Contemporary Population-Based Analysis of Bone Mineral Density Testing in Men Initiating Androgen Deprivation Therapy for Prostate Cancer

Jason Hu, MSc¹; Armen G. Aprikian, MD^{1,2,4}; Marie Vanhuyse, MD, MSc^{3,4}; and Alice Dragomir, MSc, PhD¹

ABSTRACT

Background: Androgen deprivation therapy (ADT) is a cornerstone of treatment for advanced prostate cancer (PCa); however, it accelerates the loss of bone mineral density (BMD), which increases fracture risk. Guidelines recommend BMD testing when initiating ADT to assess baseline fracture risk properly. The objective of this study was to examine the proportion of BMD testing in men initiating ADT in Quebec and to identify factors associated with receipt of this testing. **Methods:** The study cohort consisted of men extracted from Quebec public healthcare insurance administrative databases who initiated continuous ADT from 2000 to 2015 for >12 months. The primary study outcome was receipt of BMD testing in the period from 6 months before through 12 months after ADT initiation. Multivariable generalized linear mixed regression modeling with a logit link was performed to identify variables associated with BMD testing. **Results:** We identified 22,033 patients, of whom 3,910 (17.8%) underwent BMD testing. Rates of BMD testing increased from 4.1% in 2000 to 23.4% in 2015. After multivariable analyses, prior history of osteoporosis (odds ratio [OR], 1.84; 95% CI, 1.32–2.57; $P<.001$), rheumatoid arthritis (OR, 1.64; 95% CI, 1.15–2.34; $P=.006$), use of bisphosphonates (OR, 1.47; 95% CI, 1.25–1.73; $P<.001$), and long-term corticosteroid use (OR, 1.63; 95% CI, 1.15–2.31; $P=.006$) were associated with higher odds of BMD testing. Patient age >80 years (OR, 0.67; 95% CI, 0.59–0.76; $P<.001$), metastases (OR, 0.79; 95% CI, 0.70–0.89; $P<.001$), higher Charlson comorbidity score (OR, 0.65; 95% CI, 0.51–0.81; $P<.001$), and rural residence (OR, 0.77; 95% CI, 0.68–0.87; $P<.001$) were associated with lower odds of BMD testing. **Conclusions:** In our study population, BMD testing rates in men initiating ADT were low, although they increased over the years especially in the years after the publication of recommendations for BMD testing in these patients. Potential gaps identified include being older, more comorbid, and rural areas. Overall, additional efforts emphasizing the importance of BMD testing in PCa guidelines may be needed.

J Natl Compr Canc Netw 2020;18(10):1374–1381
doi: 10.6004/jnccn.2020.7576

Background

Prostate cancer (PCa) is the most common noncutaneous cancer in Canadian men and boasts a 90% 10-year net survival rate.^{1,2} Consequently, with such a large contingent of long-term survivors, morbidity induced by treatment is an important aspect to consider. Androgen deprivation therapy (ADT) is a cornerstone of advanced PCa treatment, and it is estimated that nearly 1 in 2 patients with PCa will receive some form of ADT during their disease course.^{3,4}

The role of ADT is strongly established in locally advanced PCa as multiple randomized trials have shown the survival benefits of radiotherapy with neoadjuvant and long-term adjuvant ADT.^{5–8} In that setting, long-term ADT ranging from 2 to 3 years is recommended. Furthermore, ADT was the sole first-line treatment in metastatic PCa until recently, when studies demonstrated that combining either docetaxel chemotherapy or abiraterone or apalutamide with ADT substantially improved survival over ADT alone.^{9–12} Clinical guidelines recommend that ADT treatment in patients with metastatic PCa continue until the end of life, even past the castration-resistant phase.¹³ Consequently, whether for use in locally advanced disease or metastatic disease, exposure ADT can last many years.

However, the adverse effects associated with androgen suppression are well-documented, span several health domains, and can impact the cardiovascular system, sexual function, and cognition.^{14–16} In particular, bone metabolism is highly affected and the loss of bone mineral density (BMD) is accelerated due to the deficiency of estrogen that accompanies androgen suppression.¹⁷ Consequently, ADT increases the risk of osteoporosis and fractures, as demonstrated by numerous studies.^{18–20} The impact of fractures incurs a large burden at the patient level (diminishes quality of life and increases

¹Division of Urology, Department of Surgery, McGill University; ²Department of Urology, McGill University Health Centre; ³Division of Medical Oncology, Department of Oncology, McGill University; and ⁴Department of Oncology, McGill University Health Centre, Montreal, Canada.

See JNCCN.org for supplemental online content.

mortality) and the societal level (cost of healthcare services associated with management).^{21–24}

In the early 2000s, several review articles and organizations began recommending baseline measurement of BMD via a dual-energy x-ray absorptiometry (DEXA) scan when initiating treatment as part of management to assess the risk of fracture properly.^{25–28} Some also advocated for annual or biannual follow-up testing in select high-risk populations.²⁹ However, previous studies have shown underwhelming rates of BMD testing in men initiating ADT across North American patient populations.^{30–32} Those studies did not examine population rates after 2008, when additional prominent organizations (such as NCCN and Osteoporosis Canada) began endorsing these practices as well.^{33–36} The objective of the current study was to examine the rates of BMD testing and their associated factors among patients with PCa beginning ADT in the Canadian province of Quebec, including more contemporary years.

Methods

Data Source

As with other Canadian provinces, provincial public healthcare insurance coverage is provided to all of its residents for physician visits and medical procedures. This study draws data from public healthcare administrative databases from the province of Quebec, which are administered by the Régie de l'assurance maladie du Québec (RAMQ). The RAMQ databases contain data pertaining to basic patient demographic information, medical services derived from physician billing claims, and prescription drugs dispensed at community pharmacies. Data on hospital admissions were extracted from a complementary source, the Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MED ECHO) databases.

Study Cohort

This was designed as a retrospective observational study with a cohort comprising men who initiated long-term continuous ADT from January 2000 to December 2015. The definition of ADT included luteinizing hormone-releasing hormone (LHRH) agonists and antagonists drugs and orchiectomy. Long-term continuous use was defined as treatment of at least 12 months with gaps between prescriptions no more than 30 days beyond the planned refilling date according to the formulation type (eg, trimonthly formulations were considered continuous if intervals were <120 days) or orchiectomy. Figure 1 illustrates the application of the eligibility criteria in obtaining the study cohort. For all patients in the cohort, RAMQ and MED-ECHO data were available from January

Figure 1. Study flowchart.

Abbreviations: ADT, androgen deprivation therapy; PCa, prostate cancer.

1996 until date of death or December 2016, whichever occurred first.

Outcomes

The primary outcome was receipt of a BMD test identified during the 18-month window starting from 6 months before ADT initiation and up to 12 months after (Figure 2), hereafter referred to as “the screening period.” This window was chosen to allow capturing of both baseline and follow-up BMD tests. The RAMQ procedure codes used to identify BMD testing were 08243, 08245, 08246, 08247, 08204, and 08704.

For secondary outcomes, we further divided the screening period into 2 windows to evaluate baseline BMD testing (defined as BMD testing performed 6 months before ADT initiation and including up to 90 days after) and follow-up BMD testing (defined as BMD testing from 91 days to 12 months after initiating ADT). Delimitation of baseline testing and follow-up testing at 90 days after ADT initiation was deemed to be an appropriate compromise because most ADT formulations used were trimonthly and biannual injections.

Covariables

Covariables of interest included patient age, year of ADT initiation, Charlson comorbidity score, metastatic status, region of residence (urban/rural), prior local PCa treatment, and specialty of the physician prescribing ADT. Other variables included clinical risk factors for osteoporosis and fractures based on diagnostic codes and treatments identified from medical procedure and drug dispensing claims within the 18-month period preceding the ADT initiation date: osteoporosis, diabetes, rheumatoid

Figure 2. Definition of screening window.
Abbreviations: ADT, androgen deprivation therapy; BMD, bone mineral density.

arthritis, hyperthyroidism, use of bisphosphonates, and long-term corticosteroid use (at least 6 months).

The Charlson comorbidity score was modified (excluded PCa diagnosis) and also derived using diagnostic codes from the 18-month period before ADT initiation.³⁷ Metastatic status was also defined from the 18-month period before ADT initiation as the presence of an ICD code related to metastases or use of a metastatic castration-resistant PCa drug (ICD-9 was used for the RAMQ database and ICD-10 for the MED-ECHO database). Prior local PCa treatment included radical prostatectomy, external-beam radiotherapy, and brachytherapy before and up to 3 months after initiation of ADT.

Statistical Analysis

Descriptive statistics were presented as counts and percentages for categorical variables, and as means with standard deviation for continuous variables.

Unadjusted yearly trends for the primary outcome and secondary outcomes were evaluated using the Cochran-Armitage test. Exact McNemar tests were used to evaluate the unadjusted comparison of proportion of patients receiving baseline and follow-up testing.

Multivariable analysis was performed to identify factors associated with receipt of BMD testing during the screening period. Two additional models were fitted for the secondary outcomes of baseline and follow-up BMD testing. Multivariable analyses were conducted using generalized linear mixed models with a logit link, and a binary distribution for the dependent variable while accounting for physician-level clustering (defined as the prescribing physician identified at the first prescription of the long-term continuous course of ADT). The generalized linear mixed model is more appropriate for data analysis in which subjects may be nested within larger units, also referred to as having a multilevel or hierarchical structure. In our study, patients can be considered to be nested within prescribing physicians. Results from the multivariable models are presented as odds ratios (ORs) with 95% confidence intervals. All analyses were 2-sided with the statistical significance

level set at $P < .05$ and were conducted with SAS 9.4 (SAS Institute inc.).

Sensitivity Analyses

We conducted additional analyses by using alternative definitions of the screening period to observe the robustness of the results. The aforementioned screening period definition (6 months before ADT initiation and up to 12 months after) will be referred to as the main definition. Three larger screening period definitions—definition B (12 months before and up to 12 months after ADT initiation), definition C (24 months before and up to 12 months after ADT initiation), and definition D (6 months before and 24 months after ADT initiation)—were explored in sensitivity analyses. All are represented in schematic form in supplemental eFigure 1 (available with this article at JNCCN.org).

In definition B, the baseline period was considered from 12 months before and up to 90 days after initiation, and follow-up period from 91 days to 12 months after; whereas for definition C, it ranged from 24 months before and up to 90 days after initiation, and from 91 days to up to 12 months after for the baseline and follow-up periods, respectively. In definition D, the baseline period ranged from 6 months before and up to 90 days after initiation, and follow-up period from 91 days to 24 months after.

Definition D excluded patients initiating ADT in 2015 and only included patients who were treated with ADT continuously for >24 months ($n=13,586$).

Results

Cohort Characteristics

A total of 22,033 patients were included in the cohort with a mean age of 75 years. Prior diagnosis of osteoporosis and use of bisphosphonates were found in 1.2% and 6.3% of the cohort, respectively. Most patients were prescribed ADT by a urologist or radiation oncologist (78.8%) and received their ADT in the form of an LHRH agonist/antagonist drug (97.4%). Table 1 presents full baseline descriptive statistics of the study cohort.

Proportion of Cohort Undergoing BMD Testing by Year of ADT Initiation

A total of 3,910 patients (17.8%) received a BMD test during the study period. Figure 3 illustrates the increasing proportion of patients who underwent BMD testing during the study period, from 4.1% in 2000 to 23.4% in 2015 ($P < .001$). Baseline testing increased from 1.2% in 2000 to 16.5% in 2015 ($P < .001$). Follow-up testing increased from 3.1% in 2000 to 7.2% in 2015 ($P = .002$). More patients received follow-up testing than baseline testing in 2000 (3.1% vs 1.2%; $P = .001$) and 2002

Table 1. Cohort Characteristics (N=22,033)

Variable	n (%)
Age at ADT, y	
<70	5,542 (25.2)
70–74	4,837 (22.0)
75–80	5,380 (24.4)
>80	6,274 (28.5)
Charlson comorbidity score	
0–1	15,801 (71.7)
2–3	2,773 (12.6)
≥4	3,459 (15.7)
Metastatic	3,668 (16.6)
Region of residence	
Urban	14,423 (65.5)
Rural	7,610 (34.5)
Prior osteoporosis diagnosis	268 (1.2)
Prior use of bisphosphonates	1,379 (6.3)
Prior diabetes diagnosis	3,146 (14.3)
Prior rheumatoid arthritis diagnosis	243 (1.1)
Prior hyperthyroidism diagnosis	41 (0.2)
Prior long-term corticosteroid use	258 (1.2)
Prior fracture	1,135 (5.2)
Year of ADT initiation	
2000–2001	2,957 (13.4)
2002–2003	2,713 (12.3)
2004–2005	2,790 (12.7)
2006–2007	2,858 (13.0)
2008–2009	2,732 (12.4)
2010–2011	2,644 (12.0)
2012–2013	2,734 (12.4)
2014–2015	2,605 (11.8)
Prior local PCa treatment	8,010 (36.4)
Specialty of ADT prescriber	
Urology/Radiation oncology	17,350 (78.8)
Other	4,683 (21.3)
ADT type	
LHRH agonist/antagonist	21,470 (97.4)
Orchiectomy	563 (2.6)

Abbreviations: ADT, androgen deprivation therapy; LHRH, luteinizing hormone–releasing hormone; PCa, prostate cancer.

(4.7% vs 2.4%; $P=.001$). From 2005 onwards, baseline testing was more prevalent than follow-up testing (all $P<.050$).

In sensitivity analyses using different definitions of the screening period, overall 19.4%, 21.1%, and 24.5% received testing when using the wider definitions B, C, and D, respectively (supplemental eFigures 2–4). In these

3 additional definitions, increasing yearly trends were also observed (all $P<.001$).

Factors Associated With BMD Testing

In regression analysis (Table 2), later years were associated with increased odds of BMD testing compared with 2000 to 2001 (ORs ranging from 2.56–6.17; all $P<.001$). Age >80 years (OR, 0.67; 95% CI, 0.59–0.76; $P<.001$) was associated with lower odds compared with age <70 years. Charlson comorbidity scores of 2 to 3 (OR, 0.81; 95% CI, 0.71–0.91; $P=.001$), and ≥4 (OR, 0.65; 95% CI, 0.51–0.81; $P<.001$) were also associated with lower odds relative to scores of 0 or 1. Patients with metastatic disease had lower odds of receiving testing (OR, 0.79; 95% CI, 0.70–0.89; $P<.001$). Factors associated with greater odds of BMD testing were previous radical local treatment (OR, 1.44; 95% CI, 1.31–1.58; $P<.001$), history of osteoporosis (OR, 1.84; 95% CI, 1.32–2.57; $P<.001$) and rheumatoid arthritis (OR, 1.64; 95% CI, 1.15–2.34; $P=.006$), previous use of bisphosphonates (OR, 1.47; 95% CI, 1.25–1.73; $P<.001$), and long-term corticosteroid use (OR, 1.63; 95% CI, 1.15–2.31; $P=.006$). Residence in rural areas was associated with lower odds (OR, 0.77; 95% CI, 0.68–0.87; $P<.001$).

Regarding regression analysis for both secondary outcomes, similar estimates were obtained and factors significant for BMD testing during screening remained significant, except for comorbidity score ≥4, metastasis, and rheumatoid arthritis in the analysis for follow-up testing, and long-term corticosteroid use for baseline testing.

Discussion

In our study population, the percentage of patients who received a BMD test between 6 months before and up to 12 months after starting ADT throughout the study period was low at 17.8%, although this increased during the study period and reached almost one-quarter of patients in the last year of the study. A noticeable increase occurred in 2003, when it doubled from the previous year. Large increases were also observed for baseline testing and follow-up testing that year. These improvements coincide with the publication of several articles recommending baseline BMD testing starting in 2002.^{25,26}

Our results are consistent with previous research using large population-based datasets in that rates are low; however, our BMD testing rates are higher than those reported in studies performed in the American population. In an American study using SEER and Medicare data, Morgans et al³⁰ reported the same pattern seen in our study from 2001 to 2008, with increasing rates over the years, and although their rates in 2001 through 2002 were similar to ours, they did not observe increases as large as we saw in our study from

Figure 3. BMD testing by year of androgen deprivation therapy initiation.

Abbreviation: BMD, bone mineral density.

^aYearly comparison of testing percentages with Cochran-Armitage trend test.

^bComparison of baseline BMD versus follow-up BMD with exact McNemar test.

2003 to 2008 (9.0% to 14.0% in their study vs 14.0% to 21.9% in our study).

One Canadian study conducted in the province of Ontario showed a rate of 18 per 100 person-years in 2008, which is not directly comparable to our results in percentages.³² However, if we convert our percentage of BMD testing in 2008 to rate per 100 person-years, our rate is approximately 16 per 100 person-years. Although American and Canadian studies show low rates of testing, the slightly higher rates in Canadian studies may be due to differences in the healthcare system and clinical practices in bone health management, among other reasons.

We observed lower rates of BMD testing among men aged >80 years, which is also consistent with findings in the aforementioned studies.^{30–32} One possible explanation is that physicians or patients themselves may opt for fewer interventions in older age.

Our finding of lower odds of baseline testing with increasing Charlson comorbidity was not corroborated by some of the previous research.^{30,31} As with our study, Alibhai et al³² found lower odds of baseline testing in rural areas. Patients identified as having metastatic PCa at baseline were also less likely to receive testing; this is not unexpected given the potential interpretability issues of BMD tests in those with bone lesions. It may also be driven by clinical reasoning: physicians may not consider the value of BMD testing as high in those patients given their relatively worse prognosis. Another possibility is that some patients with metastatic PCa that progresses rapidly to castration

resistance may receive bone-targeted therapies earlier and BMD testing does not impact management at that point.

Previous physician surveys regarding bone health management of patients with PCa undergoing ADT do provide an insight that render the findings of consistently low BMD testing less surprising. In 2006, Alibhai et al³⁸ showed that only a minority (<13%) of PCa-treating physicians would prescribe baseline BMD testing. A more recent survey found a greater proportion of physicians (33%) routinely measured BMD at ADT initiation.³⁹ To our knowledge, there are no recommendations of BMD testing for men initiating ADT from the major North American PCa-specific guidelines of urologists or radiation oncologists (Canadian Urological Association, American Urological Association, American Society for Radiation Oncology) except those of NCCN and ASCO (which only recently endorsed them in 2020).⁴⁰ Given that urologists and radiation oncologists most frequently prescribe ADT, endorsement from these organizations could potentially increase BMD testing rates. In contrast, these recommendations are mentioned in the European Association of Urology PCa-specific guidelines.⁴¹

In the context of breast cancer, guidelines also recommend that women treated with hormone therapy, such as aromatase inhibitors or tamoxifen, should undergo baseline BMD tests given the effect of those drugs on BMD.⁴² Given the contextual similarity between patients with breast cancer and those with PCa treated with hormonal therapy, it is interesting to compare our

Table 2. Multivariable Generalized Linear Mixed Modeling of Variables Associated With BMD Testing

Factor	Any BMD Test During Screening Period			Baseline BMD Test			Follow-Up BMD Test		
	OR	(95% CI)	P Value	OR	(95% CI)	P Value	OR	(95% CI)	P Value
Year of ADT initiation									
2000–2001	Ref			Ref			Ref		
2002–2003	2.56	(2.03–3.22)	<.001	2.67	(1.89–3.78)	<.001	2.06	(1.57–2.70)	<.001
2004–2005	5.79	(4.67–7.19)	<.001	6.93	(5.02–9.55)	<.001	3.40	(2.64–4.39)	<.001
2006–2007	5.89	(4.75–7.31)	<.001	8.93	(6.50–12.28)	<.001	2.66	(2.05–3.45)	<.001
2008–2009	6.17	(4.96–7.66)	<.001	10.26	(7.46–14.10)	<.001	2.39	(1.84–3.12)	<.001
2010–2011	5.64	(4.52–7.03)	<.001	8.72	(6.32–12.02)	<.001	2.38	(1.82–3.12)	<.001
2012–2013	5.39	(4.32–6.72)	<.001	10.10	(7.33–13.91)	<.001	1.81	(1.37–2.39)	<.001
2014–2015	5.28	(4.22–6.60)	<.001	8.99	(6.50–12.43)	<.001	2.05	(1.56–2.71)	<.001
Age, y									
<70	Ref			Ref			Ref		
70–74	1.13	(0.97–1.29)	.150	1.11	(0.97–1.27)	.117	1.11	(0.96–1.30)	.166
75–80	0.98	(0.87–1.10)	.711	1.01	(0.88–1.15)	.918	0.99	(0.85–1.15)	.869
>80	0.67	(0.59–0.76)	<.001	0.70	(0.60–0.81)	<.001	0.74	(0.62–0.88)	.001
Charlson comorbidity score									
0–1	Ref			Ref			Ref		
2–3	0.81	(0.71–0.91)	.001	0.81	(0.70–0.94)	.007	0.83	(0.70–0.99)	.036
≥4	0.65	(0.51–0.81)	<.001	0.57	(0.43–0.76)	<.001	0.82	(0.60–1.12)	.207
Metastases									
No	Ref			Ref			Ref		
Yes	0.79	(0.70–0.89)	<.001	0.76	(0.66–0.88)	<.001	0.89	(0.76–1.04)	.153
Prior local treatment									
No	Ref			Ref			Ref		
Yes	1.44	(1.31–1.58)	<.001	1.37	(1.23–1.54)	<.001	1.43	(1.25–1.62)	<.001
Rheumatoid arthritis									
No	Ref			Ref			Ref		
Yes	1.64	(1.15–2.34)	.006	1.98	(1.32–2.98)	.001	1.12	(0.68–.85)	.665
Diabetes									
No	Ref			Ref			Ref		
Yes	0.97	(0.86–1.10)	.677	1.07	(0.93–1.23)	.340	0.89	(0.75–1.06)	.183
Hyperthyroidism									
No	Ref			Ref			Ref		
Yes	0.74	(0.27–2.03)	.562	1.05	(0.35–3.12)	.933	0.37	(0.05–2.79)	.337
Osteoporosis									
No	Ref			Ref			Ref		
Yes	1.84	(1.32–2.57)	<.001	1.85	(1.26–2.72)	.002	1.56	(1.02–2.40)	.042
Fracture									
No	Ref			Ref			Ref		
Yes	1.07	(0.89–1.28)	.476	1.11	(0.89–1.38)	.354	0.94	(0.73–1.22)	.651
Prior bisphosphonates									
No	Ref			Ref			Ref		
Yes	1.47	(1.25–1.73)	<.001	1.44	(1.20–1.74)	<.001	1.41	(1.13–1.76)	.002

(continued on next page)

Table 2. Multivariable Generalized Linear Mixed Modeling of Variables Associated With BMD Testing (cont.)

Factor	Any BMD Test During Screening Period			Baseline BMD Test			Follow-Up BMD Test		
	OR	(95% CI)	P Value	OR	(95% CI)	P Value	OR	(95% CI)	P Value
Prior long-term corticosteroid use									
No	Ref			Ref			Ref		
Yes	1.63	(1.15–2.31)	.006	1.19	(0.78–1.84)	.421	1.69	(1.08–2.64)	.021
Prescribing specialty									
Other	Ref			Ref			Ref		
Urology/Radiation oncology	1.08	(0.93–1.25)	.256	1.10	(0.94–1.28)	.242	1.01	(0.85–1.19)	.940
Region of residence									
Urban	Ref			Ref			Ref		
Rural	0.77	(0.68–0.87)	<.001	0.76	(0.66–0.88)	<.001	0.83	(0.72–0.93)	.002

Abbreviations: ADT, androgen deprivation therapy; OR, odds ratio.

study with those investigating use of baseline BMD testing in patients with breast cancer treated with aromatase inhibitors. Rates of baseline BMD testing among patients with breast cancer are consistently much higher compared with the PCa population: between 32% and 68% in recent studies.^{43–45} However, it is notable that factors found to be associated with lower baseline BMD testing are similar to those identified in our study and other PCa studies, namely older patient age, higher comorbidity, and rural residence. This suggests that these factors are not specific to the PCa population treated by ADT but may in fact be generalizable to patients with cancer in general, and perhaps even the general population not experiencing cancer.⁴⁶ However, the large discrepancy in percentage between the breast cancer and PCa population may be reflective of the importance of sex differences in the prevention of osteoporosis; awareness of osteoporosis issues is much greater among postmenopausal women than men.^{46,47} It should also be noted that BMD testing rates among men in the general population are even lower than among ADT-treated men, ranging from 0.5% to 2%.^{31,48}

Limitations

Use of administrative health data imposes certain limitations on our study. First, it is not possible to determine whether the lack of baseline BMD testing was caused by patient refusal despite physician recommendations. Second, it is possible that patients underwent BMD testing in the private sector. However, this is likely to only be a small percentage of patients given the universal public healthcare coverage in the province of Quebec and, more importantly, the nonurgent nature of baseline BMD testing.

Given the lack of guideline consensus on the specific time frames appropriate for BMD testing when initiating

ADT, the main definition we chose (6 months before and up 12 months after) was intended to capture both baseline and follow-up testing and to increase comparability with existing research. However, we did include analyses with differing definitions for the screening period to account for this. The wider definitions (B, C, and D) did result in a larger percentage of patients receiving baseline BMD testing (at 19.4%, 21.1%, and 24.5%), but remain underwhelming.

Conclusions

Only a minority of patients with PCa initiating long-term ADT received a BMD test. Although the rates did increase from earlier years, they remain low even in more contemporaneous years. Patients with metastatic PCa were less likely to receive testing. Other gaps in BMD testing were identified among older patients, those with more comorbidities, and residents of rural areas. Further exploration of the factors explaining these patterns is necessary to devise appropriate strategies that could increase these rates. Regardless, our results suggest that additional emphasis regarding BMD testing and bone health management in the PCa population may be needed in clinical guidelines.

Submitted November 21, 2019; accepted for publication April 8, 2020.

Author contributions: Study concept and design: All authors. Data acquisition: Dragomir. Data analysis and interpretation: All authors. Manuscript preparation: All authors. Critical review: All authors.

Disclosures: The authors have disclosed that they have not received any financial consideration from any person or organization to support the preparation, analysis, results, or discussion of this article.

Funding: This work was supported by funding from Fonds de Recherche du Québec - Santé (A.D., Research Scholar Junior 1).

Correspondence: Alice Dragomir, MSc, PhD, Research Institute of the McGill University Health Centre/CORE (2B.45), 5252 de Maisonneuve West, Montreal, Quebec, Canada, H4A 3S5. Email: alice.dragomir@mcgill.ca

References

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2018. Toronto, ON: Canadian Cancer Society; 2018. Accessed July 16, 2020. Available at: cancer.ca/Canadian-Cancer-Statistics-2018-EN
2. Ellison LF. Progress in net cancer survival in Canada over 20 years. *Health Rep* 2018;29:10–18.
3. Gilbert SM, Kuo YF, Shahinian VB. Prevalent and incident use of androgen deprivation therapy among men with prostate cancer in the United States. *Urol Oncol* 2011;29:647–653.
4. Meng MV, Grossfeld GD, Sadetsky N, et al. Contemporary patterns of androgen deprivation therapy use for newly diagnosed prostate cancer. *Urology* 2002; 60(3, Suppl 1):7–11; discussion 11–12.
5. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol* 2010;11:1066–1073.
6. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma—long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys* 2005;61:1285–1290.
7. Roach M III, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *J Clin Oncol* 2008;26:585–591.
8. D'Amico AV, Chen MH, Renshaw AA, et al. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA* 2008;299:289–295.
9. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015;373:737–746.
10. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2017;377:352–360.
11. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016;387:1163–1177.
12. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2019;381:13–24.
13. Saad F, Chi KN, Finelli A, et al. The 2015 CUA-CUOG Guidelines for the management of castration-resistant prostate cancer (CRPC). *Can Urol Assoc J* 2015;9:90–96.
14. Levine GN, D'Amico AV, Berger P, et al. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *CA Cancer J Clin* 2010;60:194–201.
15. Sharifi N, Gulley JL, Dahut WL. An update on androgen deprivation therapy for prostate cancer. *Endocr Relat Cancer* 2010;17:R305–315.
16. Mazzola CR, Mulhall JP. Impact of androgen deprivation therapy on sexual function. *Asian J Androl* 2012;14:198–203.
17. Greenspan SL, Coates P, Sereika SM, et al. Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. *J Clin Endocrinol Metab* 2005;90:6410–6417.
18. Shahinian VB, Kuo YF, Freeman JL, et al. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005;352:154–164.
19. Alibhai SM, Duong-Hua M, Cheung AM, et al. Fracture types and risk factors in men with prostate cancer on androgen deprivation therapy: a matched cohort study of 19,079 men. *J Urol* 2010;184:918–924.
20. Poulsen MH, Frost M, Abrahamsen B, et al. Osteoporosis and prostate cancer; a 24-month prospective observational study during androgen deprivation therapy. *Scand J Urol* 2019;53:34–39.
21. Krupski TL, Foley KA, Baser O, et al. Health care cost associated with prostate cancer, androgen deprivation therapy and bone complications. *J Urol* 2007;178:1423–1428.
22. Krahn MD, Bremner KE, Luo J, et al. Health care costs for prostate cancer patients receiving androgen deprivation therapy: treatment and adverse events. *Curr Oncol* 2014;21:e457–465.
23. Adachi JD, Ioannidis G, Berger C, et al. The influence of osteoporotic fractures on health-related quality of life in community-dwelling men and women across Canada. *Osteoporos Int* 2001;12:903–908.
24. Oefelein MG, Ricchiuti V, Conrad W, et al. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. *J Urol* 2002;168:1005–1007.
25. Ross RW, Small EJ. Osteoporosis in men treated with androgen deprivation therapy for prostate cancer. *J Urol* 2002;167:1952–1956.
26. Smith MR. Osteoporosis during androgen deprivation therapy for prostate cancer. *Urology* 2002;60(3 Suppl 1):79–85, discussion 86.
27. Diamond TH, Higano CS, Smith MR, et al. Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: recommendations for diagnosis and therapies. *Cancer* 2004;100:892–899.
28. Duncan GG, Corbett T, Lukka H, et al. GU radiation oncologists consensus on bone loss from androgen deprivation. *Can J Urol* 2006;13:2962–2966.
29. Tsang DS, Alibhai SM. Bone health care for patients with prostate cancer receiving androgen deprivation therapy. *Hosp Pract* 1995 2014;42:89–102.
30. Morgans AK, Smith MR, O'Malley AJ, et al. Bone density testing among prostate cancer survivors treated with androgen-deprivation therapy. *Cancer* 2013;119:863–870.
31. Shahinian VB, Kuo YF. Patterns of bone mineral density testing in men receiving androgen deprivation for prostate cancer. *J Gen Intern Med* 2013;28:1440–1446.
32. Alibhai SM, Yun L, Cheung AM, et al. Screening for osteoporosis in men receiving androgen deprivation therapy. *JAMA* 2012;307:255–256.
33. Qaseem A, Snow V, Shekelle P, et al. Screening for osteoporosis in men: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2008;148:680–684.
34. Mohler J, Bahnson RR, Boston B, et al. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 1.2008. Accessed July 10, 2020. To view the most recent version, visit NCCN.org
35. Papaioannou A, Morin S, Cheung AM, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ* 2010;182:1864–1873.
36. Droz JP, Balducci L, Bolla M, et al. Management of prostate cancer in older men: recommendations of a working group of the International Society of Geriatric Oncology. *BJU Int* 2010;106:462–469.
37. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613–619.
38. Alibhai SM, Rahman S, Warde PR, et al. Prevention and management of osteoporosis in men receiving androgen deprivation therapy: a survey of urologists and radiation oncologists. *Urology* 2006;68:126–131.
39. Damji AN, Bies K, Alibhai SM, et al. Bone health management in men undergoing ADT: examining enablers and barriers to care. *Osteoporos Int* 2015;26:951–959.
40. Saylor PJ, Rumble RB, Tagawa S, et al. Bone health and bone-targeted therapies for prostate cancer: ASCO endorsement of a Cancer Care Ontario Guideline. *J Clin Oncol* 2020;38:1736–1743.
41. Mottet N, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. *Actas Urol Esp* 2011;35:565–579.
42. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force report: bone health in cancer care. *J Natl Compr Canc Netw* 2013;11(Suppl 3):S1–50.
43. Charlson J, Smith EC, Smallwood AJ, et al. Bone mineral density testing disparities among patients with breast cancer prescribed aromatase inhibitors. *J Natl Compr Canc Netw* 2016;14:875–880.
44. Bošković L, Gašparić M, Petković M, et al. Bone health and adherence to vitamin D and calcium therapy in early breast cancer patients on endocrine therapy with aromatase inhibitors. *Breast* 2017;31:16–19.
45. Stratton J, Hu X, Soulos PR, et al. Bone density screening in postmenopausal women with early-stage breast cancer treated with aromatase inhibitors. *J Oncol Pract* 2017;13:e505–515.
46. Solomon DH, Brookhart MA, Gandhi TK, et al. Adherence with osteoporosis practice guidelines: a multilevel analysis of patient, physician, and practice setting characteristics. *Am J Med* 2004;117:919–924.
47. Morris CA, Cabral D, Cheng H, et al. Patterns of bone mineral density testing: current guidelines, testing rates, and interventions. *J Gen Intern Med* 2004;19:783–790.
48. O'Malley CD, Johnston SS, Lenhart G, et al. Trends in dual-energy X-ray absorptiometry in the United States, 2000–2009. *J Clin Densitom* 2011;14:100–107.

See JNCCN.org for supplemental online content.

Supplemental online content for:

Contemporary Population-Based Analysis of Bone Mineral Density Testing in Men Initiating Androgen Deprivation Therapy for Prostate Cancer

Jason Hu, MSc; Armen G. Aprikian, MD; Marie Vanhuyse, MD, MSc; and Alice Dragomir, MSc, PhD

J Natl Compr Canc Netw 2020;18(10):1374–1381

eFigure 1: Definitions of Screening Periods B, C, and D

eFigure 2: Percentage of Patients Receiving BMD Test Using Screening Period B

eFigure 3: Percentage of Patients Receiving BMD Test Using Screening Period C

eFigure 4: Percentage of Patients Receiving BMD Test Using Screening Period D

eFigure 1. Definitions of screening periods B, C, and D.
Abbreviation: ADT, androgen deprivation therapy; BMD, bone mineral density.

eFigure 2. Percentage of patients receiving BMD test using screening period B (12 months prior to and up 12 months after ADT). Abbreviations: ADT, androgen deprivation therapy; BMD, bone mineral density.
^aYearly comparison of testing percentages with Cochran-Armitage trend test.
^bComparison of baseline BMD versus follow-up BMD with exact McNemar test.

eFigure 3. Percentage of patients receiving BMD test using screening period C (24 months prior to and up 12 months after ADT). Abbreviations: ADT, androgen deprivation therapy; BMD, bone mineral density.
^aYearly comparison of testing percentages with Cochran-Armitage trend test.
^bComparison of baseline BMD versus follow-up BMD with exact McNemar test.

eFigure 4. Percentage of patients receiving BMD test using screening period D (6 months prior to and up 24 months after ADT) in men receiving at least 24 months of ADT.

Abbreviations: ADT, androgen deprivation therapy; BMD, bone mineral density.

^aYearly comparison of testing percentages with Cochran-Armitage trend test.

^bComparison of baseline BMD versus follow-up BMD with exact McNemar test.