

## COMPARISON OF WHOLE BODY MAGNETIC RESONANCE IMAGING AND CONVENTIONAL RADIOGRAPHY IN ESTABLISHING MULTIPLE MYELOMA RELATED BONE DISEASE: EXPERIENCE IN A RESOURCE LIMITED SETTING

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### Abstract

**Background:** In spite of recent studies which favour whole body magnetic resonance imaging (WB- MRI) over radiographic skeletal survey in the detection of skeletal lesions in myeloma, there is relatively scarce evidence of its utilization in resource limited setting. The objective is to compare the traditional radiographic skeletal survey and the WB-MRI, including the newer diffusion weighted MRI sequences, in the detection of bone disease in the newly diagnosed patients of myeloma. **Materials and Methods:** Standard laboratory workup, baseline skeletal survey and WB-MRI (T1, STIR, Diffusion weighted sequences from vertex to ankles) were obtained in thirty newly diagnosed myeloma patients. **Result:** WB-MRI detected skeletal lesions in 93% of patients in comparison to 70% by skeletal survey. WB-MRI showed superiority in cervical spine (33% on WB-MRI vs. 3% on skeletal survey; P = 0.004), thoracic spine (50% vs. 20%; P = 0.004), lumbar spine (63% vs. 17%; P < 0.001), pelvis (73% vs. 33%; P < 0.001) and clavicle (27% vs. 3%; P = 0.016), whereas, skeletal survey performed better in skull (10% vs. 33%; P = 0.015). There was no difference between the two imaging modalities in humerus, femur, ribs, sternum and scapulae. **Conclusion:** Considering the overall superiority of WB-MRI and the detection of lesions in skull by skeletal survey, we recommend WB-MRI along with skeletal survey in the assessment of bone disease in newly diagnosed patients of myeloma.

## INTRODUCTION

Multiple myeloma is a B cell malignancy of monoclonal immunoglobulin producing plasma cells in the bone marrow. It is characterised by the development of anemia, hypercalcemia, renal failure and bone disease.<sup>[1]</sup> Bone disease develops due to the interaction of the expanding myeloma cells with the bone marrow microenvironment and leading to imbalance in the osteoclastic and osteoblastic activity. Bone disease in multiple myeloma manifests usually as multiple osteolytic lesions, but can also cause diffuse osteoporosis, which will eventually lead to the development of pathological fractures.<sup>[2]</sup>

The diagnosis of multiple myeloma is clinicopathological and hence there is a need to establish the myeloma defining events, CRAB, which are

clinical manifestations of serious end organ damage.<sup>[3]</sup> One of them being the bone disease, is established using imaging modalities. Since the description of osteolytic bone lesions by Durie and Salmon,<sup>[4]</sup> the radiological skeletal survey has been the standard imaging technique in establishing myeloma bone disease, due to its low cost and wide availability. However, appearance of osteolytic lesions in skeletal survey is relatively late as there should be at least 30 – 50% loss of trabecular bone,<sup>[4]</sup> and, also x-rays are not suitable for visualization of osteoporosis and lesions in spine and pelvis. These drawbacks of skeletal survey underscore the need for more appropriate imaging techniques.

Many studies have been done in the past 30 years comparing different imaging modalities in the management of multiple myeloma, and, magnetic

resonance imaging (MRI) is one of the most promising tools and also MRI has been stated as the gold standard method of imaging for the detection of bone marrow involvement in multiple myeloma.<sup>[5]</sup> Studies have shown that MRI detects abnormal marrow infiltration in 18 - 31% of patients with negative skeletal survey,<sup>[1,6-8]</sup> and it also helps in defining the prognosis and monitoring of the treatment response.<sup>[1,5]</sup> To overcome the main limitations of conventional MRI, namely the longer duration of image acquisition, financial constraint and restricted field of view, the whole-body MRI (WB-MRI) protocol was introduced. Currently, the International myeloma working group (IMWG) consensus statement recommendation is limited to the use of conventional MRI sequences - T1, T2, STIR and post contrast sequences, with a remark made on diffusion weighted MRI (DW-MRI).<sup>[5]</sup> DW-MRI sequences are sensitive to bone marrow infiltration and is an important tool in myeloma detection and monitoring of treatment response.<sup>[5]</sup> IMWG has now recommended WB-MRI as the first line imaging for all patients suspected with smoldering myeloma,<sup>[5]</sup> meanwhile, National Institute for Clinical Excellence recommended the whole body MRI in both newly diagnosed myeloma and smoldering myeloma.<sup>[9]</sup> Although the WB-MRI has been used in different studies in the diagnosis of myeloma bone disease, there is relatively scarce evidence about its utilization in a resource limited setting. The present study is aimed to compare the conventional skeletal survey and the WB-MRI, including the newer DW-MRI sequences, in the detection of bone disease in patients of multiple myeloma and hence to view the relevance of WB-MRI in the resource limited setting of a developing country.

## MATERIALS AND METHODS

**Patients:** Between October 2017 and March 2019, 30 newly diagnosed patients of multiple myeloma presenting at Haematology department of a tertiary care hospital were included in the study. All patients had provided written informed consent as per the institutional guidelines.

The protocol had been approved by the institutional review board. Patients diagnosed with another malignancy or metabolic bone disease which may have secondary bone lesions, patients in whom skeletal survey couldn't be done due to their morbid illness were excluded from the study.

The standard questionnaire was completed during face-to-face interviews, which included data regarding demographic features, symptomatology and then a thorough clinical examination was done in all the patients. Pre-treatment imaging and laboratory work-up was done in all patients. Both radiographic skeletal survey and WB-MRI was done within one week after the diagnosis, before the

treatment was started. Standard laboratory work-up for myeloma was done in all patients.

### Imaging

**Skeletal Survey:** All patients underwent digital radiographs of Skull (antero-posterior [AP] and lateral), Rib cage (AP), Spine (AP and lateral of Cervical, Thoracic and Lumbar regions), Pelvis (AP), Femur (AP) and Humerus (AP). Unequivocal osteolytic lesion, rounded or oval non-surrounded gap, was considered as myeloma lesion.

**Whole body MRI (WB-MRI):** All the MRI examinations were carried out on a three Tesla (3T) MR system (GE Healthcare DISCOVERY MR 750W with GEM Suite Milwaukee U.S). The MR protocol included T1 coronal sequence (Repetition time [TR] = 839 ms, Echo time [TE] = 9 ms, slice thickness 4mm, spacing 0, number of excited states [NEX] = 1, Flip angle 120 degree, matrix), STIR coronal sequence (TR = 8730 ms, TE = 42 ms, slice thickness 4mm, spacing 0, NEX = 2, Flip angle 111 degree, matrix) and Diffusion weighted imaging (DWI) axial sequence (TR = 3407 ms, TE = minimum, slice thickness 4mm, spacing 0, NEX = 4, b value = 1000 s/mm<sup>2</sup>).

The images were acquired from Vertex to Ankles (including entire upper limb) in all the three MR sequences. T1 weighted and STIR sequences were obtained in four stations, while DWI sequences were obtained in six stations. All the patients also underwent T1 weighted and STIR sagittal sequences of the whole spine. The acquisition took about 30 to 35 minutes.

False positive results due to DWI hyperintensities is mitigated by direct correlation of lesions with morphologic appearances on T1 weighted and STIR images. MRI showing focal intramedullary lesion of size more than 5 mm with appropriate signal characteristics (T1 hyposignal, STIR hyper signal, hyper intense on DWI) is considered to be focal myeloma lesion.<sup>[5]</sup>

Diffuse signal characteristics throughout the marrow is considered as diffuse pattern of myeloma lesion. Structured clinical reporting was done, which included, the site of the myeloma lesion, pattern of marrow infiltration (focal, diffuse, focal on diffuse, or variegated), extramedullary site involvement, location of vertebral fractures and cord compression and any other incidental findings.

Two Radiologists were involved in the analysis of the images and it was read in consensus between them. They were blinded to both patient baseline characteristics and the radiographic skeletal survey.

**Statistical analysis:** IBM SPSS version 22 was used for statistical analysis. McNemar's test was performed to compare the proportion of positive lesions of skeletal survey and WB-MRI according to the different sites. A value of  $p < 0.05$  was chosen as a criterion for the statistical significance.

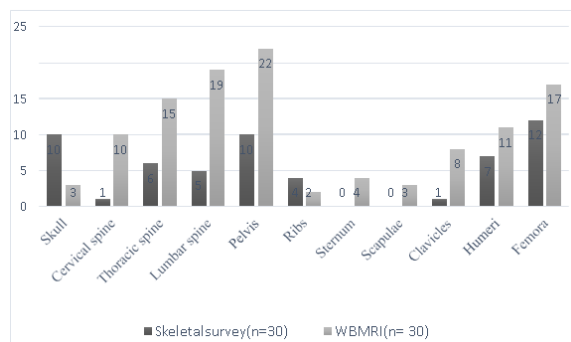
## RESULTS

Comparison of skeletal survey and WB-MRI

**Patient by patient analysis:** Among 30 patients, 21(70%) patients had bone lesions on skeletal survey, while 28(93%) patients had lesions on WB-MRI; two (7%) patients were negative for bone lesions in both the imaging techniques, whereas 21 (70%) patients had bone lesions in both skeletal survey and WB-MRI. Among nine (30%) patients without any bone lesions on skeletal survey, seven (23%) patients had lesions on WB-MRI. Vertebral fractures were identified in six (20%) patients in both skeletal survey and WB-MRI. One patient had cord compression with minimal symptoms, which was identified by MRI. One patient showed extramedullary myeloma lesion along with other skeletal lesions on WB-MRI.

Among the 28 patients with positive lesions on WB-MRI, 13 patients had focal pattern, seven had diffuse pattern, seven had both focal and diffuse pattern and one had variegated pattern of myeloma lesion.

Among the seven patients who had lesions on WB-MRI alone, six of them had lesions in lumbar spine, five had lesions in pelvis, two had in humeri, one had in cervical spine and thoracic spine, and one had in sternum. MRI pattern of lesions among them were focal pattern in four patients and diffuse pattern in three patients.



**Figure 1: Distribution of skeletal lesions on skeletal survey and WB-MRI in different anatomical sites**

**Site by site analysis:** Significantly higher proportion of patients had lesions on WB-MRI than on skeletal survey in:

- Cervical spine (33% of patients on WB-MRI vs. 3% on skeletal survey;  $P = 0.004$ );
- Thoracic spine (50% vs. 20%;  $P = 0.004$ );
- Lumbar spine (63% vs. 17%;  $P < 0.001$ );
- Pelvis (73% vs. 33%;  $P < 0.001$ );
- Clavicles (27% vs. 3%;  $P = 0.016$ ).

Significantly higher proportion of lesions were found on skeletal survey than on WB-MRI in:

- Skull (33% on skeletal survey vs. 10% on WB-MRI;  $P = 0.015$ ).

There was no significant difference in the proportion of lesions detected by WB-MRI and skeletal survey in:

- Ribs (7% on WB-MRI vs. 13% on skeletal survey);

- Sternum (13% vs. 0%);
- Scapulae (10% vs. 0%);
- Humeri (37% vs. 23%);
- Femora (57% vs. 40%).

Two (7%) patients had lesions in tibia on WB-MRI. No lesions were seen in bones distal to elbow on WB-MRI. Radiographs of appendicular skeleton distal to elbow in upper limbs and distal to knee in lower limbs were not included in the study protocol.



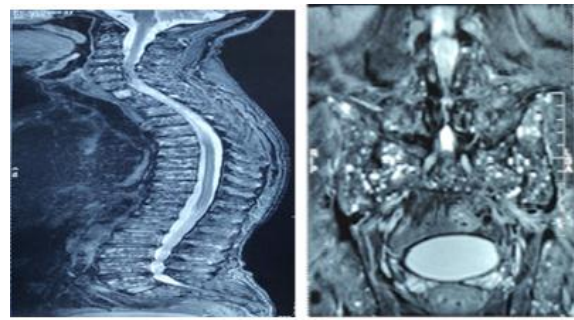
**Figure 2: A patient with ISS stage 3 myeloma with 60% bone marrow plasma cell infiltration. A Whole body T1 weighted, B Whole body STIR and C Inverted whole body DWI (b1000) coronal images displaying extensive bone marrow involvement with lesions in spine, pelvis, bilateral femur, ribs and bilateral humerus. It shows both focal and diffuse pattern of bone marrow involvement.**



**DRadiography of the skull displays numerous punched out lytic lesions, but the WB-MRI failed to demonstrate the lesions in skull. E Radiography of the lumbar spine is negative for any lesion, meanwhile the WB-MRI demonstrates multiple lesions.**



**Figure 3: A patient with symptomatic myeloma with ISS stage 2. A Radiography of the pelvis displaying destructive lytic lesion of the right iliac bone extending up to the sacroiliac joint with associated soft tissue swelling, B Whole body T1 weighted coronal images and d Whole body DWI (b1000) coronal images demonstrating large soft tissue mass of right pelvic bone with normal femur. WB-MRI also demonstrates lesions in the lumbar spine, left clavicle and left humerus (not visible in this image)**



**Figure 4: A patient with ISS stage 3 myeloma had bone marrow plasma cell infiltration of 40%. Radiographic skeletal survey didn't reveal any lesion, A STIR sagittal images of the whole spine, BT1 weighted sagittal images of whole spine and C STIR coronal images of the pelvis displaying inhomogeneous infiltration of the spine and pelvis giving variegated/salt-and-pepper appearance. Focal lesion involving the anterior two-third of T1 vertebral body is seen appearing hyperintense on STIR and hypointense on T1 weighted images**

## DISCUSSION

There is a clear association between the multiple myeloma disease burden and the skeletal involvement,<sup>[5]</sup> and hence imaging for bone lesions has prime importance in the diagnosis of multiple myeloma. 70% of the patients in our study showed osteolytic lesions on skeletal survey. Previous studies have shown that the skeletal survey is positive in 80% of the patients, wherein 10-15% of these lesions were of osteoporotic type.<sup>[11]</sup> As plain radiographs are not suitable for the diagnosis of myeloma related osteoporosis,<sup>[5]</sup> we didn't consider reporting osteoporotic lesions on skeletal survey in our study. Plain radiographs are referred to as 'morphological' imaging technique, as they represent the damage to the mineralized bone and it detects an osteolytic lesion only when 30-50% of the bone mineral density has been lost.<sup>[4]</sup> This results in low sensitivity of radiographs, ultimately leading to the underestimation of the bone involvement by skeletal survey in the range of 30-60%,<sup>[6]</sup> which is similar to the results seen in our study.

MRI is referred to as 'functional' imaging technique as it has the ability to directly visualize the bone marrow rather than its secondary effects on cortical bone. Hence it can visualize the bone lesions even before the osteolytic lesions are formed.<sup>[12]</sup> This has led to higher sensitivity of MRI over skeletal survey and it has been reciprocated in our study, showing 93% positive lesions by WB-MRI as compared to 70% positive lesions by skeletal survey in patients of multiple myeloma. Sensitivity of MRI in previous studies on multiple myeloma varies due to differences in the sequence utilized in MR imaging and the diversity in the field of view (FOV). MR imaging of only axial skeleton (spine and pelvis) will provide limited FOV and thus it could miss the lesions in the long bones, in turn leading to lower

sensitivity. This has been shown by Walker et al,<sup>[1]</sup> and Lecouvet et al,<sup>[13]</sup> demonstrating 74% and 79% sensitivity of MRI spine and pelvis, respectively. To overcome this drawback, whole body MRI protocols have been introduced. Sensitivity of whole body MRI also depends on the MR sequences utilized in imaging. Newer MRI sequence, Diffusion weighted imaging allows highly sensitive evaluation of soft tissue and bone marrow, which is quick to perform and interpret.<sup>[14]</sup> Even though IMWG recommends the use of conventional MRI sequences in the evaluation of myeloma patients,<sup>[5]</sup> it is the whole body MRI including the DWI which has become established as the most sensitive technique for the bone marrow imaging.<sup>[15,16]</sup> Ghanem et al,<sup>[6]</sup> demonstrated positive lesions in 74% of patients using whole body MRI-STIR sequences; Narquin et al,<sup>[8]</sup> and Sachpekidis et al,<sup>[15]</sup> utilized DWI with limited FOV and demonstrated lesions in 81% and 90% of patients, respectively. Larger FOV and utilization of newer DWI along with the conventional MRI sequences could have led to the higher sensitivity of the WB-MRI in our study than previous studies. To the best of our knowledge, the present study is the first in its category to utilize whole body DWI sequences in imaging myeloma patients from vertex up to ankles including entire upper limb.

Our study shows clear superiority of WB-MRI over skeletal survey by demonstrating bone lesions in additional 23% of patients who otherwise were negative on skeletal survey, which is comparable to the previous studies with 18 – 31% additional detection of bone lesions.<sup>[1,6-8]</sup>

Site by site analysis of our study shows superiority of WB-MRI over skeletal survey in vertebrae and pelvis. This superiority of MRI over plain radiograph in axial skeleton has been repeatedly demonstrated and confirmed in previous studies.<sup>[1,6,8,17-22]</sup> This might be due to the difficulty in identifying osteolytic lesions on plain radiographs in trabecular bones of spine, and also superimposition of bowel images over vertebrae hinders the identification of bone lesions in radiographs.

Historically, the demonstration of lesions in skull and ribs has been proven to be difficult by the MRI.<sup>[23]</sup> The superiority of plain radiograph in the detection of lesions in the skull as demonstrated in our study could be because of the presence of the adjacent high signal intensity of the brain on high b-value images leading to impairment in the visibility of lesions on MR imaging.<sup>[14]</sup> This is similar to the previous studies which utilized whole body DWI,<sup>[8,24]</sup> whereas other studies showed no difference between the skeletal survey and MRI in the detection of lesions in the skull.<sup>[1,6,13]</sup> Our study didn't show any difference in the detection of the lesions in the ribs by both imaging modalities. This might be due to the poor MRI resolution in the rib cage due to respiratory movements leading to discrepancies. Amidst different studies favouring

either MRI or skeletal survey in imaging the ribs,<sup>[1,8,24]</sup> Lutje et al,<sup>[25]</sup> have concluded that MRI is not a reliable tool for investigating the ribs, skull and clavicles, because of its high false negative results.

Even though higher number of lesions were demonstrated by WB-MRI in femur adheres, it failed to show significant difference from the skeletal survey in our study. Similar results were observed by Narquin et al,<sup>[8]</sup> and this might be due to the easy identification of osteolytic lesions in the cortical bones by plain radiographs because of the contrast between the defect and its background. Superiority of skeletal survey in imaging humerus and femur as demonstrated by Walker et al,<sup>[1]</sup> could be due to the limited FOV in MRI. In our study, there were two patients who had lesions in tibia in WB-MRI, but it was out of the FOV in skeletal survey, and thus recognizing the importance of the inclusion of the imaging of distal extremities in the WB-MRI protocols. One of the limitations of this study is that we didn't consider reporting the number of lesions in each bone in both the imaging techniques.

## CONCLUSION

WB-MRI shows clear superiority over skeletal survey. Whole body MRI protocols must consider to include the distal extremities of appendicular skeleton as well as to improve its sensitivity. Considering the limited time taken by the WB-MRI and its high sensitivity, it justifies its relevance to be used routinely in a resource limited setting in the diagnosis of multiple myeloma along with skeletal survey.

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