Whole skeleton ADC histogram characteristics of normal marrow and myeloma infiltrated marrow in patients with low and high disease burden

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Target Audience: Radiologists, physicists and clinicians with interest in Whole Body Diffusion Weighted MRI (WB-DWI) of myeloma bone disease.

Purpose: Staging of multiple myeloma is currently reliant upon bone trephine, serum paraproteins and skeletal survery. Bone trephine is used as the gold standard but is vulnerable to sampling errors because it represents approximately 0.02% of a patient's bone marrow. Furthermore, trephine samples are unable to interrogate heterogeneity of this often widespread disease. Also, not all patients with myeloma secrete paraproteins. Skeletal survey is an inherently insensitive technique requiring > 50 % cortical destruction before disease becomes apparent on plain film (1). WB-DWI offers an alternative for staging and response assessment particularly due to its quantitative capabilities. We have previously demonstrated that mean Apparent Diffusion Coefficient (ADC) of normal bone marrow is significantly different to myeloma involved bone marrow based on comparisons of regions of interest selected in the lumbar spine and pelvis (2) but have not as yet interrogated ADC histogram analysis (3) for assessing the presence and extent of disease. The purpose of this prospective study was to compare mean ADCs and histogram characteristics of marrow from the whole spine, bony pelvis, femora and sternum between normal volunteers and patients with myeloma and between those with low compared to high burden of disease as defined by bone trephine.

Methods: 8 healthy volunteers and 21 myeloma patients were scanned with a Siemens Magnetom Avanto 1.5T system with Total Imaging Matrix to allow multiple surface coil elements to be used in conjunction. A single shot echo-planar DW sequence using STIR fat-suppression was acquired in free-breathing 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). In volunteers 2 stations were acquired through abdomen and pelvis, compared to 5 stations in patients to cover from skull vertex to knees. Diffusion gradients with b values of 50 and 900s/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 proton density weighted 3D gradient echo sequences. Quantitative analyses were conducted using Siemens OncoTreat software to generate Apparent Diffusion Coefficient (ADC) histograms from volumetric segmentations of visible marrow within vertebral bodies, sternum, pelvis and femora.

Results: There were significant differences ($p<0.05$) in mean ADC, 25th, 50th and 75th percentiles between normal volunteers and myeloma patients (Table 1). In addition, the mean ADC of patients with <50% marrow infiltration on bone trephine was significantly lower ($p<0.05$) than those with heavier infiltration of >50%. Serum paraproteins were difficult to correlate with burden of disease as 2 out of 13 patients with < 50% infiltration and 4 out of 6 patients with >50% infiltration had no detectable serum paraproteins.

Table 1: ADC measurements *(2 patients had non quantifiable disease on bone trephine)*

Parameter	Normal volunteers n=8	Myeloma Patients n=21	p value	Parameter	< 50% marrow infiltration n=6	>50%marrow infiltration n=13	p value
Mean ADC (x10^{-6}mm^2/sec)	734.9+/-53.6	835.5+/-107.6	0.003	**Mean ADC (x10^{-6}mm^2/sec)**	798.8+/-71.2	902.3+/-143.9	0.047
10th percentile (x10^{-6}mm^2/sec)	533.0+/-28.1	541.3+/-107.5	0.748	**10th percentile (x10^{-6}mm^2/sec)**	494.6+/-73.8	612.8+/-121.4	0.065
25th percentile (x10^{-6}mm^2/sec)	586.4+/-28.0	634.8+/-100.6	0.055	**25th percentile (x10^{-6}mm^2/sec)**	589.5+/-55.5	710.4+/-123.0	0.061
50th percentile (x10^{-6}mm^2/sec)	657.4+/-36.2	750.1+/-103.3	0.001	**50th percentile (x10^{-6}mm^2/sec)**	705.9+/-57.5	833.2+/-129.3	0.061
75th percentile (x10^{-6}mm^2/sec)	778.6+/-69.9	939.0+/-139.2	0.001	**75th percentile (x10^{-6}mm^2/sec)**	907.0+/-123.1	1017.0+/-164.4	0.121
90th percentile (x10^{-6}mm^2/sec)	1041.5+/-198.7	1188.6+/-321.5	0.133	**90th percentile (x10^{-6}mm^2/sec)**	1245.3+/-220.9	1083+/-519.3	0.344
Skew	2.7+/-0.5	1.9+/-0.8	0.047	**Skew**	2.0+/-0.9	1.7+/-0.7	0.451
Kurtosis	10.5+/-5.0	7.4+/-5.8	0.176	**Kurtosis**	7.5+/-6.8	6.0+/-4.0	0.554

Discussion and Conclusion: Mean ADC and ADC histogram characteristics of normal volunteers and myeloma patients were significantly different as were ADCs in those with a low compared to a high disease burden making WB-DWI a promising quantitative technique for disease staging. This small series also demonstrates the limitations of serum paraproteins as they were undetetectable in more than half of patients who had a high disease burden (>50% infiltration on trephine). Future studies powered to interrogate the relationship between ADC histograms and disease burden and prognosis are justified. Although bone trephine allows histological assessment, it is prone to sampling errors and is an invasive technique which limits the frequency of its evaluation in longitudinal response assessments whereas WB-DWI offers advantages of non-invasive repeated quantitative assessments for assessing treatment response.

References: (1) Edelstyn GA et al. 1967, Clin Rad; 18(2):158-62. (2) Messiou C et al, 2011 Eur Rad; 21(8):1713-8. (3) Kyriazi et al 2011, Radiology 261(1):182-92.

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