Baseline bone involvement in multiple myeloma – a prospective comparison of conventional X-ray, low-dose computed tomography, and ^{18}flourodeoxyglucose positron emission tomography in previously untreated patients

Examination of bone lesions is a compulsory part of baseline assessments in patients with multiple myeloma (MM). Low-dose computed tomography (CT) scan has recently been recommended as a replacement of conventional X-ray for the diagnosis of osteolytic lesions by the European Myeloma Network.[1] In this prospective study we have compared the diagnostic performance of low-dose CT with conventional X-ray, and examined the added value of ^{18}Flourodeoxyglucose (^{18}FDG) positron emission tomography (PET), dual energy X-ray absorptiometry and serum markers of bone turnover in 35 previously untreated MM patients. Low-dose CT scan diagnosed significantly more patients with osteolytic lesions in both pelvis and spine compared with X-ray. ^{18}FDG-PET of spine and pelvis was positive in 9% of CT scans without osteolysis.

The presence of osteolytic lesions is one of the CRAB criteria that determines whether a patient with MM requires anti-myeloma treatment.[2] Skeletal X-ray is still widely used for the diagnosis of osteolytic lesions in MM, despite the limitations of 2-dimensional images for visualization of the complex anatomic structures of the spine and pelvis (Figure 1). Low-dose CT scan can visualize the bones in a 3-dimensional manner without the need for a major increase in radiation dose[3] and, in addition, provides relevant information regarding extramedullary disease. ^{18}FDG-PET scan can visualize increased metabolic activity of cells. Using ^{18}FDG-PET, a diffuse or focal accumulation of metabolically active myeloma cells may possibly be identified prior to the development of osteolytic lesions.

The bone assessments of this study serve as baseline for a set of secondary endpoints defined in a clinical trial testing an intensive 5-drug combination for first-line treatment of MM (ACVDL-trial). This clinical trial was approved by The Regional Scientific Ethical Committees for Southern Denmark (*id: 2011-0123*), registered at *clinicaltrials.gov (identifier: 01481194*) and by EUDRACT (*number 2011-002751-34*). The study was conducted in accordance with the Helsinki Declaration. All patients provided informed consent.

Thirty-five previously untreated MM patients in need of treatment according to the CRAB criteria[2] were enrolled. X-ray and low-dose CT of spine and pelvis were assessed separately as either positive or negative for osteolytic lesions. The images were reviewed by a team of radiology experts. The patients fasted for at least six hours before injection of ^{18}FDG with an activity of 4 MBq/kg (minimum 300 MBq), and then rested for one hour prior to the ^{18}FDG/PET scan. PET images were reviewed by nuclear medicine specialists. The spine and pelvis were considered as either positive or negative for focal PET-activity based on a standardized uptake value (SUV) above 2.5. Dual energy absorptiometry was preformed of the hip and lumbar spine (L1-L4). Fasting blood tests were collected for measurement of the bone resorption marker C-terminal cross-linking telopeptide of type I collagen (CTX) and the bone formation marker N-terminal propeptide of procollagen I (P1NP).

The 35 patients consisted of 21 men and 14 women, and mean age was 64 (49-81) years. Autologous stem cell transplantation was planned in twenty-three of the patients. ISS-score (international staging system) was: I=17, II=10, III=8. In one case, the CT-scan revealed a paramedullary tumor growth in the vertebral canal; asymptomatic but with imminent medullary compression (Figure 2). The findings that were confirmed by MRI showed a tumor growth with compression of the spinal cord and nerve roots. Given that the patient was asymptomatic, emergency surgery was not required; however, anti-myeloma treatment was started immediately. The individual results of X-ray, CT and PET are illustrated in Figure 3.

CT-scan was performed in all patients, whilst X-ray was carried out on 32 patients. The mean time between CT-scan and X-ray was 4 days (0-28 days). CT diagnosed significantly more patients with osteolysis than X-ray in both pelvis (P<0.01, n:32) and spine (P<0.05, n:32). However, only 6% of the patients would have been judged as asymptomatic if only skeletal X-ray had been performed, since osteolysis was diagnosed by X-ray in

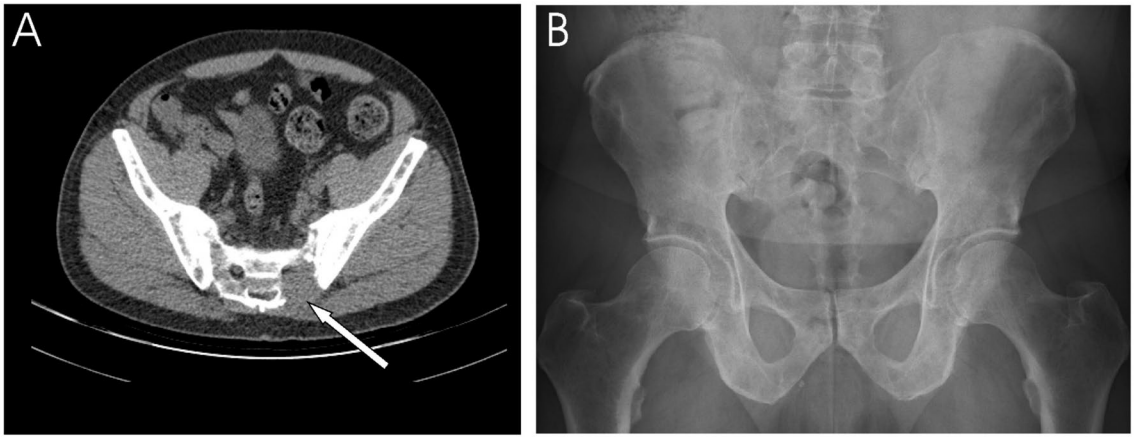

Figure 1. Low-dose CT *versus* conventional X-ray. Low-dose CT (A) and conventional X-ray (B) of a 67-year-old man with newly diagnosed multiple myeloma. X-ray performed 7 days after low-dose CT-scanning. The CT-scan shows a significant osteolytic lesion, not visualised at X-ray, of the pelvic area.

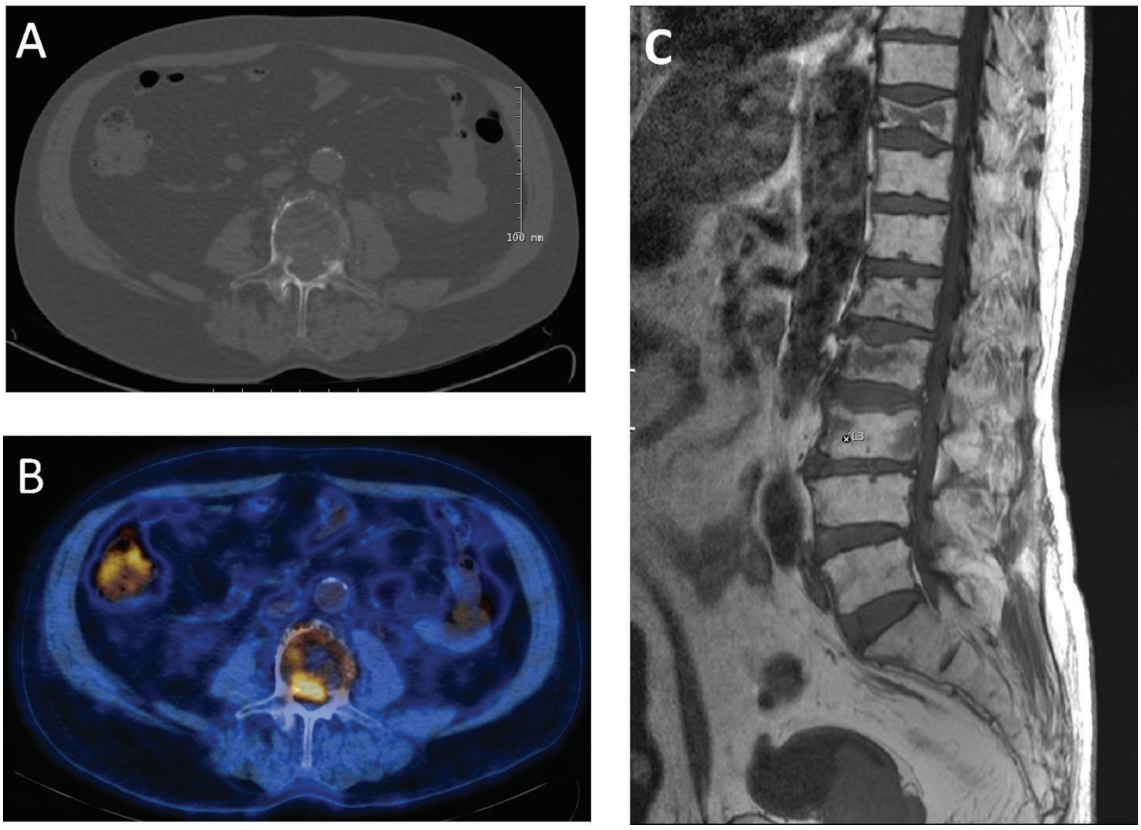

Figure 2. Imminent medullary compression revealed by low-dose CT. The low-dose CT-scan reveals tumor growth in the vertebral canal (A). This lesion was PET-positive (B). MR-scan confirmed the intra-spinal growth (C). The patient was asymptomatic.

other parts of the skeleton. Two patients were diagnosed positive for osteolysis of the pelvis using X-ray, whilst their CT scans were evaluated as negative. The first case (id 7) was later judged to be a false positive following re-evaluation of the initial X-ray and comparison with follow-up images. In the second case (id 21), re-evaluation of the CT-scan and retrospective comparison with follow-up CT-scans confirmed the presence of osteolysis. Overall, osteolytic lesions of either the pelvis or the spine were found in 50% of the patients examined by X-ray and in 74% by CT-scan.

PET imaging was carried out in all patients; however, in one of the cases the spine scan was considered inconclusive for technical reasons. The mean time between CT and PET was 3 days (0-48 days). PET positive foci were found in 37% of the patients in the pelvis and 38% of the patients in the spine, whilst 46% of the patients were PET positive in either the spine or the pelvis or both. PET positive foci were found in 9% of the negative CT-scans of the spine and the pelvis. PET was positive in 50% of the CT-scans showing osteolysis of the pelvis and positive in 52% of the CT-scans showing osteolysis of the spine.

Dual energy absorptiometry examinations were performed on all patients. The mean Z-score was 0.3 (-1.3 – 3.0) in the hip and 0.1 (-3.3 – 3.2) in the spine.

The serum levels of CTX and P1NP are shown in *Online Supplementary Figure S1.*

Correct evaluation of bone involvement is important in MM since the presence of osteolytic lesions is a "myeloma defining event"[2] and an indication for treatment. In the last decade, several studies have highlighted the limitations of X-rays for identification of osteolytic lesions in MM when compared with newer imaging modalities.[4] However, only a few studies (mainly retrospective) of mixed populations of previously treated and untreated MM patients have been made as a platform for claiming the superiority of CT-scan over X-ray for the detection of osteolytic lesions.[5-8] With a special focus on challenging areas such as the spine and pelvis,[3,6,8] our prospective study supports the superiority of CT over X-ray for detection of osteolytic lesions.

The higher sensitivity of CT-scan over conventional X-ray may lead to earlier detection of osteolytic lesions and, thereby, earlier initiation of treatment in patients with MM. Earlier detection of bone lesions by CT-scan followed by initiation of anti-myeloma treatment has not been formally proven to improve patient outcome. However, the improvement of survival seen after initiation of anti-myeloma treatment in patients with high-risk smoldering myeloma[9] makes it likely that early detection of bone lesions in MM patients, leading to initiation of therapy, will also be beneficial.

We report one case where the CT-scan showed an imminent but still asymptomatic compression of the spinal cord not detected by X-ray. This finding was confirmed by MRI. Early diagnosis of such critical bone lesions may prevent morbidity by early intervention.

The combination of PET and CT-scan is efficient for the diagnosis of osteolytic lesions in MM,[10] and may pro-

vide prognostic information.[11] We identified only one patient out of 35 with a positive PET-scan and a CT-scan without osteolysis; this patient had foci both in the spine and the pelvis. In a recently published study, Zamagni *et al*. reported that 15% of newly diagnosed, symptomatic MM patients with a positive PET-scan had a negative CT-scan.[12] The frequency of PET-positive patients in our study is lower than that reported by others.[13] The reason for this is not clear but may be due to difference in methodology, the definitions of osteolysis and PET-positivity, the MM population studied, and/or small sample size. Patients with diffuse, rather than focal, lesions of the bone marrow may escape detection by PET. Standardization of the PET-CT methodology and reporting is clearly needed.[10]

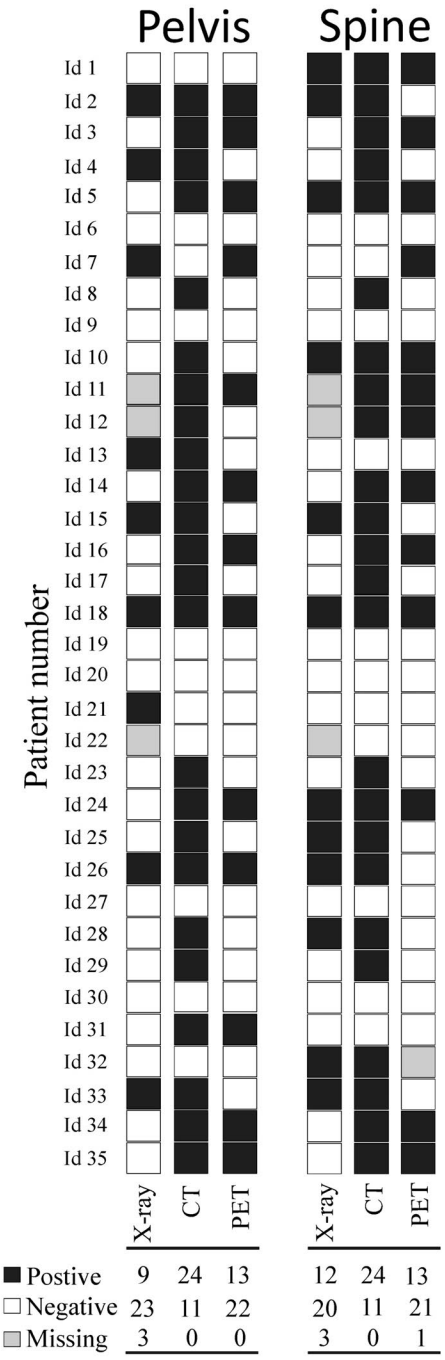

Figure 3 Results of X-ray, low-dose CT and PET. The individual results of the different imaging methods performed at baseline for the 35 previously untreated multiple myeloma patients. Below the columns are the numbers of positive, negative and missing results of each imaging modality shown. Low-dose CT identifies most patients with osteolysis. Black squares illustrate osteolysis at low-dose CT (CT), conventional X-rays (X-ray), and focal activity at ^{18}FDG-PET (PET), while white squares illustrate imaging without osteolysis of focal activity. Grey squares represent missing data.

In our study, the mean bone mineral density of newly diagnosed MM patients was similar to the normal reference and thus our results did not reproduce the finding of a generalized osteopenia in newly diagnosed MM which was reported in the 1990s.[14]

Forty percent of our patients had elevated levels of CTX, including patients without osteolysis by CT of the axial skeleton. Bone resorption markers have been reported to increase prior to progression of MM;[15] however, more studies may be needed to clarify whether they have a role in clinical practice.

We found that low-dose CT of the axial skeleton diagnoses significantly more patients with osteolysis than X-ray. In this study, ^{18}FDG-PET provided only little extra information regarding bone disease compared with low-dose CT. However, PET-CT may carry prognostic information and constitute a valuable parameter for the assessment of response.

We recommend low-dose CT rather than X-ray of the axial skeleton as a standard procedure for detection of osteolytic lesions at baseline assessments of MM patients. Low-dose CT may also provide information regarding paramedullary and extramedullary involvement, and risk of spinal cord compression. However, in cases with clinical symptoms of medullary cord or cauda equina compression, we recommend MRI for optimal visualization of the lesion. Thus, CT scan may be regarded as a powerful screening procedure to alert the clinicians to the existence of extramedullary manifestations in need of attention.

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