Dual-energy computed tomography: Virtual calcium subtraction for the assessment of bone marrow involvement of the spine in multiple myeloma

Poster No.: C-1935
Congress: ECR 2014
Type: Scientific Exhibit
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Keywords: Computer Applications-Detection, diagnosis, CT-Quantitative, CT, Oncology, Bones, Cancer
DOI: 10.1594/ecr2014/C-1935

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Aims and objectives

Multiple myeloma (MM) is a malignant haematological disease of the mature B-cell lymphocytes with a poor prognosis. Characteristic for MM is its accruement from the cells of the bone marrow mostly involving the entire bone marrow cavities. The patterns and the degree of medullary infiltration may, however, vary considerably, and determination of the tumor burden has implications for therapy and prognosis both at initial diagnosis and at the end of treatment regimens (e.g. for accurate appreciation of the tumor response) as well as for tumor surveillance (1-3 on page ).

For a long time and up to now, the assessment of the tumor burden was accomplished by serological markers like the M-gradient, β2-microglobuline, lactate dehydrogenase (LDH) and indirectly by measuring surrogate biomarkers like serum hemoglobin, creatinine and calcium in order to detect end-organ damage or replacement of normal hematopoietic cells by myeloma cells. With the advance of imaging techniques like CT, MRI and FDG-PET a more confident evaluation of the degree and pattern of myeloma infiltration has become possible and direct visualisation of myeloma cell invasion both in the bone marrow channels and extra-medullary has gained importance for the practicing haematologist. New reports about the role of imaging have encouraged their use in different clinical settings (4 on page , 5 on page ). Among modern imaging modalities, CT is the only modality that is capable of directly displaying bony structures and related bone abnormalities which are typical for MM, the so-called "myeloma bone disease". One major limitation of CT is, however, its lower sensitivity for detection of non-lytical bone marrow infiltration in the axial skeleton, where visualisation and measurement of bone marrow attenuation are in part severely hampered by the dense trabecular structure of the cancellous bone. Here, MRI and FDG-PET proved superior in this respect yielding a generally good sensitivity.

Dual Energy CT (DECT) was recently revived with the introduction of dual source CT (DSCT) (6 on page ). By simultaneous acquisition of two CT datasets at two different energy levels, certain materials with high atomic numbers such as calcium can be quantified using DECT (7-9 on page ), and can subsequently be removed from the images. This technique has been shown to be effective for the removal of iodine from datasets, creating virtual nonenhanced images (10-13 on page ). Besides iodine, also calcium can be removed. The resulting images can be called bone marrow (BM) images (14 on page ). BM images have previously been successfully used for the detection of bone marrow edema (14-16 on page ) and might consequently also facilitate the diagnosis of bone marrow infiltration by tumor cells.

The purpose of this study was thus to examine the additional benefit of DECT bone marrow images for the detection of medullary infiltration in patients with known or suspected MM with MRI as a standard of reference.
Methods and materials

Patients

The institutional review board approved this prospective study. Since June 2002, skeletal radiographs have been replaced at our institution by whole-body reduced dose multidetector CT for the assessment of bone involvement by MM. 32 patients with known MM or presenting with monoclonal gammapathy of unknown significance (MGUS) who were scheduled for whole-body CT for assessment of myeloma bone disease were prospectively enrolled into the study. All patients gave their informed consent. All included patients received clinically indicated unenhanced DECT and additional unenhanced whole-body MRI within two weeks.

DECT scanning protocol and image reconstruction

All scans were performed using a second generation DSCT-scanner (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). The DECT scanning protocol was dose-wise adapted to the regular full-body MM scanning protocol used at our institution. Tube voltages were set to 100 kV and 140 kV using additional tin filtration for hardening of the high energy spectrum. Automatic exposure control (CareDose 4D) was applied. Reference tube current time products were set to 230 mAs (100 kV) and to 178 mAs (140 kV). Collimation was 64x0.6 mm, with a pitch of 0.6 and rotation time of 0.33 s. The arms of the patients were elevated for the scan, and the scan ranged from the elbows to the knees, including the complete axial skeleton and the proximal parts of the appendicular skeleton (humeral and femoral bones).

For regular reading, sagittal and coronal multiplanar reformations (MPR) of the spine and the humeral and femoral bones are created (17). For DECT post-processing, axial slices were reconstructed using a dedicated non-edge-enhancing medium-soft reconstruction kernel (D30f) with a slice thickness of 1.5 mm and an increment of 1.0 mm and a field of view (FoV) of 25-30 cm, depending on the patient's anatomy.

MRI scanning protocol

All patients additionally received whole body MRI (1.5 T Magnetom Avanto, Siemens Healthcare). The protocol included at least coronal T1w imaging (2D turbo spin echo [TSE] sequence) in five regions from head to feet as well as sagittal T1w (2D TSE) and T2*w (2D gradient echo [GRE] sequence) imaging of the whole spine.

DECT image postprocessing and visualization
Postprocessing was performed using a software prototype written in the MATLAB environment (version 7, The MathWorks, Natick, MA) on a standard 64-bit-OS PC. The postprocessing software is based on standard DECT three material decomposition. In principle, it is assumed that voxels within the bone marrow can contain three material fractions with different x-ray absorption characteristics (fat, soft tissue and calcium), which contribute to the total attenuation within the voxel. Using a geometric approach (Figure 1), the total attenuation within the voxel can be separated into a fat/soft tissue partition and a calcium partition. Furthermore, the software prototype includes algorithms for noise reduction and bone segmentation based on thresholds and erosion. As input data, the prototype accepts the low- and high energy source data. As an output, two stacks of DICOM (Digital Imaging and Communications in Medicine) images are created: First an arithmetic average image of both input series (AV), resembling regular CT images with Hounsfield unit (HU) comparable to a scan with 120 kV, and second a series of virtual non-calcium bone marrow images (BM). Basic parameters for the three material decomposition were: Soft tissue: 57/55 HU (low/high kV), Fat: -103/87 HU (low/high kV), calcium slope 1.45.

For the evaluation of the DECT images, another MATLAB (version R2012a) program with viewing-capabilities was used, combining a 3D-MPR-viewing capability with color overlay image fusion and the propagation of region of interest (ROI) measurements to multiple datasets. In all patients, an MPR of the AV images was displayed in one viewport, while in another viewport the same image was displayed with a color overlay of the corresponding BM image. The color lookup table (LUT) for the color overlay was identical in all patients and specially designed for bone marrow reading. Negative HU-values are displayed blue, positive red, with purple-colored smooth transition around -10 to 10 HU.

**Establishment of the standard of reference**

All MRI images and all available clinical information were assessed in consensus by two readers with 18 (anonymized) and 6 (anonymized) years experience in oncologic imaging in order to establish a gold standard. In each patient, the overall level of bone marrow infiltration (none vs. moderate vs. high) and the pattern of infiltration (diffuse vs. multifocal) were graded.

**Image evaluation**

Image evaluation was performed in two reading sessions.

In the first reading session, the evaluation of the BM images was performed side-by-side with MR and was thus not blinded. This session served as a training session and was used to gain ROI measurement data. Depending on the number and locations of the lesions in MRI, a number of ROIs (10-20 per patient, depending of the total number of lesions) were drawn on representative regions in the DECT images, assessing both regions with and without infiltration as known from MRI in each patient. In patients with
diffuse infiltration or without any infiltration, larger ROIs were drawn in a number of vertebrae. Identical ROIs were applied to regular CT and BM images, and the area and the mean HU values within the ROIs in each image stack were stored. Furthermore, each ROI was characterized as lytical (inside known punched out lytical bone lesions) or non-lytical (in cancellous bone presenting no obvious bony defects) on the regular CT images.

The second reading session was performed at least 12 weeks after the training and measurement session. Here, each patient was reviewed again in consensus by both readers in a blinded fashion and in random order. At first, only the regular CT images of the spine were reviewed and rated, and then the BM images were made available additionally and rated. In each patient, the level of infiltration (none vs. moderate vs. high) was judged with CT alone and with additional BM images.

**Statistical analysis**

Statistical analysis was performed using JMP 10 (SAS, Cary, NC).

For visualization of the ROI-based HU measurements in AV and BM images, box-and-whisker-plots were created, showing the distribution of HU values in both datasets as functions of infiltration in MRI and lytic disease (Figures 2-4).

In order to find threshold values for bone marrow infiltration in lytic and non-lytic lesions, receiver operating characteristic (ROC) curve analysis and calculation of the area under the curve (AUC) were performed. Additionally, the Matthews correlation coefficient (MCC) was calculated. The MCC is a correlation coefficient between observed and predicted binary (two-class) classifications. It is based on the confusion matrix, taking into account true and false positives and negatives. The MCC returns a value between -1 and +1 with a coefficient of +1 representing perfect prediction, 0 random prediction and -1 complete disagreement between prediction and observation. An advantage of the MCC is that as a balanced measure it can be used even if the classes are of very different sizes.

We maximized the Matthews correlation coefficient. Hence, we compute the optimum thresholds, taking into account true and false positives and negatives. We report the corresponding sensitivity, specificity, accuracy, positive and negative predictive value.

Regarding the results of the blinded reading session, sensitivity, specificity, positive and negative predictive values were calculated as functions of pattern (diffuse vs. multifocal) and grading of infiltration (none vs. moderate+high and none vs. high).

**Images for this section:**
**Fig. 1:** Principle of the three material decomposition algorithm. In the low/high-diagram, every pixel can be represented with its low- and high energy coordinates. The red line connects the coordinates of pure fat and soft tissue. All mixtures of only these two materials can be found on this line. If calcium is added, the coordinates shift with the characteristic slope of calcium. Between the dashed blue lines, mixtures of soft tissue, fat and calcium can be found, and a quantification of the calcium content within the mixture is possible.
Results

Graduation of bone marrow infiltration

Using MRI and all available clinical information, bone marrow infiltration was graded as "none" in 13 patients. These patients were diagnosed with monoclonal gammopathy of unclear significance (MGUS, n=6), MM in complete remission (n=4) and unspecified amyloidosis (n=2). In 11 patients, the bone marrow infiltration was graded as "moderate" and in 8 patients as "high" (all diagnosed with MM). Altogether, 458 ROIs were evaluated. 134 ROIs were placed in areas where MRI showed bone marrow invasion, and 324 ROIs served as control in non-infiltrated areas. 37 ROIs were placed in areas with osteolyses and bone marrow invasion in MRI, and 27 ROIs were placed in osteolytic areas without active invasion.

Bone marrow attenuation in AV and BM images

Figure 2 shows box-and-whisker-plots of the distribution of HU values in AV and BM images as functions of infiltration in MRI (standard of reference) and osteolytic disease. A good separation between the attenuation values between positive and negative lesions can be observed in the BM images, whereas HU-measurements in AV images considerably overlap in non-lytical lesions.

Statistical evaluation

The results of the ROC analysis are given in table 1. While in lytic lesions, a discrimination of positive and negative lesions is possible using attenuation measurements in AV and BM images (area under the curve (AUC) of 0.877 and 0.916, respectively), AV images perform poorly in non-lytic lesions (AUC=0.577). BM images yield a good performance also in non-lytic lesions with an AUC of 0.932. Thresholds for the discrimination of pathologic and normal bone marrow in BM images with the highest sensitivity and specificity were 4 HU in lytic lesions and -3 HU in non-lytic lesions.

The highest MCC was 0.7288 for a threshold of 4 HU for the discrimination of pathologic and normal bone marrow in BM images, with a sensitivity of 89%, specificity of 85%, positive predictive value of 0.94 and negative predictive value of 0.77.

The evaluation of sensitivity and specificity in the blinded reading session revealed a sensitivity of 0 for CT alone in cases with diffuse infiltration (table 2). Using additional BM images, sensitivity could be improved to 75%, regarding only cases with high grade infiltration, and to 40% if also patients with low grade infiltration were included. In patients with multifocal lytic disease, CT alone already yielded satisfying sensitivities and specificities; in these cases the utilization of BM images lead to a slight improvement of the specificity. When combining the results of multifocal and diffuse infiltration, BM
images improved the sensitivity for bone marrow infiltration in comparison CT alone at the cost of a slight decrease in specificity due to more false positive findings.

**Radiation dose**

As recorded by the CT scanner, mean volume computed tomography dose index (CTD\textsubscript{vol}) and dose length product (DLP) were 10.8 (range 4.4-19.1) mGy and 1467 (range 606-2383) mGy*cm, respectively.

**Images for this section:**

**Fig. 2:** Box and whisker-plots of the distribution of virtual bone marrow (BM) and regular CT images (AV) as functions of bone marrow infiltration and osteolyses.
Fig. 3: Receiver operating characteristic curves, objectifying the efficiency of the detection of bone marrow infiltration in lytic and non-lytic lesions using bone marrow (BM) and regular CT images (AV)
Fig. 4: Patient with MM. The BM overlay reveals the infiltration, which is not occult in the regular CT images.
Fig. 5: Patient with high-grade diffuse infiltration of the spine following radiation therapy of the pelvis. BM image reveals diffuse bone marrow infiltration, the fatty bone marrow infiltration of the lower lumbar spine and the hemangioma in the 4th lumbar vertebra.
**Fig. 6:** Possible use for BM images in biopsy guidance. A standard biopsy of the iliac crest might lead to an underestimation of bone marrow involvement in this patient.
Conclusion

In this study, we assessed the potential of bone marrow images to detect bone marrow infiltration in patients with suspected medullary multiple myeloma. MRI served as a standard of reference. Two independent modes of evaluation were performed: First, the attenuation within ROIs, which were chosen according to MRI findings, was measured and compared between infiltrated and non-infiltrated areas of the spine. This evaluation yielded excellent results with a good separation of attenuation values between normal and infiltrated areas of the bone marrow, especially in cases of a diffuse non-osteolytic infiltration which is very difficult, if at all, to distinguish with CT alone.

In a second evaluation, complete datasets were read in a blinded fashion using CT alone and CT and BM images. Here, the sensitivity for non-lytic diffuse infiltration could be improved from zero to 75% (regarding only cases with high level of infiltration) or 40% (regarding also cases of moderate infiltration), compared to reading CT images alone. In cases with multifocal nodular infiltration, the specificity could also be slightly improved. In cases with diffuse infiltration, the specificity was slightly lower when BM images were used.

In the appendicular skeleton, bone marrow diagnosis is easily accomplished by CT, as the so-called yellow marrow of the adult exhibits negative attenuation values in the range of -10 to -80 HU which contrasts well with cell infiltrates that are highly attenuated as they consist of densely packed cell nests (18). As CT represents the work horse in the cancer diagnosis do to its high availability, relative low cost, short scan time and consequently higher patient's acceptance it would be beneficial to empower it by extending its diagnostic spectrum on the bone marrow cavities of the axial skeleton using BM images derived from DECT datasets.

DECT BM images have been used in several previous studies to detect traumatic bone marrow edema in the knee, the ankle and the spine. In the knee and the ankle, cut-off values between normal marrow and edema were found to be between -33 and -80 HU, in the only study evaluating bone marrow edema the cut-off for edema was also found to be rather low with -80 HU. The reason for this discrepancy (in our study, the cut-off for bone marrow infiltration was -3 HU for lytic and 4 HU for non-lytic lesions) might be a different post-processing algorithm or different parameters for the algorithm. The heavily computed-based and algorithm-dependent mode of post-processing clearly poses a disadvantage of this new technique. Standardization of investigational protocols as well as post-processing tools is imperative.
In conclusion, BM images created from DECT datasets of the spine have the potential to improve the sensitivity for the detection of diffuse bone marrow infiltration of the spine, especially in cases with high-grade diffuse or focal nodular infiltration.

**Personal information**

**References**


