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

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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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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.

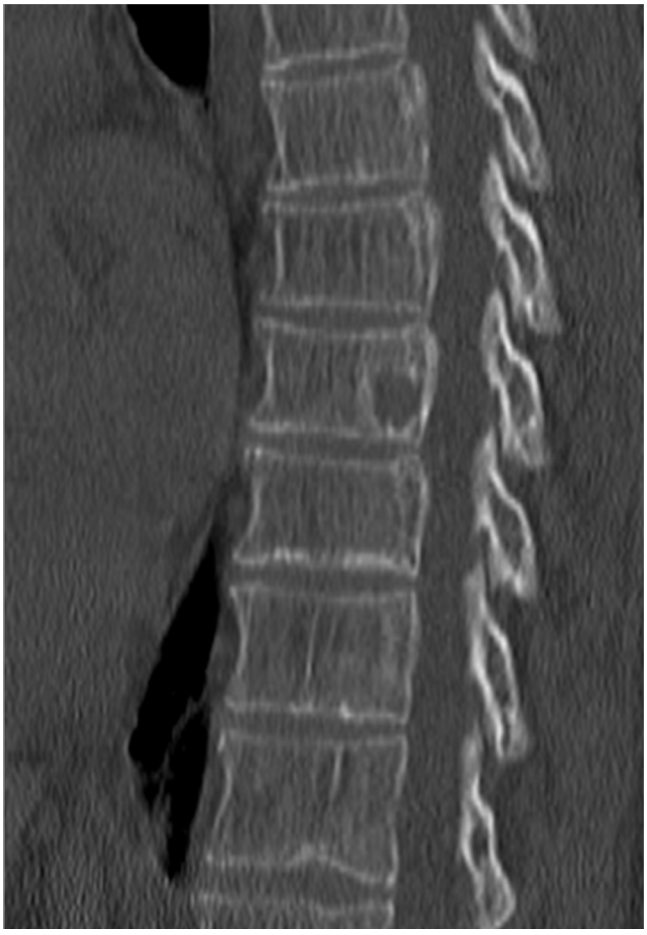

Fig. 1. Example excerpt sagittal projection from a whole body low dose CT scan of a patient with a larger osteolytic lesion of T8 as well as signs of trabecular thickening and trabecular sclerosis.

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

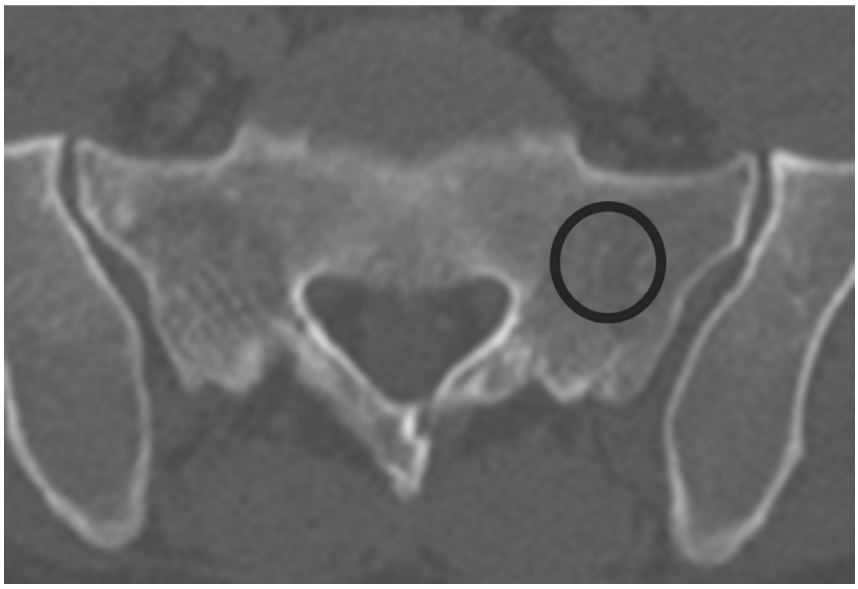

Fig. 2. VOI measurement at the massa lateralis of the os sacrum at S1 (RDS), with a cylindrical VOI of 10 mm diameter placed in the trabecular space with equal distance to the anterior and lateral cortex as well as the neural foramen. The predefined threshold of zero Hounsfield units showed a significant association to prevalent vertebral fractures.

Table 1
Characteristics of the patient cohort for all patients, men and women. Mean values of age and BMD. Prevalence of clincal parameters. RFR: Prospective fracture risk assumed in the intial clinical report, EOM = prevalent extraosseus myeloma, TTS = trabecular thickening and sclerosis of three or more vertebrae, RDS = reduced radiodensity in the massa lateralis of the os sacrum, SO = prevalent osteolytic lesions with a maximum diameter of up to 8 mm, LO = prevalent osteolytic lesions with a maximum diameter of more than 8 mm.

	All patients ($n = 128$)		Women ($n = 53$)		Men ($n = 73$)	
	Verbal fracture controls ($n = 70$)	Verbal fracture cases ($n = 53$)	Verbal fracture controls ($n = 24$)	Verbal fracture cases ($n = 29$)	Verbal fracture controls ($n = 46$)	Verbal fracture cases ($n = 29$)
Age (years)	63.3 (±12.1)	64.1 (±9.7)	63.3 (±13.3)	65.4 (±10.5)	63.3 (±11.5)	63.8 (±8.8)
BMD (mg/cc)	165.2 (±6.6)	189.0 (±6.0)	175.4 (44.8)	187 (±52.2)	191.4 (±55.2)	154.9 (45.5)
RFR	$n = 10$	$n = 23$	$n = 2$	$n = 8$	$n = 8$	$n = 15$
EOM	$n = 6$	$n = 5$	$n = 3$	$n = 3$	$n = 3$	$n = 2$
TTS	$n = 15$	$n = 28$	$n = 4$	$n = 10$	$n = 11$	$n = 18$
RDS	$n = 13$	$n = 32$	$n = 6$	$n = 15$	$n = 7$	$n = 17$
SO	$n = 38$	$n = 19$	$n = 15$	$n = 11$	$n = 23$	$n = 8$
LO	$n = 19$	$n = 36$	$n = 4$	$n = 17$	$n = 15$	$n = 19$

value of Hounsfield units measured in an axial CT reconstruction at the central anterior trabecular space of the left massa lateralis in in the segment S1 of the os sacrum, using a cylindrical VOI of 10 mm diameter and a thickness of 6 mm (RDS) (Fig. 2). Vertebral fractures were diagnosed according to Genant criteria for the purpose of the study (24). The fracture evaluation was performed by a consensus check of all CT-data including the clinical patient reports. With the retrospective analysis of the official radiological report, it was documented if increased fracture risk was suspected by the radiologist in clinical routine.

2.3. Statistical analysis

The statistical analysis was performed using JMP 9.0 software (SAS Institute, Cary, North Carolina, USA). Descriptive statistics are presented as mean ± standard deviation unless noted otherwise. Student's *t*-tests and Fisher's exact tests were performed for assessing differences between groups. Age-adjusted standardized odds ratios (sOR) for single variables and multivariate analysis were calculated from logistic regression analysis. Age adjusted areas under the curve (AUC) from receiver operating characteristics (ROC) curves were calculated and are listed as AUC ± standard deviation.The significance of difference between ROC curves was calculated with the DeLong method [25]. Medcalc software was used for AUC analysis (MedCalc Software, v13.0.2, Ostend, Belgium).

3. Results

A total of 128 patients were included in the analysis, consisting of 75 men and 53 women, aged 31 to 89 years (mean = 63.8 ± 11 years). This also included patients with MGUS ($n = 17$) or multiple myeloma without disseminated bone disease (Durie and Salmon Grade (S&D): $n = 15$). The majority of patients showed advanced MM to S&D Grade 2 ($n = 10$) or Grade 3 ($n = 86$).

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, $p = 0.5$). Extraosseous myeloma manifestations (EOM) occured in 8% of patients. The six other suspected fracture discriminators occurred in 33% or more cases (Table 1). None of these parameters differed significantly by sex. Reported fracture risk and RDS were each significantly associated to age ($p < 0.05$, $\varkappa^2 = 6.4$ and $\varkappa^2 = 3.9$, respectively).

The decrease in trabecular vBMD showed a significant association with vertebral fractures (OR 3.5 (1.4–8.8), AUC = 0.64). Despite a majority of patients with advanced myeloma bone disease and an average age of about 64 years, the average vBMD T-Score was

Table 2
Age Adjusted OR for association with vertebral fractures in all patients, men and women. PD = progression of MM disease at the time of staging, EOM = prevalent extraosseus myeloma, TTS = trabecular thickening and sclerosis of three or more vertebrae, RDS = reduced radiodensity in the massa lateralis of the os sacrum, SO = prevalent osteolytic lesions with a maximum diameter of up to 8 mm, LO = prevalent osteolytic lesions with a maximum diameter of more than 8 mm.

	All patients ($n = 128$)	Men ($n = 75$)	Women ($n = 53$)
Progress	1.4 (0.8–2.3)	1.4 (0.8–2.3)	1.9 (1.1–3.6)
EOM	1.0 (0.4–2.6)	1.0 (0.4–2.6)	1.2 (0.7–2.2)
TTS	2.0 (1.4–3.4)	2.3 (1.4–3.7)	2.1 (1.1–4.1)
RDS	2.6 (1.6–4.7)	2.8 (1.6–4.8)	2.0 (1.1–3.6)
SO	1.6 (1.1–2.2)	1.6 (1.0–2.6)	1.7 (0.9–2.9)
LO	2.1 (1.1–4.2)	2.0 (1.1–4.2)	2.6 (1.4–5.0)

normal (+0.2). Eight patients showed a T-score smaller than −2.5 as indicator for prevalent osteoporosis.

Three of the age adjusted single fracture discriminators (Table 2, Fig. 1) showed significant associations with PVF: 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). TTS showed a significant association with PVF in men, but not in women (sOR 2.3(1.4–3.7), AUC = 0.70 ± 0.07) vs. (sOR 1.5 (0.8–3.0), AUC = 0.63 ± 0.08). Progressive disease suspected by the referring clinician at the time of the investigation (PD) showed a significant association with PVF in women only (sOR 1.9(1.1–3.6)). Each of the other variables showed non-significant differences in association with fractures by sex.

We tested the AUC values of association with fractures for diverse combinations of descriptors. In the age adjusted logistic regression, large osteolyses ($p = 0.01$), and the radiodensity in the os sacrum ($p < 0.001$) contributed independently to the strongest bivariate model resulting in an AUC of 0.78. This model showed a significantly stronger association to PVF than all single descriptors ($p < 0.05$–$p < 0.0001$), except for a trend to significant improvement in comparison to the strongest single predictor LO with the de Long method ($p = 0.05$). The combination of three descriptors (RDS + LO + TTS, RDS + LO + SO) (Fig. 4) showed significant improvement in comparison to all single predictors ($p < 0.01$–$p < 0.0001$), but only non-significant improvement to bivariate models. While there were considerable differences observed between the genders in single variate models (Fig. 3), the multivariate models proved to be comparable between men and women (Fig. 4). A model of all

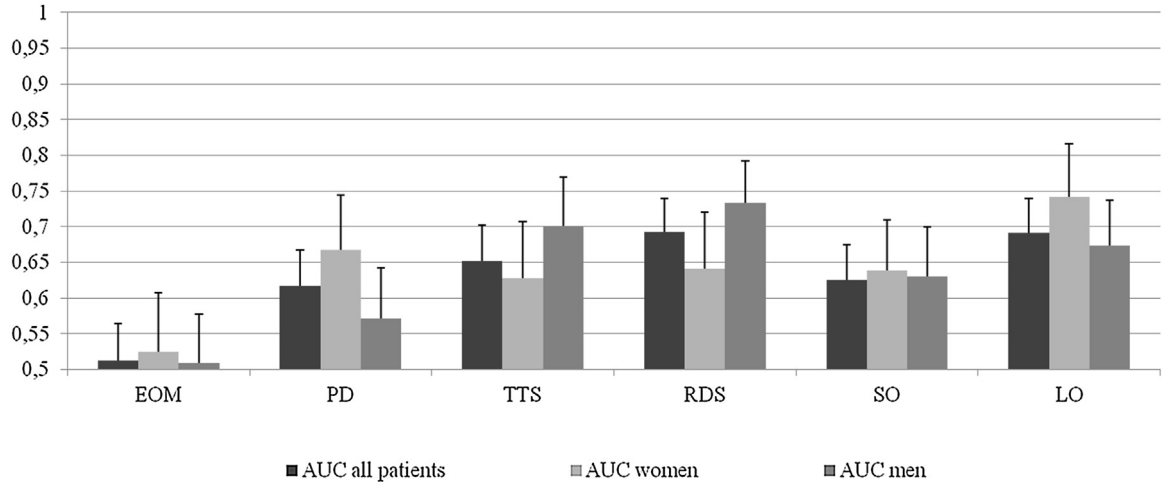

Fig. 3. AUC for the association of bone structural parameters and prevalent vertebral fractures in dependence of the bone separation threshold used. AUC for BMD for comparison. PD = progression of MM disease at the time of staging, EOM = prevalent extraosseus myeloma, TTS = trabecular thickening and sclerosis of three or more vertebrae, RDS = Reduced radiodensity in the massa lateralis of the os sacrum, SO = prevalent osteolytic lesions with a maximum diameter of up to 8 mm, LO = prevalent osteolytic lesions with a maximum diameter of more than 8 mm.

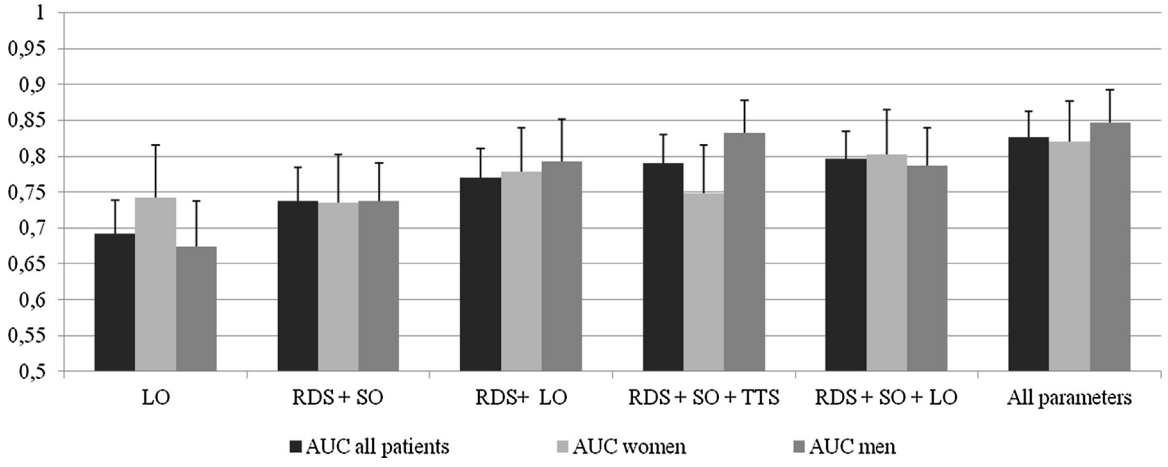

Fig. 4. Age adjusted AUC for the association of multivariate parameters in comparison and prevalent vertebral fractures. Differences in between genders appear to be generally reduced in multivariate analyses. Trabecular sclerosis and thickening appeared to perform stronger in men than in women. BMD = volumetric Bone Mineral Density of T11/T12, PD = progression of MM disease at the time of staging, EOM = prevalent extraosseus myeloma, TTS = trabecular thickening and sclerosis of three or more vertebrae, RDS = reduced radiodensity in the massa lateralis of the os sacrum, SO = prevalent osteolytic lesions with a maximum diameter of up to 8 mm, LO = prevalent osteolytic lesions with a maximum diameter of more than 8 mm.

values with maximal performance of the descriptors is listed as reference with an AUC of 0.83 (Fig. 4).

4. Discussion

Investigation into the potential for quantitative assessment of CT scans in the assessment of fracture risk in myeloma bone disease has been minimal [12,17–19]. This study shows that the radiological information derived from the low-dose staging CT shows a significant association to prevalent vertebral fractures. In particular, the two-variable model of reduced radiodensity of the os sacrum (RDS) and detection of larger osteolyses (LO) showed a relevant association to vertebral fractures. This is of particular importance due to the related comorbidity, the variety of therapeutic options [5,26] and the high prevalence of fractures in myeloma patients of approximately 45%, reported in this as well as earlier studies [27,28].

In contrast to osteoporosis patients, the QCT and DXA bone densitometry has a limited diagnostic value in the assessment of fracture risk in myeloma patients [7–10]. Therefore fracture risk is traditionally determined by the radiologists report. As previously shown by Melton et al. [3,4], our study documented that QCT vBMD was associated with fractures (OR 3.5 (1.4–8.8), AUC = 0.64). However, the patients at risk of fracture showed minimal osteopenia based on the BMD in our patient cohort as well as in earlier DXA and QCT studies [7,9,10,29]. Therefore it is difficult to define an intervention threshold and appears to be feasible to use the changes of BMD in the time-course of disease rather than singular BMD measurements to detect patients at risk.

The previous QCT and DXA studies led us to search for alternative density measurements that could be performed by the radiologist. We found that measures in the massa lateralis of the os sacrum have several advantages. Although increased artifacts and complex geometry at the sacrum did not allow precise density measurement, the trabecular space of the massa lateralis showed severe degeneration to fat isodense HU-values in 45 patients (35%), which could be measured with high reprodicibility. There were no confounding sclerotic trabecular bone changes in the os sacrum, while we observed sclerotic changes of trabecular bone of vertebrae (TTS) in 43 patients (33%). Thus, the lumbar spine BMD measurement might be affected by interfering changes of anatomy due to degeneration and sclerosis, which might not affect the lateral mass of the sacral bone due to different biomechanics and distance from articulating surfaces. This would explain the different performance of these two predictors in our model. Appearances of negative radiodensities in the massa lateralis of the os sacrum (RDS) showed a significant association with fractures as a single variable (OR 2.6 (1.6–4.7), AUC = 0.69) and was a significant independent contributor in multivariate models (Fig. 4).

As we found many patients with visible trabecular thickening and reactive sclerosis (TTS) of more than three trabecular vertebral bodies in myeloma patients, we initally hypothezised that sclerosis leads to higher BMD values and would be associated to a lower prevalence of fractures. However the results of our study showed that patients with vertebral trabecular sclerosis did not show significant differences in trabecular BMD from patients without sclerotic trabecular changes (175.3 ± 55.0 vs. 180.4 ± 50.2, $p = 0.6$). The prevalence of vertebral sclerosis was associated with fractures, both as single variable (OR 2.0 (1.4–3.2), AUC = 0.65) and as independent contributors in multivariate logistic regression models. TTS appeared to perform stronger in men than in women, for both multivariate and in single models (Figs. 3 and 4).

The clinical radiological report stated that an imminent prospective fracture risk was suspected in 38% of patients with large osteolytic lesions (LO). In patients with small osteolytic lesions (SO), pending fracture risk was only suspected in 16% of the cases. Indeed the presence of LO showed the strongest association with fractures and was superior to SO (AUC = 0.69 vs. AUC = 0.63, $p = 0.02$). However patients with LO did not show a significant difference of BMD in comparison to patients with SO (174.7 ± 54.8 vs. 180.5 ± 51.2, $p = 0.7$). We conclude that increased fracture prevalence is therefore explained by the size of disruption of the bioanatomical scaffold resulting in higher fracture likelihood with increased size of lytic bone lesions disregarding eventual cortical erosions. Other descriptors such as the clinical progession of the disease are of limited value. Extrasseous MM manifestations (EOM) did not appear to be relevant for fracture risk assessment.

The multivariate analysis showed that the combination of descriptors for fracture risk assessment is advantageous. The bivariate model of RDS and LO provided significant improvements towards single descriptors. TTS could be considered as an additional descriptor of relevance in men, but has to be confirmed by prospective studies. As we propose a multivariate models to discriminate between patients with and without fractures, our data suggest that biomechanical stability might be compromised by a combination of BMD, osteosclerosis and osteolyses.

There are several limitations to this study. The cross sectional study design provides associations to existing fractures but does not provide estimates of future fracture risk. However the results of the proposed measures are promising for prospective trials. As there are currently few strategies to determine the individual fracture risk in myeloma patients, it is important to provide clinical indicators in order to improve primary and secondary prevention. For this purpose the interobserver variability of the measurements and subjective findings should be assessed.

Future prospective studies should examine whether fracture risk assessments for MM patients can be improved and offer to develop successful strategies to prevent fractures. The clinical assessment can be refined in many ways with complex measurements of bone structure and bone strength such as CT-based finite element analyses [30]. These finite element analyses allow to evaluate the biomechanical structural changes in relation to location, size and shape of osteolystic lesions as well as the quality of surrounding bone tissue in more detail, thus offering the potential of considerable refinements in regard to the detection of structural weakness as well as automated analysis of vertebral strength. On the other hand, the diagnostic capabilities of radiologists are as important to be considered. As it appears that simple VOI measures of the os sacrum (RDS) can compete with complex vBMD measurements, it would be benefitial to determine whether bone strength measurements can improve fracture risk assessment further. In the future, the standardized radiological assessment of myeloma scans in regard to fracture risk could be used to indicate more powerful additional QCT bone strength assessments [30], in order to determine the general bone status as well as the strength of targeted vertebrae that are considered to be at risk.

In conclusion, focal skeletal changes in MM patients, which can be detected with low-dose CT, show a significant association with 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, showed the strongest association to fractures.

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