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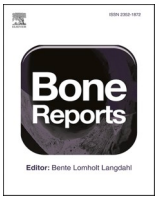

Quantitative ultrasound of the calcaneus (QUS): A valuable tool in the identification of patients with non-metastatic prostate cancer requiring screening for osteoporosis

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ABSTRACT

Non-metastatic prostate cancer (PCa) patients are at increased risk for osteoporosis and fractures mainly due to androgen deprivation therapy (ADT)-associated hypogonadism, but this remains largely underdiagnosed and untreated. In this study, we examine the value of pre-screening calcaneal QUS in identifying patients who should be referred for screening for osteoporosis using dual-energy X-Ray absorptiometry (DXA). In a single-center retrospective cross-sectional cohort study, we analysed data on DXA and calcaneal QUS measurements systematically collected between 2011 and 2013 in all non-metastatic PCa patients attending our Uro-Oncological Clinic at the Leiden University Medical Center. Receiver operating characteristic curves were used to assess the positive (PPV) and negative (NPV) predictive values of QUS T-scores of 0, −1.0, and − 1.8 in identifying DXA-diagnosed osteoporosis (T-scores ≤ -2.5 and ≤ -2) at lumbar spine and/or femoral neck. Complete sets of data were available in 256 patients, median age 70.9 (53.6–89.5) years; 93.0 % had received local treatment, 84.4 % with additional ADT. Prevalence of osteoporosis and osteopenia was respectively 10.5 % and 53 %. Mean QUS T-score was -0.54 ± 1.58. Whereas PPV at any QUS T-score was <25 %, precluding the use of QUS as surrogate for DXA in screening for osteoporosis, QUS T-scores of −1.0 to 0.0 had a NPV of ≥94.5 % for DXA T-scores ≤ 2.5 and ≤ −2 at any site, confidently identifying patients least likely to have osteoporosis, thereby significantly reducing the number of patients requiring DXA screening for diagnosing osteoporosis by up to two-third. Osteoporosis screening is a significant unmet need in non-metastatic prostate cancer patients treated with ADT, and QUS may represent a valuable alternative pre-screening strategy to overcome logistics, time demands, and economic barriers encountered with current strategies for osteoporosis screening in these patients.

Summary: Osteoporosis and associated increased fracture risk are common in non-metastatic prostate carcinoma, mainly due to androgen deprivation therapy, but these often remain underdiagnosed and untreated. We demonstrate that QUS is a safe, less costly pre-screen tool that reduces by up to two-third the number of patients requiring referral for DXA for osteoporosis screening.

1. Introduction

Prostate cancer (PCa) is the second most common cancer in men worldwide, most frequently diagnosed above the age of 65 years (Siegel et al., 2020). Androgen deprivation therapy (ADT) is the mainstay of treatment for localized, locally advanced, as well as metastatic PCa

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(Cornford et al., 2020; Lowrance et al., 2020), with treatment duration varying from <3 years to life-long, depending on the stage of the disease (Cornford et al., 2020; Lowrance et al., 2020; Sanda et al., 2018). ADT effectively prolongs overall survival (Bolla et al., 2007) but is always associated with a rapid decline in circulating gonadal hormones, in addition to the expected age-related decreases in gonadal function. The resulting hypogonadism leads to a disruption in bone remodelling, to a decrease in bone mass, and to a deterioration in bone microarchitecture, all contributing to increased risk of fracture (el Badri et al., 2019; Dalla Via et al., 2019; Looker et al., 2012). Evidence from prospective studies shows a significant decrease in bone mineral density (BMD) in the range of 2.4 % to 5.6 %, observed as early as 6 months after starting treatment with ADT, becomes maximal at one year on treatment (Greenspan et al., 2005; Morote et al., 2007; Alibhai et al., 2017), with further decreases in BMD on continuing treatment. Two large U.S. cohort studies showed that fracture rates increased from about 6.5 % per annum in PCa patients who do not receive ADT, to about 7.9 % in ADT-treated patients (Shahinian et al., 2005; Smith et al., 2006). It has been suggested that treatment with bisphosphonates may prevent the extent of BMD loss (Alibhai et al., 2017).

Large cohort studies in PCa confirmed the association between ADT treatment and increased risk for osteoporosis and fragility fractures (Shahinian et al., 2005; Smith et al., 2006; Mottet et al., 2011; Coleman et al., 2014), and associated increased morbidity, mortality and socio-economic burden in these patients. This has raised awareness for the need to screen PCa patient at the start and during treatment with ADT (Clynes et al., 2020). Although recommendations for bone health surveillance using DXA in patients with PCa at the start of ADT have been issued in urological and oncological guidelines over the past decade (Cornford et al., 2020; Lowrance et al., 2020; Parker et al., 2020; Saylor et al., 2020), these recommendations seem to have been poorly implemented (Heidenreich et al., 2012; Damji et al., 2015; Hu et al., 2020) with surveys revealing that urologists and oncologists were not adequately screening and managing osteoporosis in PCa patients (Heidenreich et al., 2012; Damji et al., 2015). A Canadian study conducted in 22,033 men who received ADT for >12 months thus showed that although BMD screening rates had risen nearly 6-fold from 4.1 % of patients studied in 2000 to 23.4 % of those studied in 2015 (Hu et al., 2020), there was still a clearly unmet need for improving the diagnosis of osteoporosis, possibly by using simpler alternative screening strategies to overcome logistic and economic barriers of current strategies for osteoporosis screening.

Dual-energy X-ray absorptiometry (DXA) is the gold standard for measuring bone mineral density (BMD) for screening for osteoporosis, with outcomes expressed as T-scores, representing standard deviations from the mean in a young female adult reference population (NHANES) (Looker et al., 2012; WHO scientific group on the assessment of osteoporosis at primary health care level, 2004). WHO criteria used for the diagnosis of osteoporosis are a T-score ≤ -2.5 at the femoral neck (FN) and lumbar spine (LS), which respectively predict osteoporotic hip- and vertebral fractures (Johnell et al., 2007; Schuit et al., 2004). However, DXA measurements of BMD are relatively expensive, and not always readily available.

Calcaneal quantitative ultrasonography (QUS) is a practical, easy to use technique for bone mass measurement, which holds several potential advantages over DXA measurements including being more easily accessible, radiation-free, simple to administer, and more economical than DXA (Nayak et al., 2011). QUS could thus potentially represent a practical outpatient tool to pre-screen ADT-treated non-metastatic PCa patients at high risk for osteoporosis, saving operator and patients' time and costs by targeting DXA testing to those likely to have osteoporosis. This assumption was based on promising data from a number of studies favourably comparing the performance of five QUS devices for the identification of osteoporosis, with those of DXA BMD measurements at lumbar spine and proximal femur. In the largest of these studies, the OPUS study, QUS measurements identified women at high risk for prevalent vertebral fractures in a large population-based sample of 2837 women with or without osteoporotic vertebral fractures (Glüer et al., 2004). Other smaller studies included a study conducted in 221 post-menopausal community-dwelling women showing a sensitivity of 67.6 % [95 % confidence interval (CI), 50.2–82.0 %] for QUS for identifying osteoporosis, and a negative predictive value of 90 % for DXA-defined osteoporosis (Boonen et al., 2005); with similar data also reported in a review of the value of QUS data in the management of osteoporosis and assessment of fracture first published in 2017 (Hans and Baim, 2017), which was recently updated by the same authors (Hans et al., 2022). There are to date no available data on the value of QUS in pre-screening ADT-treated PCa patients at high risk for osteoporosis in order to target DXA screening for osteoporosis in these patients.

The main objective of this study was to address the value of calcaneal QUS compared to the gold standard of DXA, as a pre-screening tool to identify ADT-treated non-metastatic PCa patients who would require screening for osteoporosis using DXA, thus allowing a reduction in the number of unnecessary referrals for this investigation.

2. Materials and methods

2.1. Study design and participants

In a single centre cross-sectional cohort study design, we retrospectively analysed data systematically collected from all patients with non-metastatic PCa, who attended our Uro-oncological out-patient Clinic at the Leiden University Medical Center between November 2011 and May 2013, and who were evaluated for possible ADT-induced skeletal complications of their malignancy.

All patients had been treated for their prostate cancer using standardized protocols which followed international guidelines, and which included androgen deprivation therapy and associated risk of osteoporosis (Mottet et al., 2021).

In this time period, our Clinic's standard evaluation of bone health included DXA-BMD measurements laboratory investigations including gonadal status and bone turnover markers, as well as the then successfully recently tested calcaneal QUS measurements in post-menopausal osteoporosis (Boonen et al., 2005; Glüer et al., 2004; Nayak et al., 2011).

Demographic and clinical data including age, medical history, history of fractures, clinical risk factors for fracture such as previous fractures, family history for hip fracture, corticosteroid use, secondary causes for osteoporosis, smoking, and alcohol consumption, were evaluated for a possible contributory role in the development of osteoporosis. The beneficial effect of current or past use of osteoporosis treatment such as the anti-resorptive agents bisphosphonates or denosumab and/or calcium and vitamin D supplementation were also evaluated.

Informed consent was obtained from all patients for use of their anonymised data, securing their privacy rights by ensuring that no individual case details, personal patient information or patient images, which may lead to a breach of patients' privacy, were included in any potential publication. This retrospective data study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

2.2. Bone mineral density (BMD) measurements using DXA

BMD was measured at the LS (L1-L4) and at both FNs using dual energy X-ray absorptiometry scans (DXA, Hologic QDR 4500; Waltham, MA, USA) equipped with reference values based on the National Health and Nutrition Examination Surveys, NHANES II (Looker et al., 2012), which are representative of those of the general Dutch population. World Health organization (WHO) criteria were used to define osteopenia (T-score between -1 and -2.5) and osteoporosis (T-score ≤ 2.5), based on the lowest T-score at any site. The coefficient of variation (CV) of the DXA measurements was established by repeated (approximately

1800) phantom measurements performed in our Nuclear Medicine Department, leading to a CV in the range of 0.02 to 0.03 %, depending on the anatomical location of the measurement. The T-score value at the left FN (or contralateral hip in case of hip replacement) was used for all analyses. We also conducted an analysis of data using a DXA T score of ≤ -2.0 in order to minimize the chance of missing patients who may have an increased fracture risk at this higher cut-off point, especially because of the high likelihood of ADT-induced hypogonadism known to contribute to increased fracture risk by compromising bone quality independently of a decrease in BMD (Kanis et al., 2011; Binkley et al., 2014).

2.3. Quantitative ultrasound scanning (QUS) of the calcaneus

QUS was performed by a dedicated experienced nurse at the left calcaneus site in all patients, following our standard operating procedure protocol for using the FDA-approved Lunar Achilles ultrasound device (GE Healthcare LUNAR, Madison, Wisconsin, USA). The CV of the QUS measurements, as established in our department by repeated measurements, was 2.6 and the ultrasound device was calibrated at regular intervals according to the manufacturer's instructions. Measurements obtained included speed of sound (SOS) expressed in meters/s, and broad band attenuation (BUA) expressed in dB/MHz. QUS results are expressed as T-score of the stiffness index, which is related to elasticity and mechanical stiffness, and bone strength, and takes into account both SOS and BUA (stiffness index = (0.67xBUA) + (0.28 x SOS) – 420).

The randomly selected QUS T scores of 0 and − 1.0, and of −1.8 were used based on manufacturer's recommendations to study their predictability for the operational diagnosis of osteoporosis as defined by WHO criteria of BMD T-score ≤ -2.5 as well as the higher threshold of BMD T-score ≤ -2.0, using ROC curves and the above selected QUS T score cut-offs based on trade off of sensitivity and specificity.

2.4. Fragility fractures

Data on prevalent fragility fractures including vertebral fractures, hip fractures and/or non-vertebral fractures at the time of the cross-sectional study, were retrieved from the patients' electronic medical records.

2.5. Laboratory investigations

Laboratory investigations performed at the time of the cross-sectional evaluation of bone health included a routine biochemistry panel, gonadal status as assessed by plasma concentrations of total testosterone, luteinizing hormone, and sex hormone-binding globulin (SHBG), PSA, 25(OH)D3 vitamin D concentration (normal value >50 nmol/l), and bone turnover markers including the bone formation marker: N-terminal pro-peptide of type 1 procollagen (P1NP, normal value <59 ng/ml) and the bone resorption marker: beta-carboxyl-terminal cross-linking telopeptide of type I collagen (β-CTX, normal value <0.85 ng/ml).

2.6. Statistical analysis

SPSS 28 for Windows software package (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The χ^2-test for categorical variables and Student's *t*-test or Mann–Whitney test (two-sided) for non-normally distributed variables were used as appropriate. Data are presented as mean ± SD, median and range, or as percentages A *P*-value of < 0.05 (two-tailed) was considered statistically significant. Correlation analysis was performed using a two-tailed Pearson correlation coefficient with a significance level of $p < 0.05$. Negative predictive value (NPV) and positive predictive value (PPV) were calculated for various QUS T-score thresholds compared to WHO-defined BMD T-score of ≤ -2.5 for the diagnosis of osteoporosis, as well as for BMD T-score of ≤ -2.0 as often used in cases of secondary osteoporosis.

Receiver operating characteristic (ROC) curve analysis was used to evaluate the discriminatory ability of QUS to detect osteoporosis at lumbar spine and femoral neck as measured by DXA. The area under the curve (AUC) was calculated for available DXA sites with a confidence interval of 95 %. The area under the curve (AUC) was also calculated for a DXA T-score of ≤ -2.0 at lumbar spine and femoral neck for the ROC curve analysis. Two-tailed $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Demographic data

Baseline characteristics of the 256 non-metastatic PCa patients seen at our uro-oncological out-patient clinic between November 2011 and May 2013, included age, body mass index and clinical risk factors for osteoporosis and fractures, and are shown in Table 1. Median age was 71.3 years, range 53.6–89.5. 238 men (93.0 %) were treated with local radiotherapy to the prostate (80.1 %) or prostatectomy (12.9 %) and the majority (216, 84.4 %) had received ADT for up to 3 years at the time of the cross-sectional study. Of these 216 ADT recipients, 134 patients (52.3 %) were treated with ADT at the time of evaluation (59 for <12 months and 75 for up to 3 years), and 82 (32.0 %) had received ADT at some stage before the evaluation of bone status usually for 3 years: "ever use" (Table 1). At the time of evaluation only five patients (2 %) were also using a bisphosphonate ± calcium and vitamin D supplements as treatment for a documented osteoporosis. Clinical risk factors for osteoporosis are also detailed in Table 1.

3.2. Bone measurements

3.2.1. DXA bone mineral density measurements

Mean DXA T-scores at LS and FN were respectively −0.47 ± 1.46 SD, median − 0.60 (range: − 4.20– 4.00) and − 1.03 ± 0.93, median − 1.20 (range: −3.20 - 2.50). 136 Patients (53.1 %) had osteopenia (T-score < −1.0 to > − 2.5) at either LS or FN: 5.9 % at the LS alone, and 29.7 % at the FN alone. Twenty-seven patients (10.5 %) had osteoporosis (T-score ≤ −2.5) at either LS or FN (T-score ≤ −2.5): 17 (6.6 %) at LS alone, and 15 (5.8 %) at FN alone. Thirty-nine patients (15.2 %) had a DXA T score of ≤ -2.0 at LS, and 58 (22.6 %) at FN. Overall, 75 patients (29.2 %) had a DXA T score of ≤ -2.0 at any measured bone site. BMD outcomes of the 40 patients who did not receive ADT were significantly higher than those of the 216 patients who did receive ADT ($P = 0.045$). The prevalence of osteoporosis in the patients who did not receive ADT, and those currently receiving ADT, and those ever receiving ADT (usually 3 years) was respectively 5 %, 11.2 % and 12.2 % (Table 1).

Of the 134 patients receiving ADT at the time of evaluation of skeletal status, those treated for <12 months had a lower, albeit non-significant prevalence of DXA-diagnosed osteoporosis than those who were continuously treated with ADT for up to 36 months (10.2 versus 12.0 %, respectively, Table 1).

3.2.2. Bone measurements using QUS

Mean T-score for QUS was −0.54 ± 1.58 SD, median − 0.65 (range: −3.70-4.00). Of the total 256 PCa patients evaluated, 170 (66.4 %) had a QUS T-score ≤ 0, 108 (42.2 %) had scores ≤ -1.0, and 56 (21,9 %) had scores of ≤ -1.8 (Table 2).

3.3. Prevalent fractures

At the time of the study prevalent fragility fractures were documented in only eleven of the 256 patients (4.2 %), who had a median age of 76.6 (range 58.9–83.8) years (Table 1). Four patients had one or more radiologically confirmed clinical vertebral fracture (respectively one,

Table 1
Patient demographics.

	All Patients	Normal BMD	Osteopenia	Osteoporosis	Normal BMD vs. osteopenia	Normal BMD vs. osteoporosis	Normal BMD vs. osteoporosis/ osteopenia	Fragility Fractures#
	N = 256	*N* = 93 (36.3 %)	*N* = 136 (53.1 %)	*N* = 27 (10.5 %)				*N* = 11 (4.29 %)
Patient Characteristics Mean ± SD Median (range)								
Age at time of bone measurements (yrs)	70.9 ± 6.6 71.3 (53.6–89.5)	69.1 ± 6.5 70.3 (53.6–86.7)	71.4 ± 6.4 72.1 (54.9–89.5)	74.0 ± 6.3 74.7 (58.9–85.2)	$p = 0.007$	$p = 0.001$	$p = 0.001$	75.5 ± 6.8 76.6 (58.9-83.8)
Time between primary treatment for PCa and bone measurements (yrs)	3.2 ± 3.1 2.4 (0–17.5)	2.9 ± 2.7 1.9 (0–11.7)	3.3 ± 3.3 2.4 (0.0–17.5)	1.56 ± 0.7 2.0 (0–4.0)	NS	NS	NS	4.5 ± 4.8 3.7 (0.2-17.4)
BMI (kg/m^2)	27.1 ± 3.3 26.9 (20.1–37.4)	28.1 ± 3.1 27.8 (22.3–35.9)	26.7 ± 3.2 26.5 (20.1–37.4)	25.4 ± 3.3 24.7 (20.5–33.3)	$p = 0.002$	$p < 0.001$	$p < 0.001$	27.2 ± 2.5 26.5 (22.9-30.3)
Risk factors								
Corticosteroid use *N* (%)	14 (5.5)	3 (21.4)	11 (78.6)	0 (0.0)	NS	NS	NS	1 (9.1)
Smoking *N* (%)	32 (12.6)	13 (40.6)	17 (53.1)	2 (6.3))	NS	NS	NS	1 (9.1)
Alcohol abuse (≥3 units/day) *N* (%)	60 (23.8)	30 (50)	27 (45)	3 (5)	$p = 0.03$	$p = 0.03$	$p = 0.01$	4 (36.4)
Local treatment *N* (%)	238 (93.0)							
Radical prostatectomy *N* (%)	33 (12.9)	16 (48.5)	15 (45.5)	2 (6.0)				
EBRT *N* (%)	182 (71.1)	61 (33.5)	100 (54.9)	21 (11.5)				
Brachytherapy *N* (%)	23 (9.0)	10 (43.5)	11 (47.8)	2 (8.7)				
No prior ADT *N* (%)	40 (15.6)	19 (47.5)	19 (47.5)	2 (5.0)	NS	NS	NS	0 (0.0)
Current ADT N (%)	134 (52.3)	49 (36.6)	70 (52.2)	15 (11.2)	NS	NS	NS	7
<12 months N (%)	59 (23.0)	22 (37.3)	31 (52.5)	6 (10.2)	NS	NS	NS	1
12–36 months N (%)	75 (29.3)	27 (36.0)	39 (52.0)	9 (12.0)	NS	NS	NS	6
Past "ever" ADT N (%)**	82 (32.0)	25 (30.5)	47 (57.3)	10 (12.2)	NS	NS	NS	4
Prior use of bone protective agents								
Bisphosphonates (oral) N (%)	5 (2.0)	1 (20)	3 (60)	1 (20)	NS	NS	NS	1 (9.1)

PCa prostate cancer, ADT androgen deprivation therapy, EBRT External beam radiotherapy.
Normal BMD: DXA T-score > −1 at femoral neck and lumbar spine; Osteopenia: DXA −2.5 < T-score < −1 in femur and/or lumbar spine; Osteoporosis: DXA T-score ≤ −2.5 in femur and/or lumbar spine DXA-measurements.
Obesity defined by a BMI > 30 kg/m^2.
**ADT treatment period usually 3 years.
#Eighteen patients (7.0 %) were unwilling or unable to receive any form of local treatment and received ADT only.
Reasons for (oral) bisphosphonate therapy: known osteoporosis (*N* = 2), rheumatoid arthritis (*N* = 1), or unknown (*N* = 2).
#Two (18.1 %) of the 11 patients with fragility fractures, had osteoporosis; one at the LS, another at the FN. Three of the 11 patients with fractures had slightly elevated P1NP, whereas all 11 patients had β-CTX measurements in the normal range.

Table 2
Frequencies of patients without (DXA T-scores > − 2.5) and with osteoporosis (DXA T-scores ≤ − 2.5) at LS, FN or either LS or FN according to QUS T-score thresholds 0, − 1.0 and − 1.8.

			Calcaneal QUS*						
			T-score > 0	T-score ≤ 0	T-score > −1.0	T-score ≤ −1.0	T-score > −1.8	T-score ≤ −1.8	Total
DXA measurements	LS	T-score > −2.5 (*N*)	84	155	144	95	193	46	239
		T-score ≤ −2.5 (*N*)	2	15	4	13	7	10	17
	FN	T-score > −2.5 (*N*)	83	158	143	98	194	47	241
		T-score ≤ −2.5 (*N*)	3	12	5	10	6	9	15
	LS and/or FN	T-score > −2.5 (*N*)	82	147	141	88	189	40	229
		T-score ≤ −2.5 (*N*)	4	23	7	20	11	16	27
		Total	86	170	148	108	200	56	256

QUS quantitative ultrasonography, DXA dual-energy absorptiometry, LS Lumbar spine, FN Femoral neck, NPV negative predictive value, PPV positive predictive value.
* For QUS of the left calcaneus and for DXA BMD of the Femoral Neck the lowest T-score value of either left or right hip was used (in patients with a hip replacement, the contralateral hip was used).

two, three and 4 vertebral fractures), one had a hip fracture in addition to 2 VFs and 4 rib fractures. Five patients had sustained non-vertebral fractures (humerus, femur, pelvis, ribs, shoulder). These fragility fractures were observed in 7 (5.2 %) of patients currently treated with ADT, of whom one (1.6 %) was on ADT for <12 months, and six (7.5 %) had been on ADT treatment for up to 3 years. Four of the fractures (4.8 %) occurred in patients who had ever received ADT before the start of the study (Table 1). Only three of the 11 patients had a DXA T-score of ≤ − 2.5, one at LS, and two at FN), whereas 4 of the remaining 8 patients had a T score of ≤ − 2. Median QUS T score of patients with a prevalent fracture was −2.10, range − 3.40 to 3.80. Nine of 11 patients had a QUS T-score < 0, and six had a QUS T-score ≤ − 2.0 (range − 3.40 to −2.10).

3.4. Laboratory measurements

Serum PSA, alkaline phosphatase and LDH concentrations were all

within the normal range, in keeping with non-metastatic PCa disease in state of remission (data not shown). Patients with osteoporosis had significantly abnormal gonadal hormone levels compared to those with normal BMD: respective mean ± SD for LH (4.0 ± 5.5 vs 2.1 ± 3.1; $p = 0.04$), estradiol (27.4 ± 17.4 vs. 40.2 ± 26.3; $p = 0.009$) and testosterone (3.7 ± 5.2 vs. 7.0 ± 8.6; $p = 0.03$).

All 11 patients with documented fractures had normal β-CTX measurements, 3 had slightly elevated P1NP levels (data not shown). Serum concentrations of P1NP and β-CTX did not differ significantly between patients with osteoporosis/osteopenia and those with normal BMD (data not shown).

3.5. Receiver operating curve (ROC)

There was a moderate correlation between T-scores as measured by calcaneal QUS and DXA T-score at the LS ($r = 0.43$; $p < 0.001$) and at the FN ($r = 0.46$; $P < 0.001$).

3.6. Predictive value of QUS for osteoporosis

Frequencies of patients with normal BMD or osteopenia compared to those with osteoporosis (DXA T-scores ≤ − 2.5) at LS and/or FN and corresponding distribution of three different QUS T-score thresholds 0, −1.0 and − 1.8 are shown in Table 2.

The NPVs and PPVs for the three QUS T-score thresholds of 0. -1.0 and − 1.8 are shown in Table 3. All NPVs for osteoporosis at either LS and/or FN were ≥ 94.5 % and did not change significantly when varying the QUS T-score threshold value between 0 and − 1.8 (Table 3). In contrast, PPV for osteoporosis was only <25 % at any QUS T-score. A QUS threshold of −1.0 to 0.0 would thus result in a 34.0 to 57.8 % (up to two-third) reduction in the number of DXA measurements required to diagnose osteoporosis in patients currently using or having ever received ADT for the management of their non-metastatic PCa.

ROC curves were constructed for QUS T-scores using DXA T-scores of ≤ − 2.5, and of ≤ − 2.0). The latter are shown in Fig. 1 respectively for lumbar spine (left panel; AUC 0.731, *P* value <0.001), for femoral neck (middle panel; AUC 0.753, *p* value 0.002), and for any site (right panel; AUC 0.725, p value <0.001). The area under the curve (AUC) for QUS T scores using DXA T-score of ≤2.5 was not different between the DXA sites measured, with an AUC of 0.739, p value <0.001 for the lumbar spine; an AUC of 0.753, $p = 0.753$ for the femoral neck; and an or AUC of 0.725, $p < 0.001$ for any site:

4. Discussion

The high worldwide prevalence of PCa, the inclusion of ADT in most of its treatment protocols, and the likelihood for ADT-induced hypogonadism to increase the risk for osteoporosis and fragility fractures dictate that skeletal health should be evaluated at the start of treatment with ADT, and for treatment for osteoporosis to be initiated as required. Recommendations to this effect have indeed been issued in urological and oncological guidelines in the form of advice to perform a baseline DXA at initiation of ADT. These recommendations remain unfortunately poorly adhered to in day-to-day clinical practice, with osteoporosis screening remaining a significantly unmet need in patients treated with ADT. DXA measurements are the gold standard for osteoporosis screening (Hernlund et al., 2013), but the investigation is relatively expensive, not always (readily) available, and fragility fractures may occur at T-scores thresholds higher than the operational diagnostic threshold for osteoporosis of ≤ − 2.5, particularly in the presence of factors potentially also affecting bone quality such as ADT-induced hypogonadism. On the other hand, calcaneal quantitative ultrasonography (QUS) has been shown to be a practical, easy to use, readily accessible, radiation-free, simple to administer, and less costly tool than DXA, with the performance of a number of devices favourably comparing with that of DXA bone densitometry at lumbar spine and proximal femur in a number of studies in post-menopausal women with osteoporosis (Nayak et al., 2011; Glüer et al., 2004; Boonen et al., 2005; Hans and Baim, 2017; Hans et al., 2022).

Further studies showed that QUS was at least comparable to DXA for predicting fractures in healthy men and women. In two 10-year prospective studies, one including 3,888 postmenopausal women, the second including 1,511 men and women aged ≥ 65 years, QUS was shown to be able to predict future "osteoporotic" fractures equally or better compared to DXA (Moayyeri et al., 2009; Stewart et al., 2005). In another study of osteoporotic fractures conducted in 5,607 men aged ≥ 65 years recruited from six US centres, QUS measurements predicted the risk of hip, and any non-vertebral fracture in older men, nearly as well as hip BMD measurements, although combined measurements of QUS and BMD were not superior to either measurement alone (Bauer et al., 2007).

QUS could thus potentially represent an attractive alternative outpatient pre-screening strategy for osteoporosis in patients with ADT-treated non-metastatic PCa, by allowing targeting of DXA screening to patients most likely to have the disorder. This would reduce the number of unnecessarily referrals for this investigation, and promisingly overcome the logistics, time demands, and economic barriers attached to the current strategies for screening for osteoporosis in these patients.

Our retrospective study design was cross-sectional, including all patients with non-metastatic PCa seen in our out-patient clinic in the designated time period, most of whom had been treated with ADT for varying periods prior to the study, or were currently receiving this treatment, which increased the likelihood of the presence of osteopenia/osteoporosis and increased fracture risk.

Our main objective in this scenario was to explore the performance of QUS compared to the gold standard of DXA performed at the same time. The ability of QUS to identify ADT-treated non-metastatic PCa patients with high or low likelihood for osteoporosis as defined by DXA WHO criteria of BMD T-scores of ≤ − 2.5, and those potentially at risk for fracture at a higher T-score threshold of ≤ − 2.0 would enable to establish the QUS cut-off T-score threshold correlating best with these DXA T-scores, and allow the targeted selection of patients requiring DXA referral for screening for osteoporosis.

Applying device-specific QUS T-score thresholds between 0 and − 1 established a threshold level high enough to rule out osteoporosis in non-metastatic PCa patients, with NPVs for DXA-based osteoporosis at any site being ≥ 94.5 %, translating in significantly limiting the need for referral for a diagnostic DXA for osteoporosis in up to two-third of patients, with an acceptable low osteoporosis misclassification rate of <6 %.

To our knowledge, this is the second only study addressing the value of QUS compared to DXA in the diagnosis of osteoporosis in PCa patients. A previous study conducted in 60 PCa patients showed that a QUS threshold T-score ≤ −0.5 would avoid performing 21 (35 %) of DXA scans at the cost of missing one case (5.6 %) compared with DXA T-score of ≤ − 2.0 (NPV 95 %) (van Casteren-Messidoro et al., 2014).

Table 3
Negative and positive predictive values for DXA T-score ≤ −2.5 for three QUS T-score thresholds.

	DXA T-score ≤ −2.5		Calcaneal QUS		
			T-score ≤ 0	T-score ≤ −1	T-score ≤ −1.8
DXA	LS osteoporosis	NPV	97.7 %	97.3 %	96.5 %
		PPV	8.8 %	12.0 %	15.2 %
	FN osteoporosis	NPV	97.7 %	96.6 %	97.0 %
		PPV	8.8 %	9.3 %	13.8 %
	LS and/or FN osteoporosis	NPV	95.3 %	95.3 %	94.5 %
		PPV	13.5 %	18.5 %	22.2 %

QUS quantitative ultrasonography, DXA dual-energy absorptiometry, LS Lumbar spine, FN Femoral neck, NPV negative predictive value, PPV positive predictive value. Details of DXA T score of ≤ − 2.0 as shown by Receiver operating characteristic (ROC) curves are shown in Fig. 1.

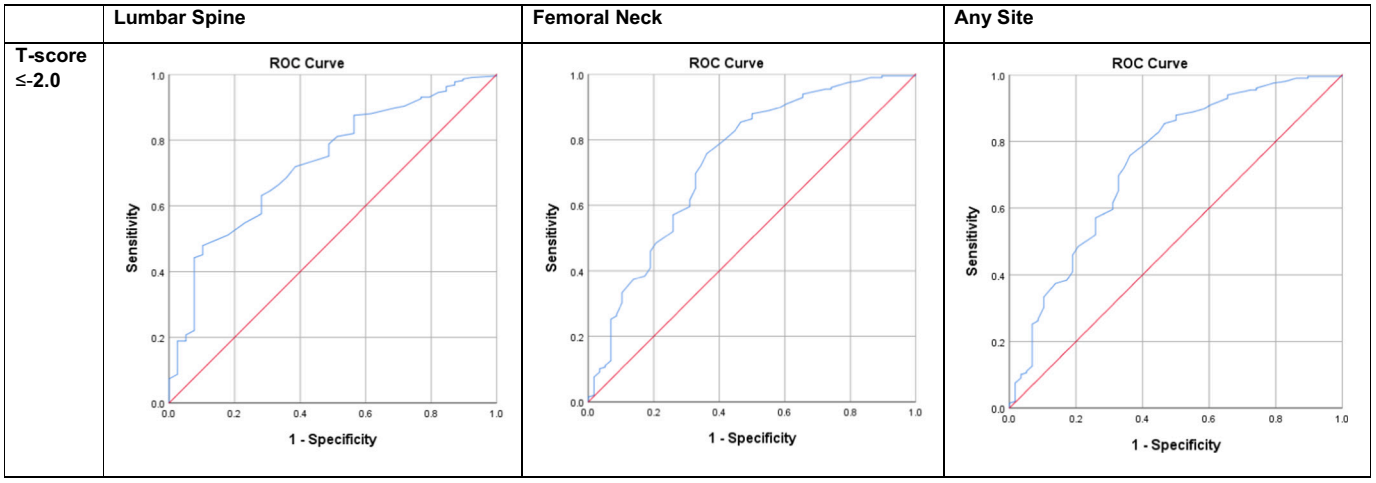

Fig. 1. Receiver operating characteristic (ROC) curves for DXA T score of ≤ -2.0.
Receiver operating characteristic (ROC) curves for DXA T score of ≤ -2.0. Details of DXA T score of ≤ -2.5 shown in Table 3.
The Figure displays ROC curves for Lumbar Spine (left panel; AUC 0.731, *P* value <0.001, and 95 % CI 0.65–0.81), Femoral Neck (middle panel, AUC 0.736, P value <0.001 and 95 % CI 0.66–0.81) and Any Site (right panel; AUC 0.736, P value 0.001, and 95 % CI 0.66–0.81).
The diagonal line indicates a reference area under the curve (AUC) of 0.50 (no better than chance alone).
ROC curves for DXA T score of ≤ -2.5 are not different.

Data from our cross-sectional study, conducted in a much larger cohort of non-metastatic PCa patiens suggests that QUS represents an attractive pre-screen tool to identify patients with low likelihood for osteoporosis, thus decreasing the need for referral for DXA screening by up to two-third. On the other hand, our data also clearly show that the low positive predictive value of QUS for osteoporosis (< 25 %) indicates that this tool lacks specificity for osteoporosis, thus precluding its use as surrogate for DXA screening for osteoporosis in these patients.

Our cross-sectional study has strengths as well as limitations. Its main strength is the relatively large cohort of strictly non-metastatic PCa patients studied, who were treated in a single centre, using standardized protocols following international guidelines, the majority of whom were at risk for osteoporosis and fractures due to possible ADT-induced hypogonadism, and all of whom had DXA and QUS investigations at less than a week interval. Exclusion of metastatic PCa disease is also a strength of our study, as it avoids potentially falsely increased BMD measurements at lumbar spine and/or femoral neck, due to mostly osteoblastic PCa metastases frequently harboured at these sites (~90 % of cases). In contrast, calcaneal QUS measurements remain unaffected by metastatic disease as calcaneal bone is a very rare site for bone metastases in PCa.

Our study also has limitations, the main of which was the low number of prevalent fractures at the time of initial evaluation, which may have underestimated the actual number of vertebral fractures, as thoracic and lumbar spinal radiology was not systematically performed at the time of the cross-sectional evaluation or at any time thereafter, so that silent non-clinical vertebral fractures, which often occur in patients with secondary osteoporosis may have been missed. These limitations precluded reaching any reliable conclusion on the value of DXA, QUS or a combination of both in predicting fracture risk in patients with non-metastatic PCa at high risk for these fractures because of ADT-associated hypogonadism. A further general limitation of the study is that QUS instruments have a relatively high coefficient of variation, and that consequently, results obtained using a specific device may not be extrapolated to another device, or to absolute QUS device thresholds (Njeh et al., 2001).

Notwithstanding, in this study, we used the FDA-approved Lunar Achilles QUS device, which uses the conventional speed of sound technology, which has remained largely unchanged over the years since our data was collected. This device stood the test of time and is one of a small number of currently used QUS heel devices, which have been most tested, most cross-validated and have the most clinical applications.

In conclusion, osteoporosis screening remains a significant unmet need in PCa patients treated with ADT, and QUS may represent a valuable alternative pre-screening strategy to overcome logistics, time demands, and economic barriers of current strategies for osteoporosis screening. Our data from this relatively large cohort study in ADT-treated non-metastatic PCa patients provide evidence that although QUS may not be used for the diagnosis of osteoporosis as traditionally defined by WHO criteria, this tool represents a simple, convenient, more economical tool, confidently identifying patients with low likelihood for osteoporosis. This outcome translates in a significant reduction in the number of patients requiring DXA screening for osteoporosis by up to two-third, with an acceptable low osteoporosis misclassification of 6 %. The potential ability of QUS to measure a feature of bone quality predictive of fracture risk not captured by DXA BMD measurements remains to be established in future studies specifically designed to address this interesting issue.

CRediT authorship contribution statement

Conceptualization: Susanne Osanto, Rob C.M. Pelger; Investigation: Bart B. Nieuwkamer, Josine P.M. Vrouwe, Melianthe P.J. Nicolai; Data curation, formal analysis, and methodology: Bart B. Nieuwkamer, Peter-Paul M. Willemse, Josine P.M. Vrouwe, Melianthe P.J. Nicolai, Rob F.M. Bevers, Rob C.M. Pelger, Neveen A.T. Hamdy, Susanne Osanto; Validation: Neveen A.T. Hamdy, Susanne Osanto; Project administration and supervision: Rob C.M. Pelger, Neveen A.T. Hamdy, Susanne Osanto; Roles/Writing - Original Draft: Bart B. Nieuwkamer, Josine P.M. Vrouwe; Writing - Review & Editing: Bart B. Nieuwkamer, Josine P.M. Vrouwe, Peter-Paul M. Willemse, Melianthe P.J. Nicolai, Rob F.M. Bevers, Rob C.M. Pelger, Neveen A.T. Hamdy, Susanne Osanto.

Final approval of manuscript

All authors have read and approved the final manuscript.

Declaration of competing interest

Bart Nieuwkamer, Josine Vrouwe, Peter-Paul Willemse, Meliante Nicolai, Rob Bevers, Rob Pelger, Neveen Hamdy and Susanne Osanto declare they have no conflict of interest related to the conduct of the

study and writing of the manuscript.

Data availability

The authors do not have permission to share data.

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References

Alibhai, S.M.H., Zukotynski, K., Walker-Dilks, C., Emmenegger, U., Finelli, A., Morgan, S. C., Hotte, S.J., Winquist, E., 2017. Bone health and bone-targeted therapies for prostate cancer: a programme in evidence-based care Cancer Care Ontario clinical practice guideline. Clin. Oncol. 29, 348–355. https://doi.org/10.1016/j.clon.2017.01.007.

el Badri, S.A.M., Salawu, A., Brown, J.E., 2019. Bone health in men with prostate cancer: review article. Curr. Osteoporos. Rep. 17, 527–537. https://doi.org/10.1007/s11914-019-00536-8.

Bauer, D.C., Ewing, S.K., Cauley, J.A., Ensrud, K.E., Cummings, S.R., Orwoll, E.S., 2007. Quantitative ultrasound predicts hip and non-spine fracture in men: the MrOS study. Osteoporos. Int. 18, 771–777. https://doi.org/10.1007/s00198-006-0317-5.

Binkley, N., Adler, R., Bilezikian, J.P., 2014. Osteoporosis diagnosis in men: the T-score controversy revisited. Curr. Osteoporos. Rep. 12, 403–409. https://doi.org/10.1007/s11914-014-0242-z.

Bolla, M., Descotes, J.-L., Artignan, X., Fourneret, P., 2007. Adjuvant treatment to radiation: combined hormone therapy and external radiotherapy for locally advanced prostate cancer. BJU Int. 100, 44–47. https://doi.org/10.1111/j.1464-410X.2007.06954.x.

Boonen, S., Nijs, J., Borghs, H., Peeters, H., Vanderschueren, D., Luyten, F.P., 2005. Identifying postmenopausal women with osteoporosis by calcaneal ultrasound, metacarpal digital X-ray radiogrammetry and phalangeal radiographic absorptiometry: a comparative study. Osteoporos. Int. 16, 93–100. https://doi.org/10.1007/s00198-004-1660-z.

van Casteren-Messidoro, C., Huisman, A.M., Birnie, E., van Gelder, M., van de Geijn, F.E., Hamberg, P., 2014. Quantitative ultrasound of the heel as triage test to measure bone mineral density compared with dual energy X-ray absorptiometry in men with prostate cancer commencing with androgen deprivation therapy. Neth. J. Med. 72, 528–532 (accessed August 14, 2017). http://www.ncbi.nlm.nih.gov/pubmed/26219758.

Clynes, M.A., Harvey, N.C., Curtis, E.M., Fuggle, N.R., Dennison, E.M., Cooper, C., 2020. The epidemiology of osteoporosis. Br. Med. Bull. 133, 105–117. https://doi.org/10.1093/bmb/ldaa005.

Coleman, R., Body, J.J., Aapro, M., Hadji, P., Herrstedt, J., 2014. Bone health in cancer patients: ESMO clinical practice guidelines † on behalf of the ESMO Guidelines Working Group *. In: ESMO Updated Clinical Practice Guidelines, 25, pp. iii124–iii137. https://doi.org/10.1093/annonc/mdu103.

Cornford, P., van den Bergh, R.C.N., Briers, E., van den Broeck, T., Cumberbatch, M.G., de Santis, M., Fanti, S., Fossati, N., Gandaglia, G., Gillessen, S., Grivas, N., Grummet, J., Henry, A.M., van der Kwast, T.H., Lam, T.B., Lardas, M., Liew, M., Mason, M.D., Moris, L., Oprea-Lager, D.E., van der Poel, H.G., Rouvière, O., Schoots, I.G., Tilki, D., Wiegel, T., Willemse, P.P.M., Mottet, N., 2020. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II—2020 update: treatment of relapsing and metastatic prostate cancer, eur urol. https://doi.org/10.1016/j.eururo.2020.09.046.

Dalla Via, J., Daly, R., Owen, P., Mundell, N., Rantalainen, T., Fraser, S., 2019. Bone mineral density, structure, distribution and strength in men with prostate cancer treated with androgen deprivation therapy. Bone 127, 367–375. https://doi.org/10.1016/J.BONE.2019.06.005.

Damji, A.N., Bies, K., Alibhai, S.M.H., Jones, J.M., 2015. Bone health management in men undergoing ADT: examining enablers and barriers to care. Osteoporos. Int. 26, 951–959. https://doi.org/10.1007/s00198-014-2997-6.

Glüer, C.C., Eastell, R., Reid, D.M., Felsenberg, D., Roux, C., Barkmann, R., Timm, W., Blenk, T., Armbrecht, G., Stewart, A., Clowes, J., Thomasius, F.E., Kolta, S., 2004. Association of five quantitative ultrasound devices and bone densitometry with osteoporotic vertebral fractures in a population-based sample: the OPUS study. journal of bone and mineralResearch 19, 782–793. https://doi.org/10.1359/jbmr.040304.

Greenspan, S.L., Coates, P., Sereika, S.M., Nelson, J.B., Trump, D.L., Resnick, N.M., 2005. Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. J. Clin. Endocrinol. Metab. 90, 6410–6417. https://doi.org/10.1210/jc.2005-0183.

Hans, D., Baim, S., 2017. Quantitative ultrasound (QUS) in the management of osteoporosis and assessment of fracture risk. J. Clin. Densitom. 20, 322–333. https://doi.org/10.1016/J.JOCD.2017.06.018.

Hans, D., Métrailler, A., Gonzalez Rodriguez, E., Lamy, O., Shevroja, E., 2022. Quantitative ultrasound (QUS) in the Management of Osteoporosis and Assessment of fracture risk: an update. Adv. Exp. Med. Biol. 1364, 7–34. https://doi.org/10.1007/978-3-030-91979-5_2.

Heidenreich, A., Witjes, W.P.J., Bjerklund-Johansen, T.E., Patel, A., for the E.R. EAU Research Foundation, 2012. Therapies used in prostate cancer patients by European urologists: data on indication with a focus on expectations, perceived barriers and guideline compliance related to the use of bisphosphonates. Urol. Int. 89, 30–38. https://doi.org/10.1159/000338810.

Hernlund, E., Svedbom, A., Ivergård, M., Compston, J., Cooper, C., Stenmark, J., McCloskey, E.V., Jönsson, B., Kanis, J.A., 2013. Osteoporosis in the European Union: medical management, epidemiology and economic burden. Arch Osteoporos. 8, 136. https://doi.org/10.1007/s11657-013-0136-1.

Hu, J., Aprikian, A.G., Vanhuyse, M., Dragomir, A., 2020. Contemporary population-based analysis of bone mineral density testing in men initiating androgen deprivation therapy for prostate cancer. J. Natl. Compr. Cancer Netw. 18, 1374–1381. https://doi.org/10.6004/jnccn.2020.7576.

Johnell, O., Kanis, J.A., Oden, A., Johansson, H., de Laet, C., Delmas, P., Eisman, J.A., Fujiwara, S., Kroger, H., Mellstrom, D., Meunier, P.J., Melton, L.J., O'Neill, T., Pols, H., Reeve, J., Silman, A., Tenenhouse, A., 2007. Predictive value of BMD for hip and other fractures. J. Bone Miner. Res. 22, 774. https://doi.org/10.1359/JBMR.050304.

Kanis, J.A., Bianchi, G., Bilezikian, J.P., Kaufman, J.-M., Khosla, S., Orwoll, E., Seeman, E., 2011. Towards a diagnostic and therapeutic consensus in male osteoporosis. Osteoporos. Int. 22, 2789–2798. https://doi.org/10.1007/s00198-011-1632-z.

Looker, A.C., Borrud, L.G., Hughes, J.P., Fan, B., Shepherd, J.A., Melton, L.J., 2012. Lumbar spine and proximal femur bone mineral density, bone mineral content, and bone area: United States, 2005–2008. Vital Health Stat 11 Mar 251, 1–132.

Lowrance, W.T., Breau, R.H., Chou, R., Chapin, B.F., Crispino, T., Dreicer, R., Jarrard, D. F., Kibel, A.S., Morgan, T.M., Morgans, A.K., Oh, W.K., Resnick, M.J., Zietman, A.L., Cookson, M.S., 2020. Advanced prostate cancer: AUA/ASTRO/SUO guideline PART I. J. Urol. https://doi.org/10.1097/ju.0000000000001375.

Moayyeri, A., Kaptoge, S., Dalzell, N., Bingham, S., Luben, R.N., Wareham, N.J., Reeve, J., Khaw, K.T., 2009. Is QUS or DXA better for predicting the 10-year absolute risk of fracture? journal of bone and mineralResearch 24, 1319–1325. https://doi.org/10.1359/jbmr.090212.

Morote, J., Planas Morin, J., Orsola, A., Abascal, J.M., Salvador, C., Trilla, E., Raventos, C.X., Cecchini, L., Encabo, G., 2007. Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. J. Reventos 69, 500–504. https://doi.org/10.1016/j.urology.2006.11.002.

Mottet, N., Bellmunt, J., Bolla, M., Joniau, S., Mason, M., Matveev, V., Schmid, H.-P., van der Kwast, T., Wiegel, T., Zattoni, F., Heidenreich, A., 2011. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur. Urol. 59, 572–583. https://doi.org/10.1016/J.EURURO.2011.01.025.

Mottet, N., van den Bergh, R.C.N., Briers, E., van den Broeck, T., Cumberbatch, M.G., de Santis, M., Fanti, S., Fossati, N., Gandaglia, G., Gillessen, S., Grivas, N., Grummet, J., Henry, A.M., van der Kwast, T.H., Lam, T.B., Lardas, M., Liew, M., Mason, M.D., Moris, L., Oprea-Lager, D.E., van der Poel, H.G., Rouvière, O., Schoots, I.G., Tilki, D., Wiegel, T., Willemse, P.-P.M., Cornford, P., 2021. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate Cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur. Urol. 79, 243–262. https://doi.org/10.1016/J.EURURO.2020.09.042.

Nayak, S., Roberts, M.S., Greenspan, S.L., 2011. Cost-effectiveness of different screening strategies for osteoporosis in postmenopausal women. Ann. Intern. Med. 155, 751–761. https://doi.org/10.7326/0003-4819-155-11-201112060-00007.

Njeh, C.F., Hans, D., Li, J., Fan, B., Fuerst, T., He, Y.Q., Tsuda-Futami, E., Lu, Y., Wu, C. Y., Genant, H.K., 2001. Comparison of six calcaneal quantitative ultrasound devices: precision and hip fracture discrimination. Osteoporos. Int. 11, 1051–1062. https://doi.org/10.1007/s001980070027.

Parker, C., Castro, E., Fizazi, K., Heidenreich, A., Ost, P., Procopio, G., Tombal, B., Gillessen, S., 2020. ESMO guidelines committee. Electronic address: clinicalguidelines@esmo.Org, prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 31, 1119–1134. https://doi.org/10.1016/j.annonc.2020.06.011.

Sanda, M.G., Cadeddu, J.A., Kirkby, E., Chen, R.C., Crispino, T., Fontanarosa, J., Freedland, S.J., Greene, K., Klotz, L.H., Makarov, D.V., Nelson, J.B., Rodrigues, G., Sandler, H.M., Taplin, M.E., Treadwell, J.R., 2018. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. Journal of Urology 199, 683–690. https://doi.org/10.1016/j.juro.2017.11.095.

Saylor, P.J., Rumble, R.B., Michalski, J.M., 2020. Bone health and bone-targeted therapies for prostate cancer: American Society of Clinical Oncology endorsement summary of a Cancer Care Ontario guideline. JCO Oncol Pract. 16, 389–393. https://doi.org/10.1200/JOP.19.00778.

Schuit, S.C.E., van der Klift, M., Weel, A.E.A.M., de Laet, C.E.D.H., Burger, H., Seeman, E., Hofman, A., Uitterlinden, A.G., van Leeuwen, J.P.T.M., Pols, H.A.P., 2004. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam study. Bone 34, 195–202. https://doi.org/10.1016/J.BONE.2003.10.001.

Shahinian, V.B., Kuo, Y.-F., Freeman, J.L., Goodwin, J.S., 2005. Risk of fracture after androgen deprivation for prostate cancer. N. Engl. J. Med. 352, 154–164. https://doi.org/10.1056/NEJMoa041943.

Siegel, R.L., Miller, K.D., Jemal, A., 2020. Cancer statistics, 2020. CA Cancer J. Clin. 70, 7–30. https://doi.org/10.3322/caac.21590.

Smith, M., Boyce, S., Moyneur, E., Duh, M., Raut, M., Brandman, J., 2006. Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. J. Urol. 175, 136–139. https://doi.org/10.1016/S0022-5347(05)00033-9.

Stewart, A., Kumar, V., Reid, D.M., 2005. Long-term fracture prediction by DXA and QUS: a 10-year prospective study. journal of bone and mineralResearch. 21, 413–418. https://doi.org/10.1359/JBMR.051205.

WHO scientific group on the assessment of osteoporosis at primary health care level, 2004. Summary Meeting Report, Brussels. https://www.dur-a-avaler.com/wp-content/uploads/2015/04/WHO-2004-Osteoporosis.pdf. (Accessed 24 October 2022).