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Original Article

Vertebral Fractures and the Misclassification of Osteoporosis in Men With Prostate Cancer

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Abstract

Androgen deprivation therapy (ADT) has become the cornerstone of treatment for both advanced and nonmetastatic prostate cancer. The presence of a nontraumatic vertebral fracture (VF) identifies a patient who has clinical osteoporosis. Vertebral fracture analysis (VFA), a dual-energy X-ray absorptiometry (DXA)-based technology identifies VFs in conjunction with a standard bone mineral density (BMD) examination. The objective of this study was to determine if VFA would increase the diagnosis of osteoporosis in men with prostate cancer on ADT.

One hundred sixteen men aged ≥60 yrs with nonmetastatic prostate cancer receiving ADT for ≥6 mos underwent DXA of the spine, hip, and 1/3 distal radius, VFA, and conventional vertebral X-rays.

Approximately 40% of the men had clinically defined osteoporosis. The use of conventional DXA criteria (spine and hip) alone resulted in the misdiagnosis of approx 75% of patients. VFA and addition of the 1/3 distal radius site performed by DXA both increased the rate of diagnosis and reduced the misclassification of osteoporosis in men with prostate cancer, compared with conventional DXA criteria alone. Analysis indicated that VFA assessment of mild, moderate, and severe fractures from all readable vertebrae (T5–L4) had a kappa statistic, sensitivity, and specificity of 0.92, 100%, and 95%, respectively, with semiquantitative radiography.

Men with prostate cancer on ADT should be screened for osteoporosis at the initiation of therapy, and evaluation should include DXA of the 1/3 distal radius in addition to the spine and hip, as well as evaluation for VFs.

Key Words: Androgen deprivation therapy; bone mineral density; osteoporosis; vertebral fractures; vertebral fracture assessment.

Introduction

Prostate cancer is the most common visceral malignancy and the second leading cause of cancer-related death in men *(1)*. Androgen deprivation therapy (ADT) has become the cornerstone of treatment for both advanced and nonmetastatic prostate cancer, nearly quadrupling in use over the past decade *(2,3)*. Despite its therapeutic benefits, ADT has been associated with bone loss and increased fracture rates *(4)*. Notably, the duration of ADT treatment has been associated with the magnitude of bone loss and fracture risk *(5)*. This is especially important given that many patients are on ADT permanently *(6)*.

Vertebral fractures (VFs) are the most common type of osteoporotic fracture. The presence of a nontraumatic VF identifies a patient who has clinical osteoporosis. VFs have been associated with increased morbidity and mortality and greatly diminished quality of life *(7,8)*. Additionally, a VF increases the risk of a new fracture up to fourfold, thereby changing the patient's therapeutic management *(9)*. However, only one-quarter to one-third of patients with VF present with symptoms associated with the fracture *(10)*. Given the significant clinical impact of VFs, their detection is of prime importance to the care of the patient.

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Lateral radiographs of the thoracolumbar spine have been the gold standard in identifying VFs. The Genant semiquantitative approach is most often used in osteoporosis evaluation because of its objectivity and reproducibility *(11,12)*. However, standard radiography requires considerable radiation exposure and often is performed at a different hospital or radiology unit. In contrast, vertebral fracture analysis (VFA) is a dual-energy X-ray absorptiometry (DXA)-based technology that identifies VFs in conjunction with a standard bone mineral densitometry examination. Thus, VFA has the potential to be a more convenient method of identifying VFs, using radiation levels similar to standard DXA and much lower than a lateral X-ray. Recent studies have indicated that VFA exhibits good agreement with radiography reliably aiding in the identification of VFs *(13,14)*.

There are currently no official bone density guidelines to assess skeletal integrity in men with prostate cancer on ADT. Furthermore, there are no guidelines to assess which men with prostate cancer are at greatest risk for bone loss. Therefore, the objectives of this study were to determine if VFA by DXA would improve the diagnosis of osteoporosis in men with prostate cancer on ADT who were being screened by BMD alone; assess the accuracy of VFA identification by DXA relative to the reference standard of vertebral radiography; and determine if the inclusion of the 1/3 distal radius site in conjunction with spine, hip, and femoral neck BMD increases the identification of men with clinically defined osteoporosis.

Methods and Materials

Design and Subjects

This cross-sectional study included men aged $\geq$60 yrs with nonmetastatic prostate cancer receiving ADT for $\geq$6 mos. ADT included orchiectomy or gonadotropin-releasing hormone agonists, with or without an antiandrogen. Patients were recruited from physicians in the Pittsburgh, Pennsylvania area and screened via telephone interviews. Men were excluded if they had metastatic prostate cancer, had nonmetastatic prostate cancer with a prostate-specific antigen level $>$4 (unless undergoing adjustments to their therapy), or used medications known to alter bone mineral metabolism within the past year (i.e., bisphosphonates, cortiocosteroids, and antiseizure medications). Patients were advised of the nature of the study and provided written informed consent before enrollment. The University of Pittsburgh Institutional Review Board approved the study.

Outcome Measures

Participants were evaluated at the Clinical and Translational Research Center at the University of Pittsburgh. Bone mineral density (BMD, g/cm^2) of the hip (total hip and femoral neck), lumbar spine, and 1/3 distal radius was assessed by DXA, using a Hologic Discovery A (Hologic Inc., Bedford, MA). Measurements were obtained and analyzed using standard manufacturer protocols. BMD was evaluated as T-scores (number of standard deviation (SD) units from adult peak bone mass). T-scores were used to classify participants according to the World Health Organization (WHO) criteria for defining osteoporosis (T-score ≤ -2.5 SD), low bone mass (T-score between -2.5 and -1.0 SD), and normal (T-score ≥ -1.0 SD) *(15)*. The coefficient of variation for our DXA machine is 1.3% for the spine and 1.4% for the total hip BMD *(16)*.

VFA was performed during the same initial visit through lateral spine imaging of T5–L4 on the Hologic Discovery A, using the manufacturer's standard protocols. The vertebral bodies from the scan were visually identified by a technician certified by the International Society of Clinical Densitometry and classified using computer-calculated reductions in vertebral height according to the method of Genant et al *(11)*. Fractures were classified as grade 1 (mild) with a 20–25% loss of vertebral height, grade 2 (moderate) with a 25–40% loss of vertebral height, or grade 3 (severe) with greater than 40% loss of vertebral height. All fractures were confirmed by lateral thoracic and lumbar vertebral X-ray, graded by a single radiologist.

Measures of Clinical Characteristics

Participants completed food frequency questionnaires to evaluate total calcium (Ca) and vitamin D intake from both diet and vitamin supplements *(17)*. Each subject completed a standardized questionnaire designed to document putative risk factors of osteoporosis. This questionnaire included questions regarding family, medical, surgical, and fracture history, in addition to information on medication, activity level, tobacco, and alcohol use. Height was obtained with a Harpenden stadiometer (Holtain Ltd., Crymych, Dyfed, United Kingdom), weight was measured with a Health-O-meter balance-beam scale (Sunbeam Inc., Boca Raton, FL), and body mass index (BMI, kg/m^2) was calculated. Patients were asked to report their tallest height from memory, and height loss was calculated as the difference between tallest height and current height.

Statistical Analysis

SAS® version 9 (SAS Institute Inc., Cary, NC) was used for all statistical analyses. We used appropriate descriptive statistics to summarize the participant characteristics and independent samples *t*-tests to compare BMD measures between those with and without VFs. We used a 2-way contingency table cross-tabulation to summarize and describe identification of those with osteoporosis who should be treated using the standard (lumbar spine, total hip, and femoral neck) BMD- and VF-based criteria. The sensitivity of the results to adding 1/3 distal radius site to the standard BMD-based criterion was also examined. We used the kappa (κ) statistic to quantify agreement between DXA and semiquantitative (SQ) radiography for VF identification and computed sensitivity and specificity of VF identification via DXA using SQ radiography as the reference ''gold'' standard. Finally, we used logistic regression models to examine whether greater duration of ADT and/or height loss increased the risk of a VF.

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