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

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Title: Baseline bone involvement in multiple myeloma – A prospective comparison of conventional X-ray, low-dose computed tomography, and 18fluorodeoxyglucose positron emission tomography in previously untreated patients.

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Letter to the editor:
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 replacement of conventional X-ray for the diagnosis of osteolytic lesions by the European Myeloma Network. In this prospective study we have compared the diagnostic performance of low-dose CT with conventional X-ray and examined the added value of 18Flourodeoxyglucose (18FDG) 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 to X-ray. 18FDG-PET of spine and pelvis was positive in 9% that had 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. 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 of radiation dose, and in addition provide relevant information about extramedullary disease. 18FDG-PET scan can visualize increased metabolic activity of cells. Using 18FDG-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 at 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 (NCT01481194) 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 with at need for treatment according to the CRAB criteria 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 at least six hours before injection of 18FDG with an activity of 4 MBq/kg (minimum 300 MBq), and then rested for one hour prior the 18FDG/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) activity above 2.5. Dual
energy absorptiometry was performed 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, 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 paramedullary tumor growth into the vertebral canal asymptomatic but with imminent medullary compression (Figure 2). The findings that were confirmed by MRI showed tumor growth with compression of the spinal cord and nerve roots. Given that the patient was asymptomatic, emergency surgery was not required, but 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, while 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 skeletal X-ray had been the only modality performed, because osteolysis was diagnosed by X-ray in other parts of the skeleton.

Two patients were diagnosed positive for osteolysis in the pelvis using X-ray, while 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 pelvis or spine were found in 50% of the patients examined by X-rays and in 74% by CT-scan.

PET imaging was carried out in all patients, but 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 pelvis and 38% of the patients in spine, while 46% of the patients were PET positive in either spine or pelvis or both. PET positive foci were found in 9% of the negative CT-scans of spine and pelvis. PET was positive in 50% of the CT-scans showing osteolysis of pelvis and in 52% of positive CT-scans 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 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. During the last decade, several studies have highlighted the limitations of X-rays for identification of osteolytic lesions in MM when compared to newer imaging modalities.\(^4\) However only few, mainly retrospective studies of mixed populations of previously treated and untreated MM patients have been made as a platform for claiming superiority of CT-scan over X-ray for 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,\(^9\) renders it likely that early detection of bone lesions leading to initiation of therapy of MM patients 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 provide prognostic information.\(^11\) We only indentified a single patient out of 35, with a positive PET-scan and a CT-scan without osteolysis, this patient had both foci in spine and 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 are lower than 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 a 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.\(^10\)

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 patients, but more studies may be needed to clarify if 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 to low-dose CT. However, PET-CT may carry prognostic information and be a valuable parameter for 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 that need attention.

**Acknowledgments**

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References


Figure 1
Title: Low-dose CT versus conventional X-ray.
Legend: Low-dose CT (A) and conventional X-ray (B) of a 67-year-old man with newly diagnosed multiple myeloma. X-ray is 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
Title: Imminent medullary compression revealed by low-dose CT.
Legend: The low-dose CT-scan reveals tumor growth into the vertebral canal (A). This lesion was PET-positive (B). MR-scan confirmed the intra-spinal growth (C). The patient was asymptomatic.

Figure 3
Title: Results of X-ray, low-dose CT and PET.
Legend: 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) and 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.
Supplementary material

Supplementary methods
Thirty-five previously untreated MM patients were enrolled in a prospective single centre phase-II study evaluating the safety and efficacy of the five drug combination of doxorubicin, cyclophosphamide, bortezomib, dexamethasone and lenalidomide as first-line treatment. All patients had biopsy proven MM that required therapy according to the CRAB criteria. Bone involvement at baseline was assessed by a set of imaging methods and serum markers of bone turnover as a secondary end point of this study. The imaging procedures encompassed conventional X-ray, low-dose CT, 18FDG-PET and dual energy absorptiometry scan. The serum markers of bone turnover were C-terminal cross-linking telopeptide of type I collagen (CTX) for bone resorption and N-terminal propeptide of procollagen I (P1NP) for bone formation. The examinations were performed at Vejle Hospital, Denmark between November 2011 and May 2014. With no minimum restriction on the size of osteolytic lesions, decisions about the significance of the findings were left to a dedicated team of radiology experts.

This clinical trial was approved by The Regional Scientific Ethical Committees for Southern Denmark (id: 2011-0123), registered at clinicaltrials.gov (NCT01481194) and by EUDRACT number 2011-002751-34. All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Imaging
Conventional X-ray: Included plain anterior-posterior radiographs of pelvis and anterior-posterior and lateral views of the total spine. Pelvis and spine were evaluated separately, and X-rays of the anatomic areas were assessed positive if at least one osteolytic lesion or malignant fractures was present and negative if not. The X-rays were reviewed by a team of five experienced radiographers certified to evaluate spine and pelvis X-rays. X-ray reviews were performed blinded to the results of the other imaging techniques.

Low-dose CT: CT-examinations were conducted as low-dose scans (120 KV, dose modulation) without the use of contrast medium, and with a reconstructed slice thickness of 3 mm on bone algorithm. Low-dose CT imaging was conducted in combination with PET or using a16-slices Philips Precedence scanner. The CT images were first assessed according to the standard procedure by two physician-specialists from the radiologic department with the aim to reach a consensus, and then reviewed by a radiologist with a specific expertise in bone examination by CT-scan.
anatomical areas of the spine and pelvis were considered as either positive or negative respectively for osteolytic lesions. Additional findings of soft tissues lesions by CT were also noted.

\textbf{18FDG-PET}: After fasting for at least six hours the patients received an injection of 18FDG with an activity of 4 MBq/kg (minimum 300 MBq), before resting for one hour prior the scan. Imaging was performed on one of two scanners: Philips Gemini TF 16 slices or Philips Gemini TF 64 slices and reconstructed with the Philips manufactory reconstruction protocol: Body-CTAC-NAC. The images were reviewed by two nuclear medicine physicians with the aim to reach a consensus. The anatomical areas of the spine and pelvis were either considered positive or negative for focal PET-activity based on the standard uptake volume (SUV) activity. A focal SUV activity above 2.5 was considered to be positive. Increased activity in tissue outside of the bone was also noted.

\textbf{DXA}: The hip and the lumbar spine (L1-L4) were scanned with dual X-ray technology on Hologic Discovery W equipment. While the left hip was the preferred choice, the right was scanned in case a patient had undergone hip replacement surgery. Those vertebrae that had either collapsed, received irradiation treatment or had been treated with vertebroplasty were excluded and the calculation was then carried out on the remaining vertebrae. Bone mineral density, the Z-values and the T-values were calculated.

\textbf{Serum markers of bone turnover}

Fasting blood tests were collected in the morning for measurement of the bone resorption marker C-terminal cross-linking telopeptide of type I collagen (CTX) (\(\beta\)-CrossLaps, Roche Diagnostics) and the bone formation marker N-terminal propeptide of procollagen I (P1NP) (Total P1NP, Roche Diagnostics).

\textbf{Statistics}

The statistical difference between the number of patients diagnosed with osteolysis by X-ray or low-dose CT-scan was calculated using Fishers exact test. P-values < 0.05 were considered statistically significant. Statistical analyses and graphical illustrations were performed using GraphPad Prism version 5.

Reference List

Supplementary figure, S1.

Supplementary figure:
Baseline levels of serum markers of bone turnover in 35 previously untreated multiple myeloma patients. Levels above the reference limits are marked with a black border. CTX reference values: Male 50-70 years < 0.84 µg/L; Male > 70 years < 1.05 µg/L; Females pre-menopausal < 0.59 µg/L; Females post-menopausal < 0.83 µg/L. P1NP reference values: Males 14-86 µg/L; Females pre-menopausal 15-59 µg/L, Females post-menopausal 16-74 µg/L. CTX: C-terminal cross-linking telopeptide of type I collagen. P1NP: N-terminal propeptide of procollagen I.