Whole body diffusion-weighted imaging (WB-DWI) to assess treatment response in multiple myeloma

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Target Audience: Radiologists, radiographers, physicists and clinicians with interest in Whole Body Diffusion Weighted MRI (WB-DWI) of myeloma bone disease.
Purpose: Myeloma, a plasma cell malignancy characterised by bone disease (1), relies on serum and urinary measurement of paraproteins and/or light chains and bone marrow histology for diagnosis, staging and response assessment. Paraproteins are not measurable in all patients and cannot detect intra-lesional differences in response, whilst bone marrow trephine is vulnerable to sampling error (2). X-ray skeletal survey (SS) is used to screen for lytic bone lesions (3), but it is poorly sensitive. The aim of this study was to investigate WB-DWI for assessing treatment response in myeloma.

Methods: 23 myeloma patients underwent WB DWI before treatment using a Siemens Magnetom Avanto 1.5T system with Total Imaging Matrix to allow multiple surface coil elements to be used in conjunction. 5 stations of a single shot double spin echo EP DW sequence using STIR in free-breathing were acquired covering skull vertex to knees in blocks of 50 slices (slice thickness 5mm, no gap, FOV 430mm, phase direction AP, GRAPPA factor 2, TR 14800 ms, TE 66 ms, TI 180 ms, voxel size 2.9x2.9x5 mm, 4 NSA, matrix 150 x 150, bandwidth 1960 Hz per pixel). Diffusion gradients with b values of 50 and 900 s/mm^2 were applied in 3 orthogonal directions and averaged to provide isotropic trace images. Morphological imaging was provided by axial T1W spin echo and coronal Vibe Dixon 3D gradient echo sequences. In 17 patients, a follow-up scan was acquired after 3 months of treatment. In 13 of the 23, SS was compared to WB DWI. Laboratory tests formed the gold standard; patients were considered responders if they achieved at least a partial response (PR) according to uniform criteria (3). Qualitative image analyses were undertaken by 2 experienced observers using a proforma scoring system to assess appearances of b900 s/mm^2 MIP images in conjunction with the morphological imaging. Quantitative analyses were conducted using Siemens OncoTreat software to generate Apparent Diffusion Coefficient (ADC) histograms from co-registered volumetric segmentations of visible marrow within vertebral bodies, sternum, pelvis and femora, from which any change in shape or position of histograms was summarised by calculating the percentage mean ADC change and the t statistic (difference in means ÷ standard error of the means) for each patient. Independent samples t tests were used to determine whether there were differences in these variables between those who responded to treatment and those who did not.

Results: Scores assigned to WB DWI were higher than for SS and there was less variation in assessment of disease between observers on DWI compared to SS (***Figure 1***).Fifteen of 17 patients were correctly classified as responders/non-responders on qualitative analysis when a ≥6% reduction in score was used as a threshold. Quantitative analysis showed significant differences in percentage change in mean ADC (p=0.008) and in the value of t (p=0.006) between 12 responding and 5 non-responding patients (***Figure 2***) with a right shift or broadening of histograms seen in responders. Whilst the number of pixels included within the segmentations varied between patients, they were constant across time points in each case. There were strong correlations between laboratory markers of response (serum paraproteins where measurable, serum light chains/bone marrow trephine where not) and percentage change in mean ADC (r = -0.77, p<0.001) and t (r = 0.855, p<0.001). Example images and histograms are shown in ***Figure 3***.

Figure 1: Scores assigned to SS and MRI in the qualitative analyses

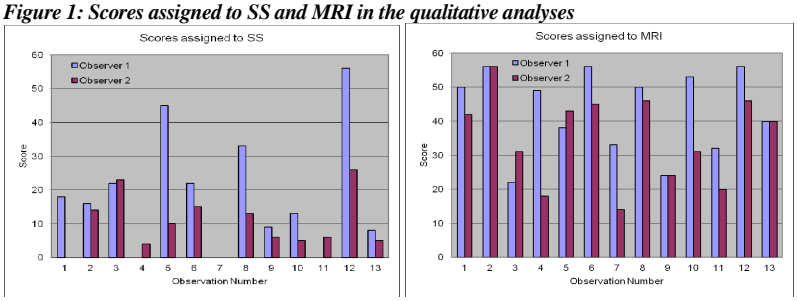

Figure 2: Box and whisker plots demonstrating differences in responders and non-responders

(a) Differences in % change in mean ADC *(b) Difference in the t statistic*

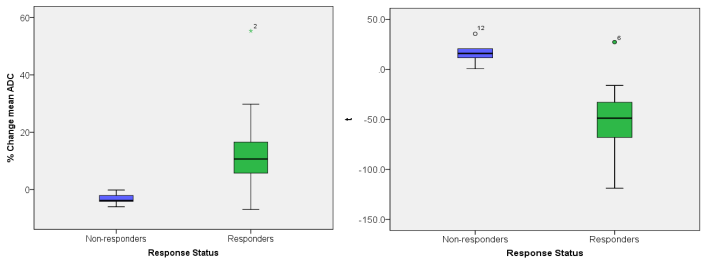

Figure 3: Example images and histograms from:
(a) responding patient ***(b) non-responding patient***

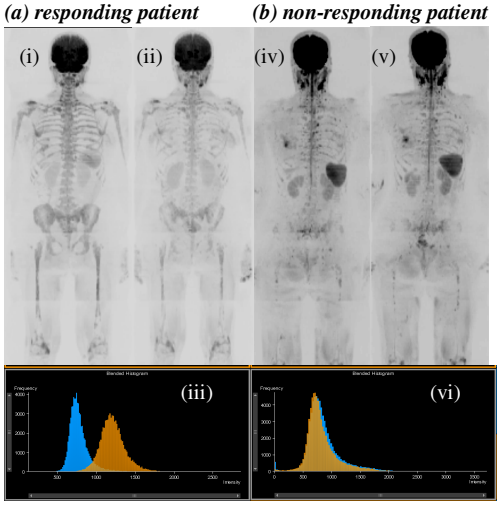

Figure 3a (i) &(ii) shows inverted grey scale b900 s/mm^2 MIP images for a patient achieving very good PR at the time of the post treatment scan; the ADC histograms (iii) show a shift to the right post treatment (orange) compared to pre treatment (blue). Figure 3b shows corresponding images (iv) & (v) and ADC histograms (vi) for a patient with stable disease without a post treatment shift.

Discussion and Conclusions: WB-DWI is a useful biomarker of treatment response in myeloma, with 88% patients correctly classified by qualitative analysis and 94% by ADC analysis. The strong correlation between ADC and laboratory markers of response is reassuring and WB-DWI also overcomes limitations of standard laboratory methods of response, being evaluable in all patients and allowing detection of differential response in lesions. In contrast to other studies (4), this study used a volumetric segmentation technique to analyse data. Limitations were the degree of change in ADC indicative of response which was in some cases relatively small, and may well be within estimates of reproducibility set by other studies at our institution (mean difference of 1.8% in ADC measurements at 2 time-points; range: 0.3-9.2%; coefficient of repeatability: 81.7%; intraclass correlation coefficients of 0.981 and 0.991 for intra- and inter-observer comparisons respectively) (abstract submitted). The relative roles for qualitative and quantitative analysis techniques need to be determined before robust response criteria can be developed.

References: (1) Walker et al, 2007, *Journal of Clinical Oncology,* 25(9), 1121-1128; (2) Horger et al, 2011, *Acta Radiologica*, 52, 881–888; (3) Rajkumar et al, 2011, *Blood*,117(18), 4691–4695; (4) Horger et al, 2011, *AJR*, 196, 790-795

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