Improvement of diagnostic confidence for detection of multiple myeloma involvement of the ribs by a new CT-software generating rib unfolded images

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Aims and objectives

Multiple myeloma (MM) accounts for approximately 10% of the hematologic malignancies and up to 90% of MM patients develop osteolytic or sclerotic bone lesions (myeloma bone disease) during the course of their disease [1,2].

The extent of myeloma bone disease has been added to the classification of MM by Durie & Salmon as an indirect measure of entire tumor burden and also as an expression of damaged end organ (bone) [3]. According to this risk classification, patients are classified as stage I if no or <2 lytic lesion are present and stage III if ≥2 lesions are detected at radiological diagnosis. Patients diagnosed with myeloma bone disease generally undergo therapy; therefore accurate bone imaging plays a crucial role in this clinical setting.

Hence, imaging is imperative and therefore improvement of lesion detection is a major requirement to all imaging techniques. CT-imaging, as an improved x-ray technique, is capable of diagnosis of tiniest bone defects as induced by MM and has therefore gained increasing attention in the last years [4-7].

Commonly multiple lesions are apparent in the spine, ribs, skull, pelvis and femoral bones [8]. According to earlier reports, the incidence of lytic lesions in the ribs reaches 60% and was thus found the most common [9]. However, ribs are known for their vaulty configuration with edges and steadily changing appearance on cross-sections exhibiting a course that is not ideally documented by transversal images.

In this study, we aimed at comparing sensitivity of CT-imaging using 5mm vs. 1mm thick CT slices vs. 1mm-based "unfolded rib" reformates for more confident skeletal diagnosis in patients with multiple myeloma.
Methods and materials

Subjects

116 consecutive patients (73 male, 43 female) were included in this study with suspected or confirmed diagnosis of multiple myeloma (n = 98) or MGUS (n = 18) as control group.

Multiple myeloma patients were all classified according to Durie & Salmon classification (1975) as stage I (17.3 %), stage II (14.3 %) and III (68.4 %).

CT image acquisition

At our institution radiological skeletal survey is performed in all stage I-III patients at least every 6-12 months.

CT examinations were performed unenhanced on a MDCT scanner (SOMATOM Definition AS+, Siemens Healthcare, Forchheim, Germany). A 128 x 0.6 mm collimation protocol with a 0.5 s rotation time was chosen. The tube voltage was 120 kV, effective tube current time product was 70 mAs [10]. The image matrix was 512 x 512, the reconstructed section thickness was 5mm and 1mm using an intermediate (B50) tissue spatial resolution kernel.

Image post-processing into "unfolded rib" images was performed using the commercially available "BoneReading" application of the syngo.via CT software package (Siemens Healthcare, Forchheim, Germany), which uses a virtual centerline as rotation axis for a scrollable plane (Figure 1). An example of the gained, rotatable images is displayed in Figure 2.

Image analysis

The presence or absence of myeloma rib involvement was assessed independently by two radiologists. Probabilities of the presence of lytic rib lesions on a per-site basis were then evaluated for transversal 5mm and 1mm CT-slices and subsequently for the "unfolded rib" ("BoneReading") software. Final diagnoses in case of discrepancy between the two readers were arrived at by consensus and by comparison to preceding and/or follow-up examinations, which were available for all MM patients.

The readers were asked to register any focal or diffuse rib lesions on an especially for this purpose prepared drawing displaying unfolded ribs of the entire thoracic cage. They recorded lesion location, number and the character of the lesion in terms of osteolytic vs. sclerotic or mixed osteolytic/sclerotic. Since in cases of diffuse myeloma bone disease or disseminated manifestations of rib osteolyses a differentiation between medullary and
cortical distribution is not reliably possible, cases with ≥20 osteolytic rib lesions (n = 31) were included in a subgroup for lesion distribution analysis.

Both readers received basic training in the use of this new technique (each >70 patients with other tumors metastatic to the bone). We drafted a layout of the thoracic cage displaying all ribs in an unfolded manner (similar to the used "unfolded rib"/"bone reading" display) counting the lesions for each rib, differentiating between right and left as well as anterior and posterior costal halves and scored them as 0, 1, <5, <10 and >10. Countings of more than 10 lesions per rib were found unnecessary due to limited lesion delineation caused by concomitant diffuse bone resorption. Nonetheless, for monitoring purposes, assessment of all skeletal lesions is mandatory for detection of progressive bone destruction.

According to the Durie & Salmon scoring system, we evaluated whether the separate reading of 5mm-, 1mm- and "unfolded rib"-images resulted in an up- or downstaging (1 lytic bone lesion = I; >2 lytic bone lesions = III and II = neither I nor III) based on either only the rib evaluation or on the assessment of the whole skeleton. Therefore, in cases with uncertain up- or downstaging, the whole-body CT was re-evaluated concerning presence of other osteolyses.

Attention was paid to excluding non-malignant rib lesions based on typical imaging characteristics.

All documented bone lesions were confirmed by follow-up whole body reduced dose MDCT studies as gold standard.

Synchronously, the reading time for each CT-analysis was recorded.

Statistical Analysis

Statistical analysis was performed using JMP 11.2 statistical software (SAS Institute Corp., Cary, North Carolina, USA).

The Kolmogorov-Smirnov test with Lilliefors significance correction was used for the normality test.

Wilcoxon signed rank test was used for significance testing concerning reading time and the differences between 5mm-, 1mm-slices and "unfolded rib" images.

Inter-observer correlation was tested using the Spearman Rank Order correlation coefficient.

Differences between 5mm-, 1mm-slices and "unfolded rib" images in lesion-wise analysis in the distribution subgroup (cortical vs. medullary) were tested using McNemar's test.

Values are given mean ± standard deviation, if not indicated otherwise.
A value of $p < 0.05$ was considered significant.
Fig. 1: Schematic draft of the way of functioning of the "Bone Reading" software: The software automatically generates a virtual centerline in the central part of the rib, which is consecutively used as rotation axis for "scrollable", plane CT slices.

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Fig. 2: Image example of unfolded rib ("bone reading") display presenting several lytic rib manifestation of multiple myeloma (note larger lytic bone lesion in the posterior/proximal part of the right 10th rib). The multi-display should simulate stepwise rotation of unfolded ribs.

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Results

Patient population

A total of 116 patients who underwent WBRD-MDCT at our institution between 2012 and 2014 were retrospectively included in this study. For follow-up confirmation of bone lesions chest-CT examinations performed at our institution were accepted as well. Since an ordinal scale (0, 1, 2, <5, <10, >10 lesions) was used, a dedicated sum of lesions cannot be given. However, based on this ordinal scale the approximated total number of myeloma-related rib lesions was 6727 (56.5 ± 127.1 per patient).

CT reading results

Results of WBRD-MDCT rib analysis for transversal 5mm, 1mm and "unfolded ribs" by 1mm slice thickness in terms of sensitivity, specificity and accuracy are tabulated in a patient by patient analysis and a lesion by lesion manner on Table 1 and 2.

Table 1: Patient-based analysis

<table>
<thead>
<tr>
<th></th>
<th>5 mm</th>
<th>1 mm</th>
<th>&quot;Unfolded Rib&quot;-Images</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>79.7 %</td>
<td>88.1 %</td>
<td>98.3 %</td>
</tr>
<tr>
<td>Specificity</td>
<td>94.7 %</td>
<td>93.0 %</td>
<td>96.5 %</td>
</tr>
<tr>
<td>Accuracy</td>
<td>87.1 %</td>
<td>90.5 %</td>
<td>97.4 %</td>
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</table>

Table 2: Lesion-based analysis

<table>
<thead>
<tr>
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<th>5 mm</th>
<th>1 mm</th>
<th>&quot;Unfolded Rib&quot;-Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>69.7 %</td>
<td>79.8 %</td>
<td>96.5 %</td>
</tr>
<tr>
<td>Specificity</td>
<td>87.2 %</td>
<td>55.9 %</td>
<td>89.7 %</td>
</tr>
<tr>
<td>Accuracy</td>
<td>70.5 %</td>
<td>78.0 %</td>
<td>96.1 %</td>
</tr>
</tbody>
</table>

Patient-based comparison of results between transversal 5mm vs. 1mm (p>0.05) and transversal 1mm CT images vs. "unfolded rib" images generated by the "BoneReading" software application (p>0.05) did not yield significant differences, but the difference between transversal 5mm vs. "unfolded rib" ("BoneReading") images proved statistically significant (p=0.01).
Lesion characteristics and distribution

31 patients with 20 osteolytic lesions were subdivided and analysed concerning lesion distribution inside the ribs (cortical vs. medullary). Inside this subgroup a total of 183 osteolytic lesions were detected (5.9 ± 5.8 lesions per patient; range: 1-18), from which 102 were classified medullary (55.7 %) and 81 cortical (44.3 %). Of the medullary lesions, 70 (68.6%) were detected in 5mm-slices, 84 (82.4%) in 1mm-slices and 100 (98%) in "unfolded rib" images (see Fig. 3). Of the cortical lesions n=53 (65.4%) were detected in 5mm-slices, n=67 (82.7%) in 1mm-slices and n=76 (93.8 %) in "unfolded rib" ("BoneReading") images (Fig. 4).

The differences between transversal 5mm and 1mm were significant both for medullary and cortical osteolyses (p = 0.03/0.002). Reading results were also significant for the comparison between 5mm and "unfolded rib" images (p=0.0001/0.0001) as well as between 1mm and "unfolded rib" ("BoneReading") images (p= 0.0008/0.03).

Analysis on per-patient basis

Focusing on the ribs, the per-patient analysis yielded 3 cases of upstaging between 5mm vs. 1mm, 20 cases (17.2%) of upstaging between 5mm transversal vs. "unfolded rib" images and 15 cases (12.9%) of upstaging between transversal 1mm CT images vs. "unfolded rib" images.

Regarding the whole skeleton, comparison between 5mm/1mm vs. "unfolded rib" images yielded 4 cases of upstaging (3.4%) and 1 case (0.9%) of downstaging. By the latter (0.9%) the use of the "unfolded rib" images resulted in a false positive upstaging.

Analysis on per-lesion basis

Sensitivity and accuracy increased significantly from transversal 5mm to 1mm (p=0.001) CT images, transversal 5mm to "unfolded rib" images (p<0.001) and transversal 1mm vs. "unfolded rib" images (p=0.02) again in favour of the latter (Table 2).

Inter-observer agreement testing yielded a correlation r of 0.74 for the 5mm-slices, 0.92 for 1mm-slices and 0.85 for the "unfolded rib" display.

Mean reading time was 178.7 ± 47.4 s (5 mm), 215.1 ± 55.9 s (1 mm) and 90.8 ± 49.9 s ("unfolded rib"), consecutively. Differences in the reading time between 5mm vs. 1mm (p<0.001), 5mm transversal vs. "unfolded rib" images (p<0.0001) and transversal 1mm CT images vs. "unfolded rib" images (p<0.001) proved all significant (Fig. 5). In MGUS patients as control group no lytic lesions were detected by both readers.
Fig. 3: Patient with multiple myeloma (IgG), multiple small osteolytic lesions in the whole rib skeleton and several rib fractures of the right 2nd-7th rib. The patient was undergoing therapy at that time and some of the osteolyses already showed some degree of sclerosis (re-mineralisation) at their edges.

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**Fig. 4:** 69-year-old female patient with newly diagnosed multiple myeloma (IgA) with predominantly medullary or subcortical localized rib lytic lesions on the left side. Note, that the subcortical/medullary osteolysis in the anterior/distal part of the left second rib is hardly detectable on 1mm axial slices (arrow).

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**Fig. 5:** Mean reading time per patient for rib diagnosis for 5mm, 1mm axial CT images and unfolded rib ("bone reading") images.

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Conclusion

Our data show that the use of "unfolded rib" display significantly improves rib lesion detection by avoiding partial volume averaging, focusing the attention of the reader on the entire course of the ribs and easing image reading by a multi-angle planar viewing approach. Moreover, we believe that advanced rib imaging using this new technical development may shorten the reading time considerably.
References


