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Abstract

Background: Androgen deprivation therapy (ADT) is a key component of therapy for patients with high-risk prostate carcinoma, but it may be deleterious for bone health. We sought to determine the frequency of dual energy x-ray absorptiometry (DXA) scanning in patients commencing adjuvant ADT for treatment of high-risk prostate cancer at a large integrated regional cancer centre.

Material and methods: The electronic medical records (EMR) of all patients with high-risk prostate carcinoma commenced on adjuvant ADT between January 1, 2016 and December 31,

2017 at the Mid-North Coast Cancer Institute, Coffs Harbour, Australia were reviewed. Patients commenced on neoadjuvant ADT and long-term suppressive ADT for metastatic disease were excluded. The following data were obtained: socio-demographic information, prostate cancer data, ADT details and DXA results.

Results: 188 men (mean age ± SD, 75.4 ± 7 years) were commenced on adjuvant ADT for a total duration (mean ± SD) of 23.4 ± 7 months. Most (n = 155/188, 82%) were commenced on *leuprorelin acetate*. While only 26/188 (14%) had a DXA scan performed prior to ADT, another 133 (71%) had a DXA scan at a median of 20 days (interquartile range 7–98), later. Of the 159 men with DXA readings, 76 (48%) were osteopaenic and 38 (24%) were osteoporotic by DXA criteria.

Conclusion: A high level (85%) of DXA scanning in men commencing ADT for prostate cancer can be achieved at a regional centre. The high prevalence (72%) of low bone mass in our unselected cohort underscores the importance of routine DXA scanning to guide bone health management during ADT.

Keywords: prostate cancer; androgen deprivation; osteoporosis; DXA; bone density

Introduction

Prostate cancer is the most prevalent male solid organ malignancy [1]. Almost half of all men diagnosed with prostate cancer will be treated with androgen deprivation therapy (ADT) to suppress testosterone levels [2]. Combination ADT and radiation therapy significantly improves disease-free and overall survival in prostate cancer [3]. However, ADT is associated with loss of bone mineral density (BMD) and increased risk of fragility fracture (trauma equivalent to fall from a standing height) [4]. These will become an increasingly common adverse event due to the ageing population and rising prevalence of both prostate cancer and osteoporosis with age. Given the excellent prognosis in men commencing adjuvant ADT, attention to bone health by treating radiation oncologists is critical for optimising long-term outcomes. Australian national guidelines for the management of prostate cancer recognise the importance of appropriate monitoring of ADT-related class effects, including sexual dysfunction, bone health, cardiometabolic risk factors and emotional/cognitive changes (www.eviq.org.au). In particular, ADT may result in BMD loss soon after commencement, increasing the risk of osteoporosis and bone fractures [5]. There is increasing recognition of the importance of regular weight-bearing exercise, dietary and lifestyle modifications, including smoking cessation, reduction of alcohol consumption and initiation of vitamin D and calcium supplements, where indicated.

Men treated with 12 months of ADT had a reduction in BMD of approximately 2.5% at the total hip, 2.4% at the greater trochanter, 2.6% at the radius, 3.3% at the total body, and 4.0% at the lumbar spine [5]. The prevalence of osteoporosis [T-score ≤ –2.5 by dual X-ray absorptiometry (DXA)] was 35.4% in hormone-naïve patients, 42.9% after two years of ADT, 49.2% after four years, and 80.6% after 10 or more years [6]. Analysis of 50,613 men with prostate cancer in the linked Surveillance, Epidemiology, and End Results (SEER) programme and Medicare database found that 19.4% of those who received ADT had a fracture, compared with 12.6% of those who did not receive ADT ($p < 0.001$) [7]. The increased risk was proportional to the number of ADT doses received [7]. One of the newer forms of ADT, *abiraterone*, requires co-prescription with *prednisone* to reduce mineralocorticoid side effects [8] — an additional risk factor for osteoporosis.

In a paper from 2006, only 28% of radiation oncologists and 5% of urologists would refer for a DXA scan prior to commencement of ADT [9]. Despite availability of effective preventive treatments [10–14] and published management guidelines [15], bone health remains poorly managed [16, 17]. An important reason for this may be inadequate patient knowledge about osteoporosis, its risk factors, causes, treatment and prevention [18]. However, educative interventions involving use of a bone health pamphlet and recommendations to the family physician/general practitioner or involvement of a bone health care coordinator were associated with increased DXA referrals [19].

The aim of this study was to determine the frequency of DXA scanning in patients commenced on adjuvant ADT for treatment of prostate cancer at a large, high-volume integrated regional cancer centre in Australia.

Materials and methods

This retrospective study examined patients with prostate cancer who commenced adjuvant ADT between January 1, 2016 and December 31, 2017 at the Mid-North Coast Cancer Institute (MNCCI), Coffs Harbour, New South Wales, Australia. Patients commenced on neo-adjuvant ADT alone and long-term suppressive ADT for metastatic disease were excluded due to the probable short duration of ADT and poor prognosis, respectively. There is sometimes debate amongst treating clinicians from different specialties about the need for bone protective therapy in both these patient groups. We have previously published on our large institutional experience regarding the diagnosis and classification of men with prostate cancer [20, 21], treatment choice [22], use of ADT [23–26] and decision regret in this group [27–29]. In our experience, it is often difficult for patients to understand and adhere to bone

protective therapy in the setting of only a short course of ADT, or in the presence of poor prognosis.

Coffs Harbour (Australian Standard Geographic Classification, RA2 – Inner Regional) is a regional city in Australia, located mid-way between Sydney and Brisbane with a population of approximately 70,000 people, but which provides medical services to 170,000 people in the surrounding area. The MNCCI is the only site providing specialist radiation therapy and integrated oncology services for several hours in all directions. Locally, it is mainly the radiation oncologists rather than medical oncologists or urologists, who prescribe ADT for prostate cancer and who refer for DXA scanning. Bone health issues are mainly managed by rheumatologists, one of whom has a strong interest in bone health (PW). As the study setting is a regional centre, there is a paucity of family physicians/general practitioners. Due to a heavy clinical workload, most family physicians/general practitioners are not involved in the management of bone health in patients on ADT. All patient encounters are captured on a dedicated oncology electronic medical record (EMR; Mosaiq®, Elekta, Crawley, United Kingdom).

The following data were obtained from the EMR:

- socio-demographic information (age, weight, height, working status, postcode);
- prostate cancer data (date of diagnosis, Gleason score, TMN staging, serum PSA level pre-ADT, cancer treatment other than ADT), ADT details (start date, duration, type) and DXA results.

Databases of the three radiology practices servicing the region with DXA scanning were searched if patients did not have a DXA scan result recorded in the dedicated oncology EMR.

Ethical approval

Approval was obtained from the Mid-North Coast Human Research Ethics Committee as a low/negligible risk (ethics application LNR184 – LNR/18/NCC/99).

Statistical analysis

Means (±SD) and medians [interquartile range (IQR)] were used as summary statistics, as appropriate. The threshold for significance was set at $p < 0.05$ (two-tailed). Analysis was performed using STATA 11.2 (College Station, TX, USA).

Results

A total of 188 men (mean age ± SD, 75.4 ± 7 years) were commenced on adjuvant ADT between January 1, 2016 and December 31, 2017 for a mean ± SD therapy duration of 23.4 ± 7 months. The majority of men (n = 155/188, 82%) were commenced on *leuprorelin acetate* (Tab. 1). The severity, grade and stage of prostate cancer are shown in Table 2. All patients had high-risk prostate carcinoma, 152/188 patients (80.9%) had Gleason 8–10 disease and 12/188 patients (6.2%) had stage IV non-metastatic disease due to regional nodal involvement.

Of the 188 men commenced on adjuvant ADT, 156 (83%) had a DXA scan recorded in the EMR. An additional three men with DXA results were identified by manually searching the databases of the three radiology practices in the region. Only 26/188 (14%) had a DXA scan performed prior to commencement of ADT at a median (IQR) of 6 [3–31] days prior to starting ADT. Overall, 133/188 (71%) men had a DXA scan done following commencement of ADT at a median of 20 days (IQR 7–98) later.

Following DXA scanning, 76/159 (48%) of men were osteopenic (T-score between -1.0 and –2.5) and 38/159 (24%) were osteoporotic (T-score ≤ –2.5), indicating that 72% of patients had low BMD (T-score < –1.0). The mean ±SD T-score at the femoral neck was –1.55 ± 1.15 (osteopenia), at the lumbar spine 0.48 ± 1.68 (normal) and the distal forearm –0.5 ± 1.0 (normal).

Discussion

Most available data assessing the frequency of DXA screening in this patient group has come from major metropolitan centres [16, 17, 30]. There is little published data from large regional centres, even though the majority of patients with prostate cancer in Australia receive their treatment in regional and rural locations. This retrospective study from a single large integrated regional cancer centre found that 85% of patients treated with adjuvant ADT for prostate cancer had DXA screening performed around the time of ADT commencement. While only 14% had it performed prior to ADT, the remaining 71% had it performed shortly afterwards — within 20 days or so.

The frequency of DXA scanning from this Australian integrated regional cancer centre was high in comparison to other studies [16, 17, 30, 31]. A retrospective study using the SEER-Medicare database from the United States (US) of 84,036 men with prostate cancer found that 11.5% of men underwent DXA testing within 12 months prior to, and three months after initiation of ADT, versus 4.4% in men with prostate cancer not initiating ADT and 3.8% in non-cancer controls [30]. A Canadian study of 33,036 men commenced on ADT found the

rate of DXA scanning within two years following commencement of ADT ranged between 0.5 per 100 person-years in 1995 to 18.0 per 100 person-years in 2008 [16]. A US study of 2290 patients with prostate cancer found that only 197 (8.6%) underwent DXA scanning within one year before, and six months after starting ADT [17]. A smaller Spanish study found that 62% (168/270) of patients on ADT underwent DXA scanning [32]. The high level of DXA testing at our centre may have been due to the efforts of a small group of clinicians with heightened awareness of the deleterious effects of ADT on bone health in the setting of accessible DXA scanning.

While most DXA scanning in our study occurred following initiation of ADT, the short delay of 20 days or so is unlikely to have a major clinical impact as BMD falls over months following ADT [5]. Our study in an unselected population showed that 76/158 (48%) of patients were osteopenic and 38/158 (24%) were osteoporotic by DXA criteria. This meant that 72% of the study sample had low BMD and suggests that all patients commencing adjuvant ADT should undergo baseline and ongoing BMD assessment by DXA to allow early intervention with bone protective measures, if required.

Previous clinical trials have demonstrated that pamidronate (60 mg IV every 12 weeks) [10], zoledronate (one infusion of 4 mg) [11], alendronate (70 mg orally once weekly) [12] and risedronate (2.5 mg orally once daily) [13] are effective at preventing ADT-related bone loss. However, these trials were not powered to show reduction in fracture risk. A double-blind study found that denosumab (60 mg subcutaneously every six months) was associated with a reduced risk of vertebral fracture at 36 months (relative risk, 0.38; 95% CI, 0.19 to 0.78; $p = 0.006$) [14].

While bone-protective pharmacotherapy may not be available in many countries due to cost considerations, it may be accessible for other indications. For example, in Australia, bone protective therapy is subsidised under the Pharmaceutical Benefits Scheme for those > 70 years old with a T-score ≤ –2.5 in the absence of a fracture, or in anyone with a fragility fracture [33]. However, increased dietary calcium intake, oral vitamin D supplementation, falls prevention strategies and a muscle strengthening program to address the catabolic effects of ADT are also appropriate bone protective interventions.

One reason for poor bone health screening in patients being treated with ADT may be poor patient knowledge about osteoporosis. Although not specifically involving patients on ADT for prostate cancer, a systemic review of 25 studies and 757 patients (105 men), found widespread awareness, but inadequate specific knowledge about osteoporosis in those with

poor bone health [18]. In particular, participants were especially uninformed about risk factors, causes, treatment, and prevention of osteoporosis.

A randomized controlled trial of 174 men initiating or commencing ADT for prostate cancer found that a patient bone health pamphlet with brief recommendations for their family physician/general practitioner or a patient bone health pamphlet with support of a bone health care coordinator were both associated with increased referrals for BMD assessment by DXA compared to usual care [19].

There were several limitations in our study. Results of DXA scans were obtained by reviewing the EMR, which relied on the scans being recorded in the EMR. As bone health management and DXA scanning may have been managed by the family physician/general practitioner, DXA results were not always included in the EMR. To address this issue, databases of the three private radiology practices in the region which offered DXA scanning were searched for outstanding DXA scans. This yielded only three patients who underwent DXA scanning, but whose results were not recorded in the EMR. Our study was also not designed to determine if an abnormal DXA result translated into appropriate bone health management.

This study from a single large regional integrated cancer centre showed that most patients with high-risk prostate carcinoma (85%) commenced on adjuvant ADT had a DXA scan recorded in the EMR. It shows what a committed team of healthcare professionals aware of the deleterious impact of treatments on bone health can achieve. However, to further improve bone health management in this at-risk population, especially prescription of bone protective therapy, we have since established a referral pathway to the existing Fracture Prevention Clinic. It would be valuable to determine if this high level of DXA screening was also seen at other regional and metropolitan sites. Given the frequent occurrence of low BMD in this at-risk population, all patients commencing ADT should have a baseline DXA scan to identify those who might benefit from bone-protective therapy.

Conflict of interest

Authors declare no competing interests.

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Data availability

Available upon request.

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Table 1. Type of androgen deprivation therapy used

Androgen deprivation therapy	**no.**	**%**
Leuprorelin acetate	169	89.9
Goserelin + Bicalutamide	1	0.5
Leuprorelin + Bicalutamide	4	2.1
Degarelix	12	6.5
Triptorelin	1	0.5
unknown	1	0.5
Total	**188**	**100**

Table 2. Prostate cancer characteristics

Cancer descriptors	**no.**	**%**

Gleason primary score		
3	29	15.4
4	136	72.3
5	19	10.2
UNK	4	2.1
Gleason secondary score		
3	32	17.1
4	81	43.1
5	71	37.8
UNK	4	2
Gleason tertiary score		
7	50	26.6
8	61	32.4
9	67	35.6
10	6	3.2
UNK*	4	2.2
Tumour stage		
T1	21	11.1
T2a	15	8
T2b	20	10.6
T2c	36	19.2
T3a	52	27.6
T3b	34	18.1
T4	4	2.2
UNK*	6	3.2
AJCC stage		
I	3	1.6
II	2	1.1
IIA	9	4.8
IIB	78	41.7
III	84	44.6
IVA	12	6.2

UKN — unknown; AJCC — American Joint Committee on Cancer