics Board. De-

identification was performed by IC/ES analysts and only aggregate data were presented in accordance with IC/ES policies. Data containing fewer than 6 participants was not identified to avoid potential re-identification of participants as per IC/ES policies. Only participating investigators for the study had access to the data which will be kept for a total of 5 years.

Outcomes and Data Analysis

Date of prostate cancer diagnosis served as the index date from which the number of days to the first use of radium-223, the last follow-up, and death were directly provided by IC/ES and expressed in days. The number of days to last follow-up or death represents overall survival from diagnosis. Overall survival from radium-223 treatment was calculated by subtracting the number of days from diagnosis to the first radium-223 administration from the number of days from diagnosis death. Patients without a death date were censored on the date of last follow-up, which is the last date the patient had contact with the Ontario health care system prior to March 31, 2023. Range of radium-223 treatment days were calculated by subtracting days from diagnosis to last radium-223 use from days from diagnosis to first radium-223 use. Time from first radium-223 treatment to death was calculated and estimated using the Kaplan-Meier method. Time to SRE is calculated by subtracting the time from diagnosis to first radium-223 treatment from time from diagnosis to surgical intervention for spinal decompression, use of radiation therapy or undergoing another orthopedic procedure as defined above. Death was considered a competing risk factor for time to SRE.

Patient and disease characteristics, treatments and outcomes were summarized using descriptive statistics. Cox proportional hazards regression analyses were used in a

primary analysis to explore for factors prognostic of outcomes. A multivariable model was constructed using forward stepwise selection to identify an optimal model of factors. Two models were constructed using this approach, one with both clinical and laboratory variables and one excluding laboratory data, given the number of missing lab data.

A secondary analysis was conducted to evaluate factors influencing access to radium-223 treatment and included patients diagnosed between 2008 and 2022. Patients who ceased to have follow up before 2013 were excluded from this analysis (radium-223 only available after 2014). Patients having very short follow up (< 30 days) and those without a prostate adenocarcinoma were also excluded. Death was considered a competing risk factor for access to radium-223 (i.e. patients are at risk of dying before accessing treatment).

Interactions were explored. No interpolation of missing data was performed and 95%, two-sided, confidence intervals were presented for outcomes of interest. All tests and confidence intervals were two-sided and statistical significance was defined at the $\alpha=0.05$ level. Dichotomisation of some variables (year of diagnosis, days from diagnosis to radium-223 treatment) was performed for highly skewed data. Normality assumptions were checked using visual inspection.

RESULTS

Patient Selection

Between 2002 and 2022, a total of 184,461 men were diagnosed with prostate cancer (Figure 1). Among these, 1684 patients had at least one instance of the radionucleotide billing code, indicating its use for prostate malignancy with metastatic disease in the bone. Prior to 2014, strontium-89 was the most commonly used radionucleotide for the treatment of prostate cancer with bone involvement, however, its use was largely abandoned in recent times. Of the patients who had a recorded instance of the radionucleotide billing code, 1607 (95% of all patients treated with a radionucleotide) had used the code after March 2014 when Health Canada approved the use of radium-223. Patients with elements of small cell, neuroendocrine or signet ring features were excluded (12 patients) resulting in 1595 patients fitting the diagnosis of a prostate adenocarcinoma. Of these, 7 patients with no pre-treatment laboratory data were excluded resulting in a total of 1588 patients for analysis (Figure 1). Following March 2014, the annual usage of radium-223 increased rapidly peaking in 2018 (Figure 2). After this peak, a gradual decrease in the use of radium-223 was observed, although its use between 2020 and 2022 could have been affected by the COVID-19 pandemic. Data collection ends on March 31st, 2023, which accounts for the lower uptake observed in that year.

Patient Demographics

The estimated median age at radium-223 treatment was 68 years (range: 44 to 94 years) with the median time from diagnosis to first radium-223 treatment 55.3 months (Interquartile Range (IQR): 26.1-101.1) (Table 1). Approximately 20% of patients were diagnosed between 2002-2008, 50% between 2009 and 2015, and 30% between 2016

and 2022. 117 patients (7%) had a prior diagnosis of a non-prostate cancer. In total, 529 patients (36.6%) were diagnosed at a teaching hospital and the Charlson comorbidity index was available for only 649 patients (40.1%) as most patients were not admitted to hospital in the two years prior to diagnosis. Only 17% of patients were living in a rural area at the time of diagnosis and with a median RIO score of 4 (IQR: 0-24). The median distance to the nearest regional cancer center was 15.6 km (IQR: 7.2-48 km). A total of 238 patients (15%) treated with radium-223 were in the lowest income quintile while 394 patients (24.8%) were in the highest quintile.

Clinical and Laboratory Characteristics

Approximately 58.4% of patients who ultimately received radium-223 were initially diagnosed with prostate cancer at an advanced stage (III and IV), with 45.8% (728 individuals) diagnosed at stage IV (Table 2). Stage at diagnosis was unknown in 17.8% (283 patients). No Gleason score or International Society of Urological Pathology (ISUP) grading was available through the IC/ES database. High tumor grade was identified in 37.9% (602 patients) but data was missing for approximately half of patients included in the analysis. ARAT use was observed in 438 patients (27.6%) prior to receiving radium-223. 12.4% of patients received ARAT therapy after radium-223 treatment. There was no clear pattern of ARAT use following radium-223 use (Supplementary Figure S1). A total of 726 patients (45.7%) received chemotherapy prior to radium-223. No patients in this cohort received PARP inhibitors prior to radium-223. Bone modifying agents were being received by 25% of patients prior to radium-223 (Table 2).

Following radium-223, 886 patients (55.8%) received chemotherapy while 6 patients (0.4%) received PARP inhibitors. The number of patients receiving bone modifying agents after starting radium-223 remained at approximately 25% indicating continued use. Palliative radiotherapy could not be distinguished from curative intent radiation so it was only analyzed for patients after receiving radium-223. A total of 709 patients (44.7%) received palliative radiation after the use of radium-223. Orthopedic interventions after radium-223 were observed in 533 patients (33.6%); 95% of these interventions were for spinal cord decompression (Table 2).

Pre-treatment laboratory data is summarized in Table 3. Testosterone was used as an internal control as all patients receiving radium-223 should be castrate and thus have a serum testosterone of less than 1.7 nmol/L. Pre-radium-223 electrolytes were more likely to be missing while complete blood count components were the most likely to be recorded (Table 3).

Survival and Time to Event Outcomes

The median estimated number of days between the first and last radium-223 treatment was 85 (range: 1-1,514 days), which corresponds to approximately 3 cycles of treatment (Table 4). 1,249 deaths were observed in this cohort, with a median overall survival from diagnosis of 85.6 months (95% CI: 80.9 to 90.9 months), and a median overall survival from radium-223 administration of 12.3 months (95% CI: 11.4 to 13.3 months). In patients requiring spinal decompression surgery (n=505), the median time from the start of radium-223 treatment to surgical intervention was 288 days (range: 4 to 2,956 days).

Prognostic Model for Overall Survival

Clinical and laboratory data was analyzed to determine if there are any factors associated with the mortality of patients treated with radium-223. Univariate analyses identified multiple factors, including most laboratory data, associated with overall survival (Table 5). In multivariate analysis including laboratory values, the use of chemotherapy and ARATs prior to radium-223 treatment was associated with a higher risk of mortality (Table 6). A higher risk of mortality was also associated with higher pre-treatment ALP (HR 1.08, 95%CI 1.06-1.11, $p < 0.001$), PSA (HR 1.02, 95% CI 1.01-1.03, $p < 0.001$) and neutrophil count (HR 1.08, 95% CI 1.05-1.11, $p < 0.001$). Conversely, a lower risk of mortality was associated with higher pre-treatment hemoglobin (HR 0.82, 95% CI 0.78-0.85, $p < 0.001$) and calcium (HR 0.21, 95% CI 0.14-0.32, $p < 0.001$). Interestingly, in this model, a longer time (>5 years) from diagnosis to treatment was also associated with a lower risk of death (HR 0.85, 95% CI 0.75- 0.97, $p = 0.018$).

In a multivariate analysis done including only clinical and pathological factors (Table 7), a higher risk for mortality was again observed in patients who received prior chemotherapy (HR 2.81, 95% CI: 2.45-3.22, $p < 0.001$) and/or ARAT (HR 1.16, 95%CI 1.01-1.32, $p = 0.031$) treatment. Increasing age at diagnosis (HR 1.02, 95% CI 1.02-1.03, $p < 0.001$) and a longer time from diagnosis to radium-223 treatment (>5 years) (HR 1.21, 95% CI 1.06-1.39, $p = 0.004$) were associated with increased risk of mortality. Higher stage at diagnosis, especially stage IV, was also related to increased risk of mortality (HR 1.15, 95% CI 0.98-1.36, $p < 0.001$).

Given the discrepancy in the time from diagnosis to radium-223 treatment (>5 years) between the two multivariate analyses, a more detailed subgroup analysis was

performed. Notably, the OLIS data was incomplete after 2021 and, between 2014 and 2018, up to 25% of patients had missing data. When including year of diagnosis to the multivariate analysis excluding laboratory parameters, the harmful effect noted in the time from diagnosis to radium-223 treatment (>5 years) was no longer observed (HR 0.93, 95% CI 0.78-1.10, $p = 0.4$). These findings suggest the presence of confounding between year of diagnosis and time from diagnosis to initiation of radium-223 therapy.

Access to Radium-223 Treatment

In Ontario, access to radioisotope therapy is typically centralized to large urban cancer centers, which may impact access to treatment. Access to care is a major determinant of health outcomes, particularly impacting marginalized and remote or rural communities. To evaluate this, a secondary analysis was performed focused on the demographic and clinical data of patients with prostate cancer who were potentially candidates for radium-223 during their cancer journey. We identified patients diagnosed with prostate cancer between 2008 and 2022 (see Supplementary Figure 2). The majority of patients treated with radium-223 in Ontario were diagnosed after 2008, with only 20% diagnosed between 2002 and 2008. As a result, patients diagnosed before 2008 were unlikely to have received radium-223 due to the extended delay between diagnosis and treatment. Additionally, patients have a competing risk of mortality and might die prior to having the chance to be considered for radium-223. Patients who ceased to have follow up before 2013 would not have had the opportunity to receive radium-223 as it only received Health Canada approval in 2014. Lastly patients having very short follow up (<30 days) and those without prostate adenocarcinoma were eliminated, leading to a total of 105,996 patients

potentially eligible for radium-223 treatment. Of these, a total of 1277 received radium-223 and the remaining 104,719 patients did not.

The majority of patients not treated with radium-223 were diagnosed between 2017-2022 (40.9%) and the majority of those receiving radium-223 were diagnosed between 2013-2016 (42.5%) (Supplementary Table 1). Patients not treated with radium-223 compared with those who received at least one treatment cycle had similar age at diagnosis (68 vs 69 years), Charlson score of zero (71.7% vs 75.5%), diagnosis at a teaching hospital (31.8% vs 34.2%) and prior cancer diagnosis (9.5% vs 8.5%). Patients treated with radium-223 were more likely to be metastatic at diagnosis (i.e. Stage IV, 55.4% vs 8.9%), have a higher grade (grade 3, 46.5% vs 16.3%) and have a higher PSA (8.1 vs 38.6%) when compared to patients who did not receive radium-223.

Predictive Model of Likelihood to Receive Radium-223

Various socioeconomic factors including income, material resources, household/ dwelling and rurality did not differ between patients who received radium-223 and those who did not (Supplementary Table 2). Univariate analyses were carried out to identify the most important factors influencing the risk of receiving radium-223 amongst all patients diagnosed with prostate cancer (Supplementary Table 3). In multivariate analysis, higher age (HR 1.02, 95% CI 1.01-1.02, $p < 0.001$) and PSA (HR 1.16, 95% CI 1.11-1.20, $p < 0.001$) at diagnosis were correlated with a higher likelihood of receiving radium-223 (Supplementary Table 4). The highest likelihood of receiving radium-223 was seen in patients diagnosed with stage IV disease (HR 7.79, 95% CI 5.56 - 10.93, $p < 0.001$). Conversely, patients diagnosed with earlier stages had the lowest likelihood of receiving

radium-233 treatment (Stage I: HR 0.08, 95% CI 0.05 - 0.15; Stage II: HR 0.39, 95% CI 0.27 - 0.56; Stage III: HR 0.78, 95% CI 0.53 - 1.14). Rurality was associated with a lower likelihood of receiving radium-223 (HR 0.80, 95% CI 0.64 - 0.99, p = 0.044). Other socioeconomic factors such as income, age and labour force, material resources, racialized and newcomer, and household and dwellings were not significantly associated with risk of receiving radium-223.

DISCUSSION

This study focused on Ontario patients is the largest report of radium-223 treatment using real-world data done to date. The use of radium-223 was quickly adopted in Ontario after Health Canada approval with a peak of use between 2016-2018. Use of cytotoxic treatments during the COVID-19 pandemic (2020-2022) did not change drastically, so it is unlikely this was a factor associated with lower use for radium-223 during these years (Fu et al., 2023; Walker et al., 2022). Although this study cannot estimate how many patients would be appropriate candidates for radium-223, we estimate 100,000 patients diagnosed between 2002-2022 could potentially be eligible for radium-223 along their cancer journey. Although, available since 2014, only 1588 were treated with Radium-223, suggesting that in Ontario its use has been quite selective. Anecdotally, patient selection and overall efficacy concerns have been quoted as reasons to avoid radium-223 use. This study focused on how factors affecting access and patient clinicopathological characteristics could affect outcomes of patients treated with radium-223 in Ontario.

Most patients treated with radium-223 in Ontario resided in urban centers or in relatively close proximity to a regional cancer centre (median RIO score of 4, 7% were living in a population center of less than 10,000 individuals, and median distance to a Regional Cancer Centre was only 15km). In multivariate analysis (Supplementary Table 4), rurality was a significant negative predictor of radium-223 treatment. This is consistent with other studies which show that access to oncology care in remote communities has been a challenge in Ontario, with prostate cancer being one of the least likely cancer diagnoses to be seen by a specialist (Conlon et al., 2019; Febbraro et al., 2020). This raises concerns about equitable access to other radionucleotide treatments such as 177Lu-

PSMA-617, which is given similarly to radium-223, but has broader treatment implications. Rurality was the only demographic factor which was significantly correlated with likelihood of radium-223 treatment. In multivariate analysis, no additional demographic variables demonstrated a significant association with survival, suggesting that, despite potential barriers to treatment access, the overall disease trajectory in this patient population remains unaltered. In our study, patients from the highest income quintile were observed to have a 10% higher use of radium-223 compared to those in the lowest quintile. Although, household income has been a factor influencing access to health care in many jurisdictions, in our multivariate analysis, the effects of income do not appear to have a significant effect on survival or probability of treatment with radium-223. The observed income differences can be attributed to the fact that the majority of patients receiving radium-223 resided in urban areas, which are generally more affluent than rural regions.

The median estimated number of days on radium-223 treatment was 85 which indicates 3 or fewer cycles of Radium-223. More prolonged exposure to radium-223 (4 or more treatments) has been associated with improved survival in other reports (Al-Ezzi et al., 2021; Bhoil et al., 2022; Liu et al., 2022). Although factors such as disease progression and/or toxicity are likely responsible for the early discontinuation of radium-223 treatment, the IC/ES database cannot provide an accurate analysis of the underlying reasons for treatment discontinuation. Spinal cord compression is a significant factor in morbidity and mortality in this analysis with up to one third of all patients experiencing this event after radium-223 use. In the ALSYMPCA trial approximately 35% of patients experienced a symptomatic skeletal event but the proportion with spinal cord compression was only 4%.

Regardless of this, the median time from radium-223 start to surgical intervention for spinal decompression was 288 days, suggesting that spinal cord compression was unlikely to be a factor in early treatment stop for most patients. Radium-223 only works in bone sites where there is active bone turnover due to prostate cancer but micro-metastatic disease present in other areas of the body is often not assessed prior to treatment. Data on the use of PSMA-PET to identify non-boney micro-metastatic lesions would greatly improve our understanding of why radium-223 was stopped and where progression occurred.

It is difficult to compare the data in our report to the ALSYMPCA trial, as more effective treatments such as ARATs and cabazitaxel chemotherapy are now available. In our study, approximately 75% of patients received ARATs and/or chemotherapy prior to radium-223 treatment, indicating that most patients received radium-223 in subsequent lines of treatment rather than as a first-line treatment. This study shows that pre-treatment with chemotherapy or ARATs are associated with an increased risk of death, suggesting that earlier use of radium-223 might be more effective. However, it is also unknown whether delaying ARATs and/or chemotherapy, which are also life-prolonging therapies, for radium-223 treatment would similarly negatively influence the benefits of these treatments. The optimal sequencing of systemic therapies for the treatment of castration-resistant prostate cancer, including radium-223, is not known and likely varies with individual patients (Ko et al., 2024).

The increase in mortality with pre-radium-223 chemotherapy and ARATs could be a phenomenon linked to the biology of the tumor itself. It is known that cancers become

more resistant when exposed to repeat systemic therapies, and this data suggests that novel radiation treatments like radium-223 cannot avoid this resistance. Worse outcomes with older age at treatment are not surprising and likely related to increased health frailty. Moving Radium-223 further up the treatment sequence, however, might not be justifiable given that multiple trials have shown survival benefit in using ARATs alone or, in high volume disease, in combination with docetaxel chemotherapy in the castrate sensitive setting (Beer et al., 2014; Fizazi et al., 2022; Ryan et al., 2013; Smith et al., 2022). When compared to each other, however, the prior use of ARATs appears to be less significant than that of prior chemotherapy. This suggests a possible role for radium-223 before docetaxel in patients who have received a prior ARAT for low-volume castrate sensitive disease.

Although toxicity could not be analyzed from our IC/ES data, using clinical and laboratory data for patient selection remains important in the use of radium-223. Patients with an advanced stage at diagnosis show a worsening outcome when exposed to radium-223 compared to those diagnosed at an earlier state. This may suggest more aggressive cancer biology or be more likely to harbour metastatic disease outside of boney sites susceptible to the effects of radium-223. However, it may also suggest a limit on the effectiveness of radium-223 with the dose and schedule currently used. Radium-223 dosing is based on body weight and there are no dose modifications dosimetry data used to adjust for higher disease burden.

In general, the laboratory data analyses in this study indicate that markers of more aggressive and/or higher burden of disease are linked to worsening outcome in patients

treated with radium-223. Firstly, our work confirms the work of others linking an elevated neutrophil count with worse outcomes in these patients. This phenomenon, either in isolation or reported as an elevated neutrophil-to-lymphocyte ratio, has been associated with a poor prognosis in multiple cancer types including prostate (Cao et al., 2016; Ocana et al., 2017). Increases in neutrophils and other inflammatory markers have shown to be correlated with poor response to ARATs, docetaxel chemotherapy, and radium-223 (Bauckneht et al., 2022; Leibowitz-Amit et al., 2014; Templeton et al., 2014). This inflammatory response is related with multiple mechanisms of tumorigenesis and often represents more active and aggressive disease (Cao et al., 2016). Furthermore, other markers of disease aggressiveness and burden such as higher PSA and ALP were also predictive of worsening outcomes.

This study also identified some factors which decrease the risk of death in patients treated with radium-223. Presence of osteoblastic bone metastases is pathognomonic for prostate cancer and is associated with high levels of bone turnover which often leads to hypocalcemia. In fact, 75% of patients had a pre-treatment calcium level of less than 2.4 which is within the normal range (Table 3). The decreased risk of death with increasing calcium levels is thus likely related to lower osteoblastic activity which can often translate to less active disease. This can thus be a mechanism by which radium-223 is less effective. The effect of bisphosphonates on the calcium level was not assessed in this study but bisphosphonate use was analyzed in the survival outcomes. Lastly, the only factor related to radium-223 toxicity associated with better outcomes was pre-treatment hemoglobin. The higher the pre-treatment hemoglobin the more likely patients are to do better after radium-223 treatment. This observation is consistent with observations of

others suggesting anemia as another reflection of aggressive disease biology and/or burden. The most common adverse effect in ALSYMPCA trial was anemia with up to 30% of patients being affected. A low pre-treatment hemoglobin may lead to recurring anemia and end up causing treatment delays and mortality. The influence of transfusions could not be properly captured and were largely available for inpatient visits only. Given that radium-223 and oncology care in general is delivered in the outpatient setting, this limits the study's ability to interrogate the effects of prophylactic transfusions on survival outcomes. Overall bone marrow function can be affected by the use of radium-223 but prostate cancer infiltrating the bone marrow can also explain some of these findings. Given that radium-223 embeds itself into the cortical bone, bone marrow could be a sanctuary site for disease to escape and cause further reduction in values such as hemoglobin. On way to interrogate this phenomenon is to assess marrow involvement by using bone marrow scintigraphy or PSMA-PET scan which is cannot be directly interrogated by using the IC/ES data.

Time from diagnosis to use of radium-223 shows some discrepancy between the two multivariate models. In the multivariate model without laboratory values, patients who had a longer time from diagnosis to radium-223 treatment were less likely to benefit from it. These patients were more likely to have received earlier treatments and stayed on treatment for a longer period of time. Conversely, in the multivariate model with laboratory values, a longer time from diagnosis to radium-223 treatment showed an improvement in survival. When comparing the two models, there is a 40% difference in the number of patients which were analyzed because of missing data. There is no good clinical reason to receive radium-223 treatment without pre-treatment laboratory values indicating that

the data is simply not available on the IC/ES database. There appears to be a protective effect for time from diagnosis to radium-223 use (>5 years) if radium-223 was given between 2020-2022, but it reverts to a harmful effect if radium-223 was given between 2016 to 2019. When including the year of diagnosis in the multivariate analysis (excluding laboratory data), the effect reverts back to a protective effect but is not statistically significant. This indicates that the harmful effect is likely a false result from a confounding effect between year of diagnosis and time from diagnosis to radium-223 treatment.

Limitations

Although this study aimed to interrogate a vast number of variables to determine which patients will benefit most from radium-223 treatment, a number of limitations should be noted. First, the IC/ES database lacks some important clinical and pathological factors which could affect outcomes for patients treated with radium-223. Prostate cancer pathologic grade is generalized to other types of cancer and lacks information specific to prostate cancer (i.e. using pathologic grade instead of Gleason score). Gleason score is particularly significant for risk stratification, with higher scores correlating with more aggressive disease subtypes. Despite this, prior radium-223 studies did not find it to be significant in multivariate analyses (Bauckneht et al., 2022; Parikh et al., 2018). The impact of the Gleason score in this study is uncertain due to the larger patient cohort and the inclusion of different co-variables that could differently influence outcomes in a multivariate analysis. A surrogate for Geason score in this study was the use of grade at diagnosis which is not the standard way of rating morphology in prostate cancer. Second, some clinical (e.g. stage, grade and Charlson score) and laboratory (phosphate, testosterone and blood counts) variables had significant amounts of missing data which

weakens the analysis. The date and age of radium-223 use was estimated based on the number of days from diagnosis to radium-223 use. Number of cycles of radium-223 could not be directly established and had to be estimated based on first and last use of the radium-223 billing code. This indicates that although IC/ES can provide useful data for analysis, it is not always complete and statistical considerations must be taken to help determine estimate data inputs.

The data available for treatments given pre- or post-radium-223 was also limited. The use of ARATs in this study, assuming no overlap between pre- and post-radium-223 treatment, was approximately 40%. This percentage is relatively low, considering that ARATs are considered a standard of care for metastatic prostate cancer treatment. Furthermore, only 6 patients received a PARP inhibitor while the estimated number of patients with metastatic prostate cancer carrying a homologous recombination repair defect is estimated to be at approximately 30% (Abida et al., 2017; Pritchard et al., 2016). Radium-223 could be more effective in this population given that its mechanism of action is by causing DNA breaks which are harder to repair when these mutations are present. The low use of ARATs could be explained in part by a limitation of the IC/ES database which only captures data from the Ontario Health Exceptional Access Program (EAP) for patients over the age of 65 or individuals who are on government supports. Information about the treatment of younger patients or those who access ARATs through compassionate use programs or private insurance would not be captured. The low use of PARP inhibitors is likely explained by their only very recent approval for use in prostate cancer in August of 2020, giving little time for use during the time period of our study. Furthermore, radiation billing codes cannot distinguish between curative versus palliative

radiotherapy. Likewise, orthopedic surgical codes cannot distinguish between procedures for cancer induced fractures and those needed for other conditions. This was mitigated by only using radiation and surgical codes post-radium-223 given that these patients would have end-stage castration-resistant disease to be eligible for this treatment, and thus would only receive palliative interventions. This is supported by the observation that most of the surgical interventions post-radium-223 were for spinal cord decompression which would almost exclusively be from bony metastatic disease. Because of these limitations, the use of SREs as an outcome would be inaccurate and would miss fractures/spinal decompression which did not receive an intervention (i.e. no surgical code or radiation code used) or any pain events.

IC/ES uses the Canadian census data to track certain demographic factors around housing, race, immigration, labour force and material resources. These variables are tracked through area-based measures which are only surrogates for individual-level data and could lead to ecological fallacy. Some of this is mitigated by the fact that a small area unit is used for rural areas (less than 10000 people) which can reduce this measurement error.

The data available for this study is exclusively gathered from patients in Ontario and there are limits to its generalizability to outside jurisdictions. Although access to new therapeutics would be a challenge in many different parts of the world, the delivery of novel therapeutics can be different even within each Canadian province. Thus, the socioeconomic and demographic factors which determine use, outcomes and access to radium-223 in this study might differ from those in other parts of Canada or the world.

Despite this, our access to treatment findings can be used to guide improvements to accessing novel drugs in Ontario and other provinces in Canada. These findings can also be applied to other radioactive nucleotides therapeutics like ^{177}Lu-PSMA-617 which are subject to similar logistical and funding constraints.

Administrative databases are designed to collect data for non-research purposes and challenges may arise when these data are used to infer causality. Some studies have cast doubt on the accuracy of using billing and diagnostic codes to identify diagnoses or procedures because they may suffer from clerical error, be omitted because of perceived irrelevance or may lack the detail needed to accurately describe the circumstance (Johnson & Nelson, 2013). Although data from the United States shows some variability in reliability (Semins et al., 2010; Tamariz et al., 2012; Woodworth et al., 2009), some Canadian data appears to validate the accuracy of this method (Hussain et al., 2016; Roifman et al., 2018; Tu et al., 2010). These differences may be abrogated by the single payer system in Canada which expects the relationship between government and physician to accurately code each medical interaction. Through this payment system, the government can scrutinize billing and diagnostic codes providing motivation for accuracy.

Selection bias may be a potential concern affecting patients in the latter portion of the cohort, as patients who did not receive radium-223 during this time could receive newly available treatments and still be prescribed radium-223 in future. Additionally, some patients with laboratory data suggestive of more aggressive disease might have been selected away from early radium-223 use. In this scenario, radium-223 use would be a means of last resort and the relationship between a worse laboratory profile and survival

would be biased by patient selection. Finally, the models in this study were developed from retrospective data and thus causality could not be determined. Future prospective, phase III studies, focusing on radium-223 combination treatments can try to address patient selection based on the findings of this study.

Future Needs

Although radium-223 was the first radionucleotide to show improvement in survival and delay in SREs in mCRPC, it only targets bone predominant disease without visceral organ involvement. The VISION study showed that the beta-emitting radioligand ^{177}Lu-PSMA-617 improved progression free survival, overall survival and time to SREs in men with metastatic castration-resistant prostate cancer (Sartor et al., 2021). ^{177}Lu-PSMA-617 targets PSMA-expressing prostate cancer cells and so offers more versatility than radium-223 as it is able to target disease in extraskeletal sites. There are no data comparing the two modalities to each other but the use of radium-223 does not seem to affect subsequent efficacy of ^{177}Lu-PSMA-617 (Rahbar et al., 2023). The use of ^{177}Lu-PSMA-617 is limited to patients who have a positive uptake on PSMA PET scans and approximately 12% of patients were excluded from this study for low PSMA uptake. Incidentally this latter group of patients had a worse overall disease trajectory and shorter survival (Hotta et al., 2022; Thang et al., 2019) indicating a potential indication for radium-223.

In recent years, the use of ARATs in combination with radium-223 has been tested. The use of abiraterone with concurrent radium-223 did not improve symptomatic skeletal event-free survival in patients with mCRPC and was associated with an increased frequency of bone fractures. The addition of enzalutamide to radium-223, however, did

show improvement in radiographic progression-free survival and overall survival in an interim analysis. Data regarding combination treatments is lacking through the IC/ES database given that in Ontario, radium-223 is only funded on its own (i.e. without using other agents concurrently). Future studies should look to identify factors which may help select patients who will respond better to these combination treatments.

In patients with oligometastatic castration-resistant prostate cancer, the role of stereotactic body radiation therapy (SBRT) has not been directly compared to the use of radium-223 for disease control. In the ALSYMPCA study, approximately 16% of patients had less than 6 metastases along with a similar number of patients which received radiation therapy after randomization for pain control. SBRT has been shown to improve progression-free survival when paired with abiraterone in controlling oligometastatic castrate resistant prostate cancer (Francolini et al., 2023). Future studies assessing the efficacy and sequencing of SBRT compared to radium-223 could show improvement in disease control for men with low burden disease.

Data on the use of Radium-223 in the castration-sensitive setting are also lacking. The effects of SBRT on oligometastatic disease with 3 or fewer bony deposits suggests some benefit (Ost et al., 2018; Phillips et al., 2020) but there is no data for more multifocal disease which can be addressed by radium-223. Although the addition of docetaxel chemotherapy to ARATs in high volume disease has shown improvement in survival, not every patient will be a candidate for such aggressive treatment. Paired with ARATs, radium-223 can fill in this gap to help improve outcomes in these patients. To date no data is available but there is at least one proposed study looking at pairing radium-223 to

SBRT to help delay systemic therapy for patients with low volume oligometastatic disease (Hasan et al., 2020).

Conclusion

Radium-223 can be an effective means of disease control for patients with castration-resistant prostate cancer metastatic to the bone but patient selection should be taken into account to optimize efficacy. Our study suggests that prior use of docetaxel and ARATs may reduce the effectiveness of radium-223 and use of this radionucleotide earlier in the natural history of metastatic prostate cancer might be warranted. Patients with more aggressive disease as defined by higher pre-treatment PSA, ALP and neutrophils have a lower survival when treated with radium-223. Although direct data is not available, modifiable factors like hemoglobin might help improve survival in these patients. Lastly, our study identified reduced access to radium-223 for individuals living in rural areas in Ontario, suggesting that more resources and efforts should be dedicated to ensuring equitable access to radionucleotide treatments.

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TABLES AND FIGURES:

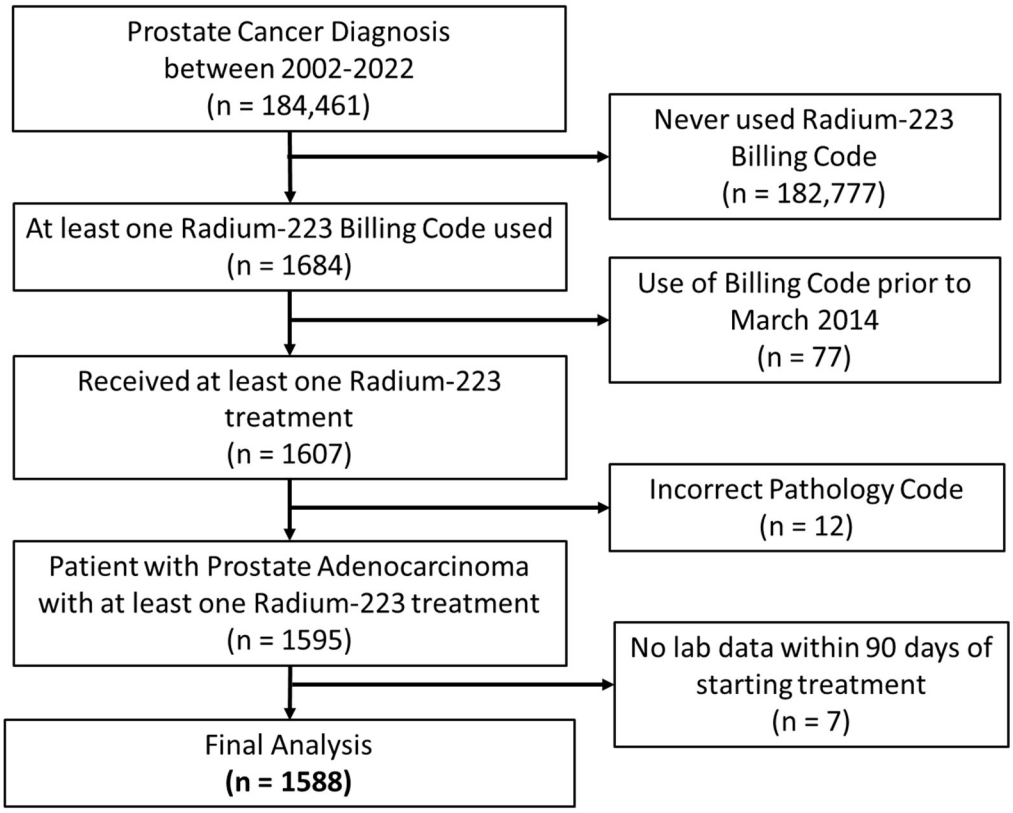


Figure 1 – Schema showing number of total patients diagnosed with prostate cancer between 2002 and 2022. Patients were excluded if they never used a radium-223 billing code, used a billing code before the health Canada approval (ie prior to March 2014), had a pathology code other than adenocarcinoma and had no laboratory data within 90 days of first Radium-223 use.

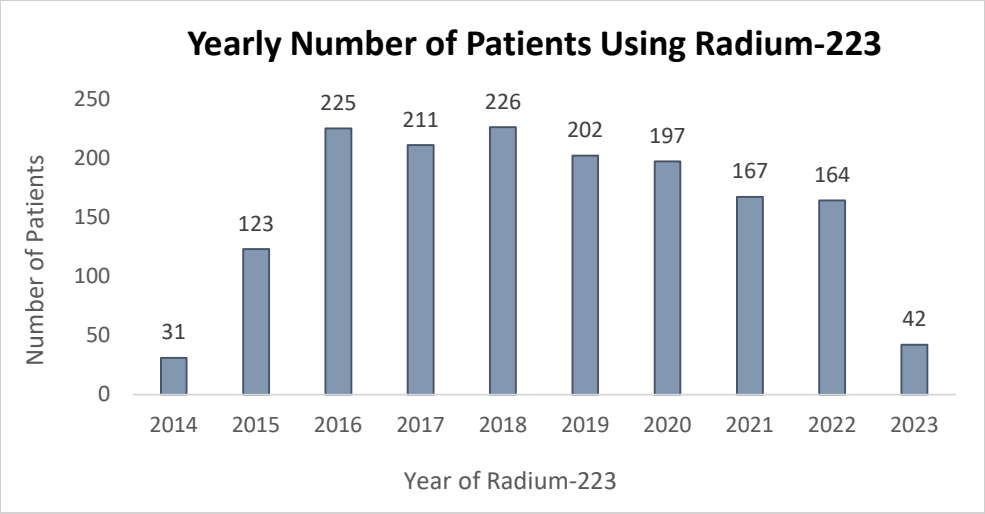


Figure 2 – The estimated number of patients treated with radium-223 each year from March 2014 until March 31st, 2023.

Table 1 - Demographics and Socioeconomic Status of Patients Treated with Radium-223		
Age at Radium-223 Treatment*	Median (range)	68 (44, 94)
Year of Diagnosis	2002-2008 2009-2015 2016-2022	322 (20.3 %) 754 (47.5 %) 512 (32.2 %)
Months from Diagnosis to First Treatment	Median (IQR) Range	55.3 (26.1, 101.1) 1.6, 244
Prior History of Cancer	N (%) Yes N (%) <5 Years	117 (7.4 %) 42 (2.6 %)
Diagnosis at Teaching Hospital	N (%) Yes No Unknown	529 (36.6 %) 917 (63.4 %) 142 (8.9%)
Charlson Comorbidity Index	0 1 2 Unknown (No Admission)	506 (31.9 %) 71 (4.5 %) 72 (4.5 %) 939 (59.1 %)
Living in Rural Area	N (%) Yes No Unknown	269 (17.0 %) 1315 (83%) 4 (0.2%)
Rurality Index for Ontario (RIO) Score	Median (IQR) Unknown: n (%)	4 (0, 24) 26 (1.6%)
Distance to Nearest Regional Cancer Centre	Median (IQR) Unknown: n (%)	15.6 (7.2, 48.0) 3 (0.2%)
Income Quintile	1 (Lowest) 2 3 4 5 (Highest)	238 (15%) 307 (19.3%) 312 (19.6%) 332 (20.9%) 394 (24.8%)
*Patients who were classified as <45 years old were deemed to be 44 years old for the purposes of calculation age. Age was an approximation based on time of diagnosis.		

Table 2 – Pathological and Clinical Characteristics of Patients Treated with Radium-223

Variable		N (%)
Best Stage at Diagnosis	I	23 (1.5)
	II	354 (22.3)
	III	200 (12.6)
	IV	728 (45.8)
	Unknown	283 (17.8)
Grade at Diagnosis	1	22 (1.4)
	2	164 (10.3)
	3	602 (37.9)
	Unknown	800 (50.4)
PARP Inhibitor Use	Pre-Radium	0 (0)
	Post-Radium	6 (0.4)
ARAT Use	Pre-Radium	438 (27.6)
	Post-Radium	197 (12.4)
Bone Modifying Agents	Pre-Radium	401 (25.3)
	Post-Radium	387 (24.7)
Chemotherapy	Pre-Radium	726 (45.7)
	Pre-Radium* (Excluding prior cancer)	665 (45.2)
	Post-Radium	886 (55.8)
Palliative Radiotherapy	Post-Radium	709 (44.7)
Palliative Surgery	Total	533 (33.6)
	Spinal Decompression	505 (31.8)
	Arthroplasty	22 (1.4)
	Arthroscopy	<6
	Denervation	<6
	Excision	7 (0.4)
	Reduction	29 (1.8)

*Analysis excludes patients with prior diagnosis of non-prostate of cancer (n = 1471)

Table 3 – Laboratory data available up to 90 days prior to first radium-223 treatment

Variable	Patients available for analysis (N)	Median (IQR)
Albumin	1158	40 (36,42)
Creatinine	1395	81 (69, 96)
Testosterone	901	0.4 (0.2, 0.5)
Calcium	1042	2.32 (2.22, 2.40)
PSA	1157	49.4 (14.1, 156.0)
Platelets	1486	221 (184, 276)
Hemoglobin	1488	124 (111, 135)
Leukocytes	1438	6.7 (5.5, 8.2)
Neutrophils	1489	4.4 (3.4, 5.8)
Lymphocytes	1490	1.3 (0.9, 1.7)
Phosphate	600	1.03 (0.92, 1.18)
ALP	1285	119 (81, 223)

Table 4 – Survival and outcomes for patients receiving Radium-223

Estimated Number of Days on Radium-223	Median (range)	85 (1, 1514)
Overall Survival, from Diagnosis	N (%) Deaths Median Months (95% CI) 5-year OS (95% CI)	1249 (78.6) 85.6 (80.9, 90.9) 67.2 (64.8, 69.5)
Overall Survival, from Radium-223 Start	N (%) Deaths Median Months (95% CI) 1-year OS (95% CI) 2-year OS (95% CI) 5-year OS (95% CI)	1249 (78.6) 12.3 (11.4, 13.3) 50.9 (48.4, 53.5) 27.0 (24.7, 29.4) 10.4 (8.7, 12.3)
Days from Radium-223 to Spinal Decompression*	Median (IQR) Range	288 (146, 551) 4, 2956
*A total of 505 patients had a spinal decompression event		

Table 5 – Univariate analysis of clinical and laboratory factors that affect survival in patients treated with prostate cancer.

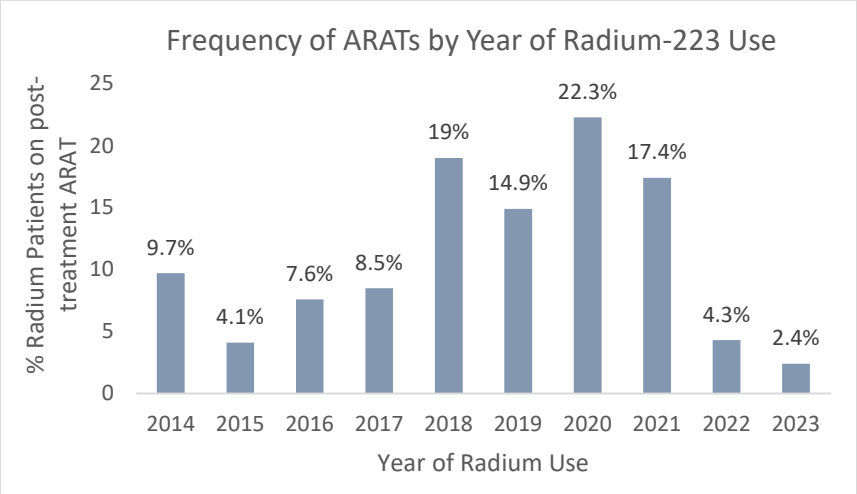
Factor	n	Comparator	HR (95% CI)	p-value
Age	1588	/year	1.02 (1.01, 1.03)	<0.001
Charlson Comorbidity Index	649	1+ vs 0/NA	1.21 (1.00, 1.45)	0.053
Days from Diagnosis	1588	>5 years vs <5 years	1.14 (1.02, 1.28)	0.022
Prior Cancer	1588	Y vs N	1.13 (0.91, 1.39)	0.26
Est. Year of Radium	1588	2019+ vs <2018	1.19 (1.06, 1.34)	0.003
Income Quintile	1583	1 2 3 4 5	0.92 (0.76, 1.10) 1.14 (0.97, 1.35) 1.00 (0.85, 1.19) 1.09 (0.93, 1.28) Reference	0.17
Rural	1584	Y vs N	0.74 (0.63, 0.87)	<0.001
Best Stage at Diagnosis	1588	1 2 3 4 Unknown	0.31 (0.18, 0.56) 0.68 (0.57, 0.81) 0.99 (0.80, 1.21) 1.13 (0.97, 1.31) Reference	<0.001
Grade at Diagnosis	1588	1 2 3 Unknown	0.27 (0.14, 0.50) 0.51 (0.42, 0.63) 1.03 (0.91, 1.15) Reference	<0.001
Prior ARAT	1588	Y vs N	1.38 (1.22, 1.57)	<0.001
Prior Bone Modifying Agents	1588	Y vs N	1.37 (1.21, 1.55)	<0.001
Prior Chemotherapy*	1588	Y vs N	3.06 (2.67, 3.50)	<0.001
Albumin	1158	/unit	0.93 (0.91, 0.94)	<0.001
Creatinine	1395	/10	1.01 (0.99, 1.02)	0.41
Testosterone	901	/unit	0.78 (0.69, 0.87)	<0.001
Calcium	1042	/unit	0.25 (0.19, 0.34)	<0.001
PSA	1157	/100	1.04 (1.04, 1.05)	<0.001
Platelets	1486	/100	1.16 (1.08, 1.26)	<0.001
Hemoglobin	1488	/10	0.72 (0.70, 0.75)	<0.001
Leukocytes	1438	/unit	1.07 (1.04, 1.10)	<0.001
Neutrophils	1489	/unit	1.10 (1.08, 1.14)	<0.001
Lymphocytes	1490	/unit	0.67 (0.61, 0.74)	<0.001
Phosphate	600	/unit	0.57 (0.39, 0.83)	0.003
ALP	1285	/100	1.12 (1.10, 1.13)	<0.001

*Patients receiving chemotherapy after prostate cancer diagnosis.

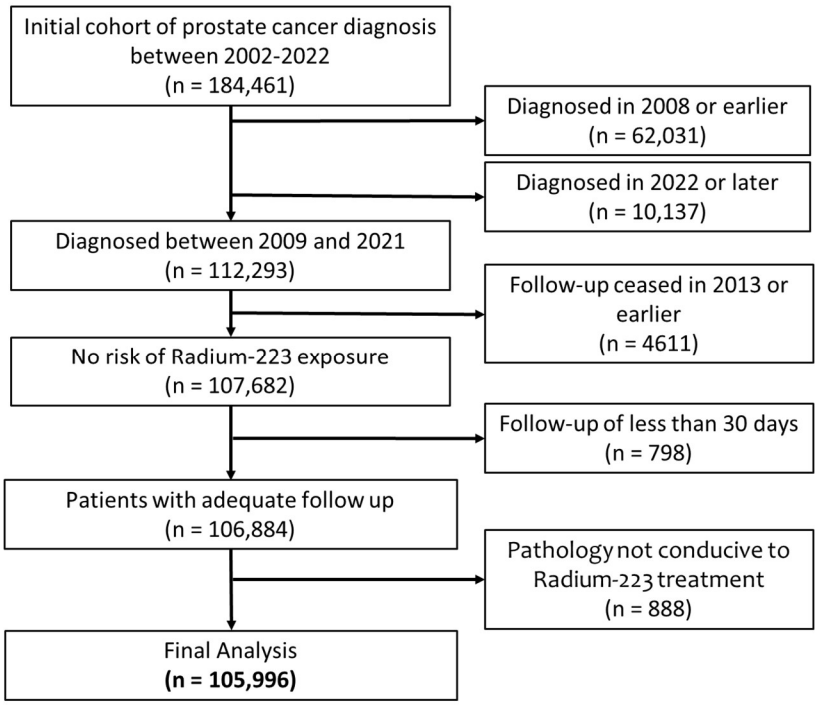
Table 6 - Multivariable Prognostic Model of Overall Survival for Patients Treated with Radium-223 (N = 983)			
Factor	**Comparator**	**HR (95% CI)**	**p-value**
Pre-Radium Chemotherapy*	Y vs N	2.11 (1.78, 2.51)	<0.001
Hemoglobin	/10	0.82 (0.78, 0.85)	<0.001
Calcium	/unit	0.21 (0.14, 0.32)	<0.001
ALP	/100	1.08 (1.06, 1.11)	<0.001
PSA	/100	1.02 (1.01, 1.03)	<0.001
Time from Diagnosis	>5 vs <5 years	0.85 (0.75, 0.97)	0.018
Neutrophils	/unit	1.08 (1.05, 1.11)	<0.001
Pre-Radium ARAT	Y vs N	1.24 (1.06, 1.45)	0.006
*Chemotherapy given post prostate cancer diagnosis			

Table 7 - Multivariable Prognostic Model of Overall Survival for Patients Treated with Radium-223 (Excluding Labs) (N = 1588)			
Factor	**Comparator**	**HR (95% CI)**	**p-value**
Pre-Radium Chemotherapy*	Y vs N	2.81 (2.45, 3.22)	<0.001
Age	/year	1.02 (1.02, 1.03)	<0.001
Best Stage at Diagnosis	I II III IV Unknown	0.41 (0.23, 0.74) 0.73 (0.61, 0.88) 0.94 (0.77, 1.16) 1.15 (0.98, 1.36) Reference	<0.001
Time from Diagnosis	>5 vs <5 years	1.21 (1.06, 1.39)	0.004
Pre-Radium ARAT	Y vs N	1.16 (1.01, 1.32)	0.031
*Chemotherapy given post prostate cancer diagnosis			

SUPPLEMENTARY MATERIAL



Supplementary Figure 1 – Proportion of patients that used post-radium-223 ARATs by year of radium use.



Supplementary Figure 2 – Factors which determine access to Radium-223. Patients diagnosed before 2009 were eliminated as they are less likely to be exposed to Radium-223 while those diagnosed after 2021 were eliminated as their chance of Radium-223 exposure was low. Patients with no follow up after Health Canada approval of Radium-223 and those who did not have adequate follow up of at least 30 days were also eliminated.

Supplementary Table 1 - Demographics and Clinical Characteristics of Patients at Risk for Being Treated with Radium-223				
		Combined Results (n = 105996)	**No Radium** (n = 104719)	**Any Radium** (n = 1277)
Age at Diagnosis	Median (range)	68 (44, 95)	68 (44, 95)	69 (44, 94)
Year of Diagnosis	2009-2012 2013-2016 2017-2022	32353 (30.5) 30469 (28.7) 43174 (40.7)	31994 (30.6) 29926 (28.6) 42799 (40.9)	359 (28.1) 543 (42.5) 375 (29.4)
Charlson Comorbidity Index	0 1 2+ No Admission	32908 (71.7) 5404 (11.8) 7570 (16.5) 60114	32495 (71.7) 5337 (11.8) 7503 (16.6) 59384	413 (75.5) 67 (12.3) 67 (12.3) 730
Diagnosis at Teaching Hospital*	N (%) Yes No Unknown	33698 (31.8) 62336 (58.8) 9962	33261 (31.8)	437 (34.2)
Prior Cancer	N (%) Yes N (%) <5 Years	10039 (9.5) 5118 (4.8)	9931 (9.5) 5079 (4.9)	108 (8.5) 39 (3.1)
Best Stage at Diagnosis	1 2 3 4 Unknown	19093 (18.0) 48102 (45.4) 14943 (14.1) 10068 (9.5) 13790 (13.0)	19069 (18.2) 47801 (45.7) 14773 (14.1) 9360 (8.9) 13716 (13.1)	24 (1.9) 301 (23.6) 170 (13.3) 708 (55.4) 74 (5.8)
Grade at Diagnosis	1 2 3 Unknown	14034 (13.2) 28103 (26.5) 17688 (16.7) 46171 (43.6)	14010 (13.4) 27938 (26.7) 17094 (16.3) 45677 (43.6)	24 (1.9) 165 (12.9) 594 (46.5) 494 (38.7)
PSA#	Median (IQR)	8.2 (5.7, 14.5)	8.1 (5.7, 14.2)	38.6 (11.5, 212)

*Analysis was done on 96034 patients for which data was available.
#Analysis was done on 62639 patients for which data was available within 90 days of diagnosis.

Supplementary Table 2 - Socioeconomic Status of Patients at Risk for Being Treated with Radium-223					
	n		**Combined Results**	**No Radium**	**Any Radium**
Income Quintile	105688	1 2 3 4 5	16920 (16.0) 20097 (19.0) 21033 (19.9) 22166 (21.0) 25472 (24.1)	16729 (16.0) 19864 (19.0) 20773 (19.9) 21897 (21.0) 25152 (24.1)	191 (15.0) 233 (18.3) 260 (20.4) 269 (21.1) 320 (25.1)
Age and Labour Force Quintile	105284	1 2 3 4 5	17432 (16.6) 18714 (17.8) 19727 (18.7) 21586 (20.5) 27825 (26.4)	17226 (16.6) 18500 (17.8) 19507 (18.8) 21336 (20.5) 27447 (26.4)	206 (16.3) 214 (16.9) 220 (17.4) 250 (19.7) 378 (29.8)
Material Resources Quintile	105284	1 2 3 4 5	24241 (23.0) 22761 (21.6) 21187 (20.1) 19733 (18.7) 17362 (16.5)	23935 (23.0) 22505 (21.6) 20931 (20.1) 19485 (18.7) 17160 (16.5)	306 (24.1) 256 (20.2) 256 (20.2) 248 (19.6) 202 (15.9)
Racialized and Newcomer Populations Quintile	105284	1 2 3 4 5	22381 (21.3) 21639 (20.6) 20596 (19.6) 19638 (18.7) 21030 (20.0)	22052 (21.2) 21377 (20.6) 20354 (19.6) 19406 (18.7) 20827 (20.0)	329 (26.0) 262 (20.7) 242 (19.1) 232 (18.3) 203 (16.0)
Households and Dwellings Quintile	105284	1 2 3 4 5	20025 (19.0) 21860 (20.8) 21791 (20.7) 20192 (19.2) 21416 (20.3)	19815 (19.1) 21585 (20.8) 21520 (20.7) 19941 (19.2) 21155 (20.3)	210 (16.6) 275 (21.7) 271 (21.4) 251 (19.8) 261 (20.6)
Rural	105840	N (%) Yes	14652 (13.8)	14424 (13.8)	228 (17.9)
Distance to Nearest RCC	105834	Median (IQR)	15.3 (6.8, 42.5)	15.3 (6.8, 42.4)	15.9 (7.0, 49.5)
RIO Score	104902	Median (IQR)	3 (0, 20)	3 (0, 20)	4 (0, 25)

Supplementary Table 3 – Univariate Analysis of Prognostic Factors of Time to Receipt of Radium-223 Treatment (n=105996)			
Factor	**Comparator**	**HR (95% CI)**	**p-value**
Age	/year	1.03 (1.03, 1.04)	<0.001
Charlson Comorbidity Index	1+ vs 0/NA	1.00 (0.98, 1.01)	0.40
Prior Cancer	YvsN	1.11 (0.91, 1.35)	0.32
Year of Diagnosis	/year	1.12 (1.10, 1.14)	<0.001
Income Quintile	1 2 3 4 5	0.98 (0.82, 1.18) 0.97 (0.82, 1.14) 1.02 (0.87, 1.20) 0.98 (0.83, 1.15) Reference	0.98
Age and Labour Force Quintile*	1 2 3 4 5	0.83 (0.70, 0.99) 0.80 (0.68, 0.95) 0.79 (0.67, 0.93) 0.82 (0.70, 0.97) Reference	0.017
Material Resources Quintile	1 2 3 4 5	1.05 (0.88, 1.26) 0.95 (0.79, 1.14) 1.02 (0.85, 1.23) 1.06 (0.88, 1.27) Reference	0.74
Racialized and Newcomer Populations Quintile	1 2 3 4 5	1.61 (1.35, 1.92) 1.32 (1.10, 1.58) 1.24 (1.03, 1.49) 1.26 (1.04, 1.52) Reference	<0.001
Households and Dwellings Quintile	1 2 3 4 5	0.82 (0.68, 0.98) 0.99 (0.84, 1.18) 0.99 (0.84, 1.18) 1.00 (0.84, 1.19) Reference	0.15
Diagnosis at Teaching Hospital	Y vs N	0.99 (0.88, 1.11)	0.81
Rural	Y vs N	1.39 (1.21, 1.61)	<0.001
Best Stage at Diagnosis	1 2 3 4 Unknown	0.13 (0.08, 0.21) 0.64 (0.50, 0.83) 1.39 (1.06, 1.82) 16.14 (12.70, 20.51) Reference	<0.001
Grade at Diagnosis	1 2 3 Unknown	0.09 (0.06, 0.13) 0.29 (0.24, 0.34) 1.75 (1.54, 1.97) Reference	<0.001
PSA at Diagnosis	/1000	1.27 (1.24, 1.30)	<0.001
*The higher the quintile the more likely you are to be marginalized based on the variable			

Supplementary Table 4 - Multivariable Analysis of Factors Affecting the Risk Exposure to Radium-223 Treatment (n=105996)			
Factor	**Comparator**	**HR (95% CI)**	**p-value**
Age	/year	1.02 (1.01, 1.02)	<0.001
Charlson Comorbidity Index	1+ vs 0/NA	0.99 (0.98, 1.01)	0.43
Prior Cancer	Y vs N	0.85 (0.64, 1.12)	0.25
Year of Diagnosis	/ year	1.03 (1.00, 1.05)	0.062
Income Quintile	1 2 3 4 5	0.83 (0.58, 1.19) 0.98 (0.74, 1.31) 1.03 (0.80, 1.32) 1.05 (0.84, 1.31) Reference	0.69
Age and Labour Force Quintile	1 2 3 4 5	1.16 (0.90, 1.49) 0.87 (0.68, 1.10) 0.86 (0.68, 1.08) 0.99 (0.81, 1.22) Reference	0.11
Material Resources Quintile	1 2 3 4 5	0.86 (0.62, 1.19) 0.69 (0.51, 0.94) 0.77 (0.58, 1.04) 0.83 (0.64, 1.09) Reference	0.11
Racialized and Newcomer Populations Quintile	1 2 3 4 5	1.46 (1.10, 1.92) 1.29 (0.99, 1.69) 1.20 (0.92, 1.56) 1.29 (1.00, 1.66) Reference	0.098
Households and Dwellings Quintile	1 2 3 4 5	1.00 (0.76, 1.33) 1.15 (0.89, 1.50) 1.13 (0.88, 1.45) 0.95 (0.74, 1.22) Reference	0.43
Diagnosis at Teaching Hospital	Y vs N	0.99 (0.85, 1.16)	0.93
Rural	Y vs N	0.80 (0.64, 0.99)	0.044
Best Stage at Diagnosis	1 2 3 4 Unknown	0.08 (0.05, 0.15) 0.39 (0.27, 0.56) 0.78 (0.53, 1.14) 7.79 (5.56, 10.93) Reference	<0.001
PSA at Diagnosis	/ 1000	1.16 (1.11, 1.20)	<0.001
* Grade was excluded due to its high level of correlation with stage.			

APPENDIX A – IC/ES linkable databases used in this study

IC/ES Linked Dataset	Description
Registered Persons Database (RPDB)	Database which provides demographic information like age, sex, date of birth, date of death and residence, for individuals with an Ontario health insurance number.
Ontario Cancer Registry (OCR)	Database collected through Cancer Care Ontario which contains information on all Ontario residents who are newly diagnosed with cancer or who have died of cancer.
New Drug Funding Program (NDFP) Database	A database of the publicly funded drug program aimed at covering new high-quality intravenous (IV) cancer drugs.
Canadian Institute of Health Information - Discharge Abstract Database (CIHI-DAD)	Contains administrative, clinical, and demographic data information for all admissions to acute care hospitals, rehab and day surgery institutions in Ontario.
Ontario Health Insurance Plan (OHIP) Claims Database	Contains payment claims from OHIP which covers all health care providers like physicians, physician-groups and laboratories.
National Ambulatory Care Reporting System (NACRS)	Contains administrative, clinical, demographic, and administrative information for all patient visits made to hospital- and community-based ambulatory care centres.
Canadian Institute of Health Information - Same Day Surgery Database (SDS)	Patient-level demographic, diagnostic, procedural and treatment information on all day surgeries.
Ontario Census Area Profiles (CENSUS)	Contains demographic information derived from the Census of Population by Statistics Canada which provide demographic information on population by age, households and dwelling types, language group, household tenure, immigration, mobility, ethnic origin and visible minorities, education and labour force, income and shelter cost.
Cancer Activity Level Reporting (ALR)	Database which includes patient-level activity focused on radiation, systemic therapy services and other outpatient oncology clinic visits required to produce the quality, cost and performance indicators for Ontario's cancer system.
Ontario Drug Benefit Claims (ODB)	Containing information on the publicly funded drug program that covers prescription medications in patients who are: ≥65 years or ≤24 years and not covered by a private insurance plan; living in a long-term care home, home for special care, or community home for opportunity; receiving professional home

	and community care services; covered under alternative insurance programs like the Ontario works, Ontario disability support program or the Trillium Drug Program.
Ontario Laboratories Information System (OLIS)	The OLIS database at IC/ES consists of 3 distinct datasets: 1. Lab orders: contains the order-level information, including patient demographics, and provider information; 2. Test requests: contains the test ID code and specimen information, in addition to ordering, performing and reporting facilities among other variables; 3. Observations: contains the test result information, including the result ID code, values and units.

APPENDIX B – OHIP Billing Codes

Radium-223 Billing Codes:
X336 – radionucleotide code for prostate malignancy
X329 – Radioisotope metastatic disease in bone

Chemotherapy Billing Codes:
G345 - Complex single agent or multi-agent therapy – chemotherapy and/or biologic agent(s) that can cause vesicant damage, infusion reactions, cardiac, neurologic, marrow or renal toxicities that may require immediate intervention by the physician
G381 - Standard chemotherapy - agents with minor toxicity that require physician monitoring.
G281 - Each additional standard chemotherapy agent (additional to G381), other than the initial agent
G359 - Special single agent or multi-agent therapy – chemotherapy and/or biologic agent(s) with major toxicity that require frequent monitoring and prolonged administration periods and may require immediate intervention by the physician.

Radiation Therapy Billing Codes:
X310 - Radiation treatment planning - Level 1 Simple Treatment Planning
X311 - Radiation treatment planning - Level 2 Intermediate Treatment Planning
X312 - Radiation treatment planning - Level 3 Complex Treatment Planning
X313 - Radiation Oncology treatment plan Level 4

Spinal Decompression Billing Codes:
N510 - Cervical / Thoracic - One level – bilateral
N520 - Cervical / Thoracic - One level - laminoplasty (includes fixation of lamina)
N509 - Cervical / Thoracic - One level – unilateral
N512 - Lumbar - One level – bilateral
N511 - Lumbar - One level – unilateral
N524 - Lumbar - One level bilateral canal enlargement - unilateral approach
N571 - Lumbar - Percutaneous discotomy
N574 - Removal of Vertebral Body including Pedicles for Osteotomy - Above cord and conus (includes partial rib resection) each level
N575 - Removal of Vertebral Body including Pedicles for Osteotomy - Below conus each level
N576 - Removal of Vertebral Body including Pedicles for Osteotomy - Smith Peterson steotomy each level

Arthrodesis Billing Codes:
R470 - Hip
R469 - Sacro-iliac joint
R514 - Symphysis pubis

Arthroplasty Billing Codes:
R488 - Removal only - cemented

R443 - Removal only – non-cemented
R491 - Removal only - Replacement acetabular liner and/or femoral head
R241 - Revision total arthroplasty hip - one or both components - acetabular or femoral
R481 - Revision total arthroplasty hip - one or both components - Reattachment of greater trochanter (late)
R440 - Total hip replacement - acetabulum and femur
R553 - Total hip replacement with take down of fusion
R439 - Unipolar

Arthroscopy Billing Codes:
R686 - Hip arthroscopy set up, includes when rendered debridement, synovectomy, removal of loose body(ies) and/or screw, drilling of defect, microfracture, abrasion arthroplasty, and/or synovial biopsy

Arthrotomy Billing Codes:
R415 - Hip - with removal of loose body
R547 - Sacro-iliac joint

Denervation/Decompression Billing Codes:
N285 - Exploration and/or decompression and/or transposition and/or neurolysis of major nerve (excluding carpal tunnel nerve).
R427 - Exploration, decompression, division, excision, biopsy, neurolysis and/or transposition -
Denervation of hip.
N188 - Exploration, decompression, division, excision, biopsy, neurolysis and/or transposition – minor nerve including digital, cutaneous or lateral femoral cutaneous nerve.
N177 - Exploration, decompression, division, excision, biopsy, neurolysis and/or transposition – Sciatic nerve in buttock.

Examination/Manipulation Billing Codes
Z252 - Manipulation - under general anaesthetic

Excision Billing Codes:
F115 - Bone - Coccyx
R315 - Bone - Head and neck, femur
R330 - Bone - Major resection tumour
R216 - Bone - Radical resection tumour
R263 - Hip
R423 - Joint - Synovectomy/debridement
R273 - Osteotomy - Pelvis
R328 - Pseudoarthrosis - Hip
R364 - Pseudoarthrosis – Pelvis

Reduction Billing Codes:
F098 - Fractures - Femoral neck trochanteric, subtrochanteric - closed reduction/traction

R600 - Fractures - Femoral neck trochanteric, subtrochanteric - delayed/staged graft
F100 - Fractures - Femoral neck trochanteric, subtrochanteric - open reduction pin and plate/screws (cannulated included)
F099 - Fractures - Femoral neck trochanteric, subtrochanteric - open reduction pin only
F101 - Fractures - Femoral neck trochanteric, subtrochanteric - open reduction primary prosthesis, femur only (includes Moore, Thompson, Unipolar, Bipolar)
F134 - Fractures - Pelvic ring - closed reduction
F135 - Fractures - Pelvic ring - open reduction
R642 - Fractures - Slipped epiphysis - closed reduction/internal fixation
R607 - Fractures - Slipped epiphysis - closed reduction/traction
R627 - Fractures - Slipped epiphysis - open reduction/fixation

APPENDIX C – Drug Identification Numbers

Drug Type	DIN	Trade Name	Dose
*ARAT Therapy	2473917	APO-ABIRATERONE	250 MG
	2496100	APO-ABIRATERONE ACETATE FILM COATED TABLETS	500 MG
	2525372	ABIRATERONE	250 MG
	2540452	PRZ-ABIRATERONE	250 MG
	2540460	PRZ-ABIRATERONE	500 MG
	2521652	SANDOZ ABIRATERONE	1000 MG
	2473356	TEVA-ABIRATERONE	250 MG
	2487446	TEVA-ABIRATERONE	500 MG
	2491397	APO-ABIRATERONE FILM COATED TABLETS	250 MG
	2491400	APO-ABIRATERONE FILM COATED TABLETS	500 MG
	2477114	REDDY-ABIRATERONE	250 MG
	2533251	REDDY-ABIRATERONE	500 MG
	2525380	ABIRATERONE	500 MG
	2502305	JAMP ABIRATERONE	250 MG
	2529629	JAMP ABIRATERONE	500 MG
	2503980	MAR-ABIRATERONE	250 MG
	2503999	MAR-ABIRATERONE	500 MG
	2494132	NAT-ABIRATERONE	250 MG
	2492601	PMS-ABIRATERONE	250 MG
	2501503	PMS-ABIRATERONE	500 MG
	2486393	SANDOZ ABIRATERONE	250 MG
	2521644	SANDOZ ABIRATERONE	500 MG
	2478374	ERLEADA	60 MG
	2540185	ERLEADA	240 MG
	2407329	XTANDI	40 MG
	2496348	NUBEQA	300 MG
#PARP Inhibitor	2454408	LYNPARZA	50 MG
	2475200	LYNPARZA	100 MG
	2475219	LYNPARZA	150 MG
	2538555	AKEEGA	50 MG
	2538563	AKEEGA	100 MG
	2489783	ZEJULA	100 MG
	2530031	ZEJULA	100 MG
	2492032	TALZENNA	0.25 MG
	2492040	TALZENNA	1 MG
	2343541	PROLIA (DENOSUMAB)	60 MG / ML
	2343541	PROLIA (DENOSUMAB)	60 MG / ML

Bone Modifying Agents	2343568	PROLIA (DENOSUMAB)	60 MG / ML
	2343568	PROLIA (DENOSUMAB)	60 MG / ML
	2368153	XGEVA (DENOSUMAB)	120 MG / 1.7 ML
	2368153	XGEVA (DENOSUMAB)	120 MG / 1.7 ML
	2248296	Zometa (ZOLEDRONIC ACID)	4mg/5mL
	2401606	Zoledronic Acid-Z	4mg/5mL
	2407639	Zoledronic Acid for Injection	4mg/5mL
	2415186	Taro-Zoledronic Acid Concentrate	4mg/5mL
	2422425	Zoledronic Acid for Inj. Concentrate	4mg/5mL
	2434458	Zoledronic Acid for Injection	4mg/5mL
	2444739	Zoledronic Acid for Injection	4mg/5mL
	2472805	Zoledronic Acid for Injection	4mg/5mL
	2482525	Jamp-Zoledronic Acid	4mg/5mL

* Androgen receptor axis-targeted (ARAT)
# Poly (ADP-ribose) polymerase
https://health-products.canada.ca/dpd-bdpp/

APPENDIX D – Logical Observation Identifiers Names and Codes (LOINC)

PSA
2857-1 – total PSA – mass per volume – ug/L
35741-8 – total PSA – by detection limit <0.01
Testosterone
14913-8 – total testosterone moles per volume – nmoles/L
Creatinine
14682-9 - Creatinine [Moles/volume] in Serum or Plasma
Platelets
13056-7 - Platelets [#/volume] in Plasma by Automated count
26515-7 – Platelets [#/volume] in Blood
777-3 -Platelets [#/volume] in Blood by Automated count
Albumin
1751-7 - Albumin [Mass/volume] in Serum or Plasma
Blood Counts
20509-6 - Hemoglobin [Mass/volume] in Blood by calculation
718-7 - Hemoglobin [Mass/volume] in Blood
26464-8 - Leukocytes [#/volume] in Blood
26474-7 - Lymphocytes [#/volume] in Blood
26499-4 - Neutrophils [#/volume] in Blood
6690-2 - Leukocytes [#/volume] in Blood by Automated count
731-0 - Lymphocytes [#/volume] in Blood by Automated count
732-8 - Lymphocytes [#/volume] in Blood by Manual count
751-8 – Neutrophils [#/volume] in Blood by Automated count
753-4 - Neutrophils [#/volume] in Blood by Manual count
804-5 - Leukocytes [#/volume] in Blood by Manual count
Alkaline Phosphatase (ALP)
6768-6 - Alkaline phosphatase [Enzymatic activity/volume] in Serum or Plasma
Phosphate
14879-1 - Phosphate [Moles/volume] in Serum or Plasma
24519-1 -Phosphate [Moles/volume] in Blood
Calcium
1996-8 - Calcium [Moles/volume] in Blood
2000-8 - Calcium [Moles/volume] in Serum or Plasma
Lactate Dehydrogenase
2537-9 -Lactate dehydrogenase 1 [Enzymatic activity/volume] in Serum or Plasma