European Journal of Radiology 84 (2015) 2269–2274

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Association of osteolytic lesions, bone mineral loss and trabecular sclerosis with prevalent vertebral fractures in patients with multiple myeloma

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ARTICLE INFO

Article history:
Received 1 February 2015
Received in revised form 16 May 2015
Accepted 27 July 2015

Key words:
Multiple myeloma
Osteolytic lesions
Vertebral fracture
Bone structure
Bone mineral density

ABSTRACT

Purpose: In patients with multiple myeloma (MM), computed tomography is widely used for staging and to detect fractures. Detecting patients at severe fracture risk is of utmost importance. However the criteria for impaired stability of vertebral bodies are not yet clearly defined. We investigated the performance of parameters that can be detected by the radiologist for discrimination of patients with and without fractures.

Methods and materials: We analyzed 128 whole body low-dose CT of MM patients. In all scans a QCT calibration phantom was integrated into the positioning mat (Image Analysis Phantom®). A QCT-software (Structural Insight) performed the volumetric bone mineral density (vBMD) measurements. Description of fracture risk was provided from the clinical radiological report. Suspected progressive disease (PD) was reported by the referring clinicians. Two radiologists that were blinded to study outcome reported on the following parameters based on predefined criteria: reduced radiodensity in the massa lateralis of the os sacrum (RDS), trabecular thickening and sclerosis of three or more vertebrae (TTS), extraosseous MM manifestations (EOM), visible small osteolytic lesions up to a length of 8 mm (SO) and osteolytic lesions larger than 8 mm (LO). Prevalent vertebral fractures (PVF) were defined by Genant criteria. Age-adjusted standardized odds ratios (sOR) per standard deviation change were derived from logistic regression analysis and area under the curve (AUC) from receiver operating characteristics (ROC) analyses were calculated. ROC curves were compared using the DeLong method.

Results: 45% of the 128 patients showed PVF (29 of 75 men, 24 of 53 women). Patients with PVF were not significantly older than patients without fractures (64.6 ± 9.2 vs. 63.3 ± 12.3 years: mean ± SD, $p = 0.5$). The prevalence of each parameter did not differ significantly by sex. Significant fracture discrimination for age adjusted single models was provided by the parameters vBMD (OR 3.5 [1.4–8.8], AUC = 0.64 ± 0.14), SO (sOR 1.6[1.1–2.2], AUC = 0.63 ± 0.05), LO (sOR 2.1[1.1–4.2] AUC = 0.69 ± 0.05) and RDS (sOR 2.6[1.6–4.7], AUC = 0.69 ± 0.05). Multivariate models of these four parameters showed a significantly stronger association with the development of PVF (AUC = 0.80 ± 0.04) than single variables. TTS showed a significant association with PVF in men(sOR 1.5 [0.8–3.0], AUC = 0.63 ± 0.08), but not in women (sOR 2.3[1.4–3.7], AUC = 0.70 ± 0.07). PD was significantly associated with PVF in women (sOR 1.9[1.1–3.6], AUC = 0.67 ± 0.08) but not in men (sOR 1.4[0.9–2.3], AUC = 0.57 ± .07). EOM were not associated with PVF (sOR 1.0[0.4–2.6], AUC = 0.51 ± .05).

Conclusion: In multiple myeloma, focal skeletal changes in low dose CT scans show a significant association with prevalent vertebral fractures. The combination of large osteolytic lesions and loss in radiodensity as can be detected with simple CT Hounsfield measurements of the os sacrum or BMD measurements showed the strongest association to fractures and may be of value for prospective studies.

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http://dx.doi.org/10.1016/j.ejrad.2015.07.024
0720-048X/

1. Introduction

Multiple myeloma (MM) is a malignant plasma cell disease that amounts to approximately 1% of all malignancies [1]. It typically evolves from monoclonal gammopathy of undetermined significance (MGUS), a pre-malignant stage without relevant bone marrow infiltration (<5% plasma cells) and without skeletal events. Diffuse and/or focal lytic bone destruction as well as osteoporosis is found in 80% of MM patients [2]. These changes lead to a high incidence of fractures of which vertebral compression fractures are the most common, occurring in 20–70% of patients [3–5]. The vertebral fractures in MM patients are associated with a high impairment of quality of life, morbidity and mortality [3,6]. However, in contrast to osteoporosis patients, the bone densitometry has a limited diagnostic value in the assessment of fracture risk in myeloma patients [7–10]. Therefore, the radiologists statements on the risk of imminent fracture is of particular interest to the referring clinician, in order to decide about additional surgical treatments, vertebroplasty, pharmaceutical interventions or a radiotherapy [11–13]. However, the criteria for impaired stability of vertebral bodies are not yet clearly defined. Some authors suggest the number of focal lesions as indicator for diffuse bone infiltration [14], while others refer to cortical erosion as a major threat for vertebral fractures [12]. Other recommendations are based on the clinical experience the size of osteolytic lesion is associated with fracture risk [15]. However these crude criteria for focal osteolytic lesions lack the backup of larger longitudinal studies for specific tumors and investigations of the individual vertebral biomechanical strength, e.g., with finite element analyses, which have become technically feasible with recent developments of CT technology [16]. For a comprehensive assessment of vertebral fracture risk of the entire spine, the commonly performed low dose spiral CT provides extensive data on the vertebral bone status of myeloma patients [17–21]. In this cross sectional study we tested, if parameters that are detectable by investigators of low-dose whole body scans in clinical routine can discriminate patients with and without prevalent vertebral fractures. The investigation of CT findings and their association to vertebral fractures may have clinical benefit, permitting the development of more sensitive and objective ways to define indications for preventive measures in MM patients at risk of fracture.

2. Materials and methods

2.1. Study design and participants

We acquired CT scans of 178 patients referred to our department for non contrast enhanced CT scans with clinical indication. In a cross-sectional analysis we analyzed each patient's first CT scan imaged between January 2010 and January 2012, disregarding the later course of the patient's disease. The study was approved by the local ethics commission and was designed to meet GCP criteria. Patients were excluded from the investigation if they had not permitted data use for study purpose at admission or if they met following exclusion criteria: previous malignoma, known metabolic bone disorders, history of sprue, abnormal thyroid function. 50 of 178 patients were excluded due to these criteria.

2.2. Scan protocol and data analysis

All patients were scanned on the same Somatom Sensation 64CT-scanner (Siemens, Forchheim, Germany) from skull to knee. Scans were conducted with the preexisting CT-protocol (120 kVp, 100 mAs and a 1.5 mm slice thickness resulting in a dose of approximately 4.0–6.5 mSv (IRCP 103)). The InTable® calibration phantom (Image Analysis Inc., Columbia, Kentucky, USA) embedded in the CT-mat underneath the patient was scanned with all CT scans, thus permitting QCT analyses. Longitudinal quality assurance to ensure stability of the scanner throughout the study and cross calibration between patients was performed using the QA and Calibration phantom, Type 3 (Mindways®, Austin, Texas, USA). The in-house developed QCT software Structural *Insight* (V3.0) [22–24], was adapted to perform bone mineral calibration and vBMD analysis using the In-Table® phantom. A regular resolution reconstruction including the entire cross section of the patient was used for the calibration of CT values to mineral scale. A high resolution reconstruction of the vertebra with a 120×120 mm field of view and 512×512 pixel matrix was used for the 3D segmentation of the vertebral bodies. The vBMD of the trabecular bone compartment was determined automatically using a peeling algorithm that excluded the cortical bone. In order to describe osteoporosis according to the definition of the WHO, the corresponding vBMD T-score was provided in addition.

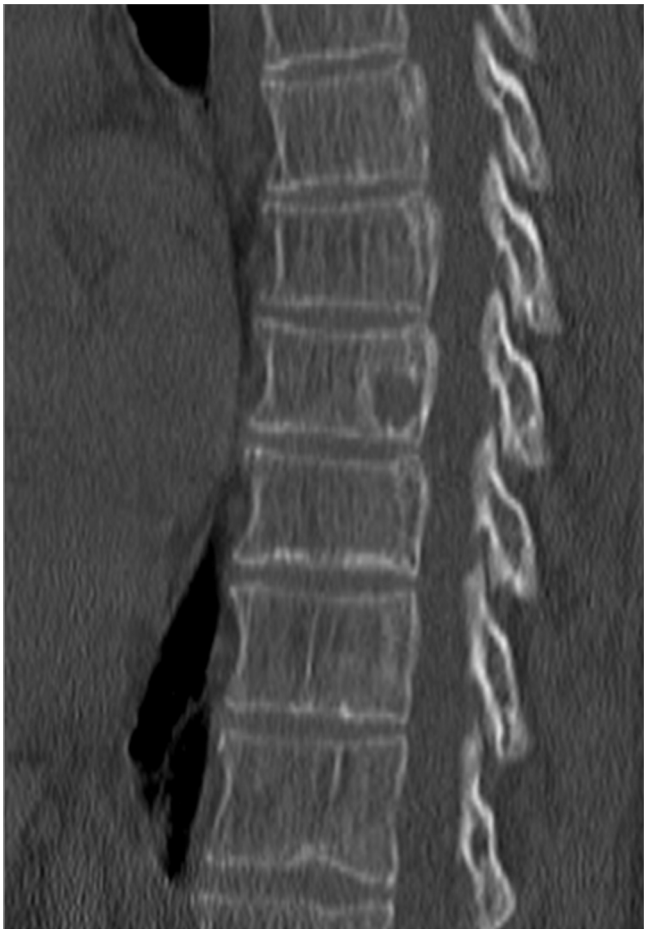

Fig. 1. Example excerpt sagittal projection from a whole body low dose CT scan of a patient with a larger osteolytic lesion of T8 as well as signs of trabecular thickening and trabecular sclerosis.

Data on clinical progression of the MM disease (PD) at the time of the CT scan were provided by the referring clinicians. PD was defined as the search for osteolytic lesions due to increases of M-compenent in Serum electrophersis, increases of M-component in the urine electorphoresis, increases bone marrow plasma cell percentage or hypercalcemia attributed to the plasmacell disease. Two radiologists reported on the following radiological parameters in consensus: (1) prevalent visible osteolytic lesions of any vertebra of the entire spine with a size smaller than 8 mm (SO), (2) prevalent osteolytic lesions of the spine with a size greater than 8 mm (LO) (Fig. 1), (3) visible vertical trabecular thickening and sclerosis of three or more vertebral bodies (TTS) (Fig. 1), (4) negative mean