Bone and joint disorders: screening and early clinical drug development

Vrouwe, J.P.M.

CHAPTER 3

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

J.P.M. Vrouwe[1,2], B.B. Nieuwkamer[1,3], P.M. Willemse[4], M.P.J. Nicolai[5,6], R.F.M. Bevers[5], R.C.M. Pelger[5], N.A.T. Hamdy[7], S. Osanto[1]

B.B. Nieuwkamer and J.P.M. Vrouwe contributed equally

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1 Leiden University Medical Center (LUMC), Leiden, NL – *Department of Medical Oncology*
2 Centre for Human Drug Research (CHDR), Leiden, NL
3 Reinier de Graaf Hospital (RdGG), Delft, NL – *Department of Urology*
4 University of Utrecht (UMCU), Utrecht, NL – *Department of Urology*
5 Leiden University Medical Center (LUMC), NL – *Department of Urology*
6 Netherlands Cancer Institute, NL – *Department of Urology*
7 Leiden University Medical Center, NL – *Department of Medicine, Division of Endocrinology, and Center for Bone Quality*

ABSTRACT

PURPOSE 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 undertreated. In this study, we examine the value of pre-screening calcaneal QUS in the identification of patients who should be referred for screening for osteoporosis using dual-energy X-Ray absorptiometry (DXA).

PATIENTS AND METHODS In a single-center cross-sectional study, all non-metastatic PCa patients attending our Uro-Oncological Clinic between 2011-2013 had DXA and calcaneal QUS measurements to assess positive (PPV) and negative (NPV) predictive value of QUS in identifying DXA-diagnosed osteoporosis (T-scores ≤2.5 and ≤-2) at lumbar spine and/or femoral neck by analysis of receiver operating characteristic curves at QUS T-scores 0, -1.0, and -1.8

RESULTS We studied 256 patients, median age 70.9 (53.6-89.5) years, 93.0% of whom had local treatment and 84.4% ADT. Prevalence of osteoporosis and osteopenia was respectively 10.5% and 53%. Mean QUS T-score was -0.54±1.58. Whereas PPV of any QUS T-score was <25%, QUS T-scores between -1.0 and 0.0 had a NPV of ≥94.5% for DXA T-scores ≤2.5 and ≤-2 at any site, ruling out osteoporosis and significantly reducing the number of patients requiring DXA screening by up to two-third.

CONCLUSION Calcaneal QUS is an easy, inexpensive pre-screen tool with an excellent NPV for osteoporosis for osteoporosis in non-metastatic PCa. Pre-screening PCa patients with QUS allows the safe and cost-effective limitation of referrals for unnecessary DXA by confidently identifying patients least likely to have osteoporosis.

Introduction

Prostate cancer (PCa) is the second most common cancer in men worldwide, most frequently diagnosed above the age of 65 years.[1] Androgen deprivation therapy (ADT) is the mainstay of treatment for localized, locally advanced, as well as metastatic PCa[2,3], with treatment duration varying from <3 years to life-long depending on the stage of the disease.[2-4] ADT effectively prolongs overall survival[5] but is always associated with a rapid decline in circulating gonadal hormones, in addition to the expected age-related decrease in gonadal function. This results in a disruption in bone remodelling, a decrease in bone mass and a deterioration in bone microarchitecture, and associated increased risk of fracture.[6-8] Evidence from prospective studies show a significant decrease in bone mineral density (BMD) in the range of 2.4% to 5.6%, observed as early as 6 months and maximal in the first year of treatment with ADT,[9-12] with continuing further decreases in BMD on continuing treatment. The prevalence of osteoporosis has thus been reported to be 49% after 4 years of treatment, 66% after 8 years, and 81% after 10 or more years on continuous ADT.[10] 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 those who do receive this treatment.[13,14] It has been suggested that treatment with bisphosphonates may prevent the extent of BMD loss.[11,12]

Dual-energy X-ray absorptiometry (DXA) is the gold standard for screening for osteoporosis, with the World Health Organization (WHO) reference standard for the diagnosis of osteoporosisoutcomes expressed as T-scores, representing standard deviations from the mean in a young female adult reference population (NHANES).[15,16] WHO criteria are used for the diagnosis of osteoporosis (T-score ≤2.5) at the femoral neck (FN) and lumbar spine (LS) and to respectively predict osteoporotic hip- and vertebral fractures.[17,18]

For long, there had been no clear urological or medical oncological guidelines for screening bone health in PCa patients at the start or during treatment with ADT,[19,20] until data from large cohort studies prompted awareness for the increased fracture risk observed in PCa patients undergoing this treatment.[13,14] Although current Urological and oncological Societies' guidelines clearly recommend bone health surveillance using DXA in patients with PCa at the start of ADT,[2,3,21,22] and the higher rates of osteoporosis and fragility fractures translate in increased morbidity, mortality and socio-economic burden in these patients,[23] it appears that bone health monitoring

still does not meet current guideline recommendations in patients with PCa who are treated with ADT.[24–26]

Surveys conducted among urologists and oncologists revealed that physicians were not confident in screening for and managing osteoporosis in PCa patients.[24,25] 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 in 2000 to 23.4% studied in 2015, there is still an unmet need for improving the diagnosis of osteoporosis, perhaps by using alternative screening strategies to overcome logistic and economic barriers of current strategies for osteoporosis screening.[25] 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 holding several potential advantages over DXA measurements by being portable, radiation-free and inexpensive. QUS could thus represent a simple, quick outpatient tool to pre-screen patients with PCa for osteoporosis, saving operator and patients' time and costs by avoiding referral for unnecessary DXA investigations.[27] Whereas prescreening by QUS was found to be more cost-effective than screening with DXA in postmenopausal women,[28] there are to date no available data on the value of QUS in pre-screening large cohorts of PCa patients for osteoporosis.

The main objective of this study was to investigate the value of calcaneal QUS in identifying patients with non-metastatic PCa who require screening for osteoporosis using DXA, thus allowing the reduction of the number of unnecessary referrals for this investigation.

Patients and methods

PATIENT POPULATION

All patients with non-metastatic PCa treated with ADT who attended our Uro-oncological out-patient Clinic at the Leiden University Medical Center between November 2011 and May 2013 were included in this single centre cross-sectional study (Figure 1). Patients were treated for their prostate cancer using standardized protocols that followed up to date international guidelines.[29]

All patients studied underwent an evaluation of their bone health, which included DXA BMD and calcaneal QUS measurements, performed within a week of each other, and a venepuncture for laboratory investigations including gonadal status and bone turnover markers.

Demographic and clinical data were retrieved from the patients' electronic medical records and included medical history, history of fractures and documentation of prevalent fractures, fracture risk factors such as previous fracture, family history for hip fracture, corticosteroid use, secondary causes for osteoporosis, smoking and alcohol consumption and records of osteoporosis treatment such as bisphosphonates or denosumab and use of calcium and vitamin D supplementation.

A telephone survey was conducted in 2019 in PCa survivors, in an extension of the study, to collect follow-up information on incident new fractures sustained in the years since the initial cross-sectional evaluation, on current use of ADT, and on use of osteoporosis medication such as bisphosphonates, denosumab and calcium and vitamin D) (Figure 1).

BONE HEALTH EVALUATION

Bone mineral density measurements by 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),[15] which are compatible with those of a Dutch control 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. CV of the DXA measurements was established by repeated (approximately 1800) phantom measurements in our nuclear medicine department, leading to a CV of 2-3%, depending on the anatomic location. For all analyses, the left FN value (or contralateral hip in case of hip replacement) was used for all analyses. In addition to using the T-score of ≤2.5, the WHO operational definition of osteoporosis, 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 also compromising bone quality.[30,31]

Quantitative ultrasound scanning of the calcaneus

QUS was performed by a dedicated experienced nurse at the left calcaneus site using the FDA approved Lunar Achilles ultrasound device (GE Healthcare LUNAR, Madison, Wisconsin, USA), which has a coefficient of variation <2.0%. Measurements obtained included Speed Of Sound (SOS) expressed

in meters/sec 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 = (0.67×BUA) + (0.28×SOS) – 420). The LUNAR Achilles ultrasound device was calibrated at regular intervals, according to manufacturer's instructions.

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.

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 dossier.

Data on incident new fractures were obtained by telephone interview of PCa survivors at a fixed date spanning a week in 2019, between 5 and 7.5 years after initial evaluation. The date and type of the fracture and its radiological confirmation were retrieved from medical records when available.

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 >50nmol/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)

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 BMD T-score ≤2.5 -defined osteoporosis and BMD T-score ≤2.0.

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 < .05 was considered statistically significant.

Results

CROSS-SECTIONAL STUDY

Demographic data

Baseline characteristics of the 256 non-metastatic PCa patients studied, including age, body mass index and clinical risk factors for osteoporosis, 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 prior to the cross-sectional study (average 24 months): 44 patients (17.2%) had received ADT for less than 6 months, and 172 (67.2%) received ADT for a period of 6 to 36 months at the time of the evaluation, at which time only five patients (2%) were using a bisphosphonate ± calcium and vitamin D supplements as treatment for a documented osteoporosis (Table 1). Clinical risk factors for osteoporosis are also detailed in Table 1.

BONE MEASUREMENTS

DXA

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 the lumbar spine or the femoral neck: 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 the spine, and 58 (22.6%) at either left or right FN. Overall, 75 (29.2%) patients 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 not significantly different from the 216 patients who did.

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).

Prevalent fractures

Only eleven of the 256 patients (4.2%), median age 76.6 (range 58.9-83.8) years, had documented prevalent fragility fractures at the time of the cross-sectional study (Table 1). Four patients had a vertebral fracture (one each with 1,2,3 and 4 VF, respectively), 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). Only 3 of these 11 patients had osteoporosis (1 at LS, and 2 at FN).

Median QUS T-score 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).

All 11 patients had normal β-CTX measurements, 3 had slightly elevated P1NP plasma levels (data not shown), and in all fractures occurred 1 to 25 years after the start of their ADT treatment.

LABORATORY MEASUREMENTS

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).

PREDICTIVE VALUE OF QUS FOR OSTEOPOROSIS

Frequencies of patients without osteoporosis (DXA T-scores ≤-1.0 >-2.5) and with osteoporosis (DXA T-scores ≤-2.5) at LS, FN or either LS 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's were only <25% at any QUS T-score. A QUS threshold of -1.0 to 0.0 would thus lead to a 34.0 to 57.8% reduction of DXAs required to diagnose osteoporosis.

ROC curves were constructed for QUS T-scores using DXA T-scores of ≤2.5, and for DXA T-scores of ≤2.0). The latter are shown in Figure 2 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 were not different, namely for lumbar spine: AUC of 0.739, p-value 0.001; for femoral neck: AUC 0.753, p-value 0.753 and for any site: AUC of 0.725, p-value of <0.001.

FOLLOW-UP DATA ANALYSIS (TELEPHONE INTERVIEW)

A follow up telephone interview could be conducted in 155 of 163 survivors (Figure 1). Of these 155 patients, 11 (7%) were on ADT for biochemical recurrence or metastases.

Forty-two patients (27.1%) reported episodes of sudden back pain, of whom 5 (3.2%) had radiologically confirmed vertebral fractures (VF). Among survivors in remission from their PCa, 15 reported radiologically confirmed fractures; 11 (7.1%) after adequate and 4 (2.6%) after inadequate trauma. Initial QUS T-scores of the 4 fracture patients were low (median -3.05, range -3.6 – 0.2), and only one would have been diagnosed with osteoporosis based on LS/FN DXA T-scores. One of 4 survivors with an incident fracture at follow up also had a prevalent fracture at baseline. His baseline DXA showed normal BMD at LS and osteopenia in the FN, whereas calcaneal QUS T-score was -3.40.

Discussion

Findings from our cross-sectional study of 256 non-metastatic PCa patients followed in the out-patient clinic of our uro-oncological clinic, confirm a diagnosis of osteoporosis based on a WHO DXA T-score of ≤-2.5 to be present in 10.5 %, and of osteopenia in 53.1% of patients, despite the majority (84.4%) having been on ADT at some stage prior to the study or were currently using this therapy for at least 6 months. A DXA T-score of ≤-2.0, a cut-off we chose to include in the analysis because of the high likelihood of

ADT-induced hypogonadism, which may not only contribute to a decrease in BMD, but also to a BMD-independent decrease in bone quality, both increasing fracture risk, was present in 29.2% of patients.

The high worldwide prevalence of PCa, and the high percentage of PCa patients who will receive treatment with ADT and will be at high risk for osteoporosis and fractures, raises the need for a simple outpatient selection tool to enable the identification of patients who require screening for osteoporosis and thus reduce the number of unnecessarily referrals for DXA. Whereas DXA measurements remain the gold standard for osteoporosis screening,[33] the investigation is costly, not always (readily) available and fractures may occur at T-scores thresholds higher than the operational diagnostic threshold ≤-2.5 particularly in the presence of factors potentially affecting bone quality such as hypogonadism. Low threshold, cheaper and faster, screening methods such as QUS have been found to be cost-effective,[28] and could improve the screening rate for osteoporosis, ultimately resulting in improvement of the economic and patient burden of osteoporosis.[32]

DXA and QUS measure different aspects of bone strength. Whereas DXA measures bone mineral density and content, reflecting material properties of bone, QUS measures trabecular sound transmission reflecting trabecular microarchitecture and thus structural properties of bone, both important components of bone quality and thus bone strength, thus representing potentially complementary tools in the prediction of fracture risk. Others found a moderate correlation between DXA T-scores and QUS outcomes in prostate cancer patients.[33] Previous studies conducted in healthy men and women showed that QUS was at least comparable to DXA for predicting fractures in healthy men and women [34,35]. In two 10-year prospective studies, one including 3,883 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.[34,35] 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.[36]

The main objective of our study was to evaluate the pence of QUS in identifying non-metastatic PCa patients found to have osteoporosis using the DXA WHO criteria (BMD T-scores of ≤-2.5), or those potentially at risk for fracture at a higher T-score threshold of ≤-2.0, and to establish the QUS cut-off T-score threshold correlating best with these DXA T-scores to 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 certainty 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 study addressing the value of QUS compared to DXA in the diagnosis of osteoporosis in PCa patients. A first study conducted in 60 PCa patients,[33] 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%).[33]

Our findings from this cross-sectional study conducted in a much larger cohort of non-metastatic PCa patients show that although QUS represents an attractive pre-screen tool to rule out a diagnosis of osteoporosis in these patients, as shown by the very high negative predictive value of QUS T-score thresholds of 0, -1 and -1.8 (94.5% to 97.7%) for osteoporosis, the low positive predictive value of this tool for osteoporosis (<25%) indicates that QUS lacks specificity to replace DXA in establishing a diagnosis of 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, treated in a single centre, using standardized protocols following international guidelines, the majority at whom were at risk for osteoporosis and fractures due to ADT-induced hypogonadism and all had DXA and QUS investigations at no longer 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 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 of bone metastases in PCa.

Our study also has limitations, the main of which is that the number of prevalent fractures at the time of initial evaluation and the number of incident new fractures self-reported by survivors at the time of the telephone survey may have underestimated the actual number of vertebral fractures and their grades 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. Incident fractures were also self-reported and radiological confirmation was not always available from the patients' medical records. These limitations precluded reaching any reliable conclusion on the value of DXA, of QUS or a combination of the two in the prediction of fracture risk in patients with non-metastatic PCa who are 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 variation coefficient and that consequently, results obtained using a specific device may not be extrapolated to another device or to absolute QUS device thresholds.[37]

In conclusion, our data show that although QUS may not be used for the diagnosis of osteoporosis as traditionally defined by WHO criteria in non-metastatic PCa patients, we provide evidence that outpatient pre-screening for osteoporosis using a device-specific threshold of QUS T-scores represents a simple, convenient, cosT-effective tool, confidently ruling out patients who are highly unlikely to have 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 acceptably 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.

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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 %)				
Patient Characteristics								
	Mean ± SD Median (range)	**Mean ± SD Median (range)**	**Mean ± SD Median (range)**	**Mean ± SD Median (range)**				**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/m²)	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								
Obesity *N* (%)	50 (19.7)	33 (18.8)	15 (22.4)	2 (18.2)	NS	NS	NS	2 (18.2)
Corticosteroid use *N* (%)	14 (5.5)	3 (3.2)	11 (8.1)	0 (0.0)	NS	NS	NS	1 (9.1)
Smoking *N* (%)	32 (12.6)	13 (14.1)	17 (12.6)	2 (7.7))	NS	NS	NS	1 (9.1)
Alcohol abuse (≥3 units/day) *N* (%)	60 (23.8)	30 (33.0)	27 (20.0)	3 (11.5)	*p=0.03*	*p=0.03*	*p=0.01*	4 (36.4)

(Continuation Table 1)

	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 %)				
Local treatment N (%)	238 (93.0)							
Radical prostatectomy *N* (%)	33 (12.9)	16 (6.3)	15 (5.9)	2 (0.8)				
EBRT *N* (%)	182 (71.1)	61 (23.8)	100 (39.1)	21 (8.2)				
Brachytherapy *N* (%)	23 (9.0)	10 (3.9)	11 (43.0)	2 (0.8)				
No prior ADT N (%)	40 (15.6)	19 (20.4)	19 (13.9)	2 (7.4)	NS	NS	NS	0 (0.0)
Prior or current ADT *N* (%)	216 (84.4)	74 (79.6)	117(86.0)	25 (92.6)	NS	NS	NS	11 (100)
≤ 6 months *N* (%)	44 (17.2)	15 (16.1)	23 (16.9)	6 (22.2)				2 (18.2)
6-36 months* *N* (%)	172 (67.2)	59 (63.4)	94 (69.1)	19 (70.4)				9 (81.8)
Prior use of bone protective agents								
Bisphosphonates (oral) *N* (%)	5 (2.0)	1 (0.01)	3 (0.22)	1 (0.03)	NS	NS	NS	1 (9.1)

*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/m² / * We lumped together ADT treatment periods which varied between 6 months and the maximal period of 3 years as long-lasting castrate levels of testosterone are induced already after 6 months of ADT / # 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. / PCA prostate cancer, ADT androgen deprivation therapy, EBRT External beam radiotherapy*

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						
DXA measurements			T-score > 0	T-score ≤ 0	T-score > -1.0	T-score ≤ -1.0	T-score > -1.8	T-score ≤ -1.8	Total
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

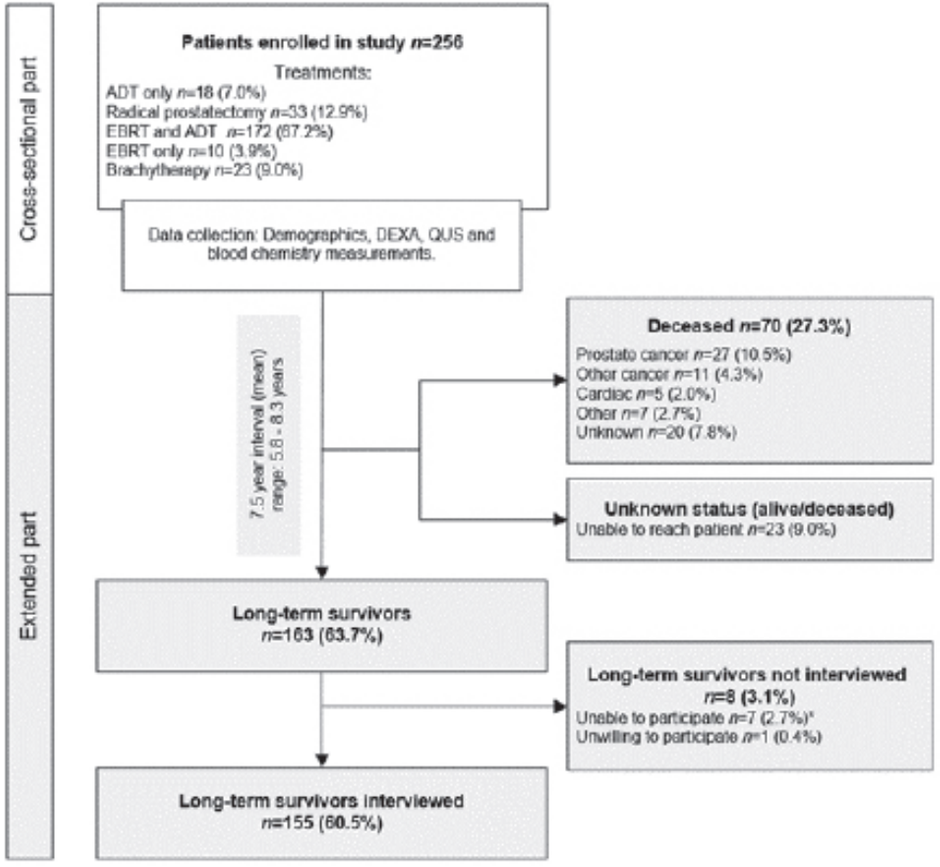
*QUS quantitative ultrasonography, DXA dual-energy absorptiometry, LS Lumbar spine, FN Femoral neck. / * For QUS of the left calcaneus and for DXA BMD of the Femoral Neck the lowest T-score value of either left or right hip was used (in patients with a hip replacement, the contralateral hip was used).*

Table 3 Negative and positive predictive values for the three QUS T-score thresholds shown.

		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 Figure 2

Figure 1 Cross-sectional study (n=256) and follow up study in long-term survivors (n=155). Flow diagram of patients included in the initial cross-sectional study, and follow up data obtained by telephone survey, and reasons for not performing follow-up.



** Patients with confirmed cognitive disorders unable to take part in the survey.*

Figure 2 Receiver operating characteristic (ROC) curves for DXA T-score of ≤2.0. 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). Receiver operating characteristic (ROC) curves for DXA T-score of ≤2.0. Details of DXA T-score of ≤2.5 shown in Table 3.