Assessing response of myeloma bone disease with diffusion-weighted MRI

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Objectives: To measure apparent diffusion coefficient (ADC) values in patients with active myeloma and remission and to determine whether changes differ in those responding/progressing on treatment. The relationship between changes in marrow fat and ADC was also explored.
Methods: 20 patients were recruited. T_1 weighted, T_2 weighted, short tau inversion-recovery, diffusion-weighted and two-point Dixon MRI of the lumbar spine and pelvis were performed at baseline, 4–6 weeks and 20 weeks.
Results: ADC values of active disease (mean $761.2 \pm 255 \times 10^{-6}$ mm^2 s^{-1}) were significantly higher ($p=0.047$) than marrow in remission (mean $601.8 \pm 459 \times 10^{-6}$ mm^2 s^{-1}). Changes in ADC in responders showed a significant increase at 4–6 weeks ($p=0.005$) but no significant change between baseline and 20 weeks ($p=0.733$). ADCs in progressing and stable patients did not change significantly between either time point. Pearson's correlation coefficient between change in fat fraction and change in the number of pixels with an ADC of $\leq 655 \times 10^{-6}$ mm^2 s^{-1} was 0.924, indicating a significant correlation ($p<0.001$).
Conclusion: ADC values in active myeloma are significantly higher than marrow in remission, indicating the potential for diffusion-weighted MRI to quantify the transition from active disease to remission and *vice versa*. This study confirms significant changes in ADC in patients responding to treatment and indirect evidence from two-point Dixon MRI suggests that these changes are influenced by changes in marrow fat.
Advances in knowledge: ADC of active myeloma is significantly higher than marrow in remission; the direction of ADC changes on treatment is dependent on the timing of measurements and is influenced by changes in marrow fat.

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In myeloma, response assessment relies on serum paraproteins and bone marrow examination [1], which indicate an individual patient's disease status without information on response at individual disease sites. Current guidelines recommend MRI only in cases of suspected cord compression, to stage apparently solitary plasmacytoma and to clarify ambiguous radiograph or CT findings [2]. On MRI of bone, where standard T_1 weighted (T_1W) and T_2 weighted (T_2W) techniques measure structural changes, responding focal lesions may remain stable in size within fixed bony defects, so that size measurements are non-informative [3]. Robust and reproducible measures of functional changes that occur with treatment together with criteria that indicate the time course of treatment-induced changes in individual lesions would provide significant benefits in myeloma, particularly in the assessment of response to novel therapeutic agents.

Diffusion-weighted MRI (DWI), which bases tissue contrast on microscopic water movement within tissues, is a non-invasive technique that can quantify structural and functional changes within tissues [4] and provide information on individual lesions within the entire skeleton [5], thus overcoming sampling error inherent in marrow biopsy. The quantified parameter derived from diffusion-weighted imaging is the apparent diffusion coefficient (ADC), which is a direct indicator of water movement within extracellular and intracellular space and is thus directly related to tissue cell density [4]. In tissues of high fat content, such as bone marrow, the paucity of free water and the effect of fat on water diffusivity [6] lowers the ADC. The purpose of this study, therefore, was to measure ADC values in patients with myeloma in active and remission status and to determine whether changes over time are significantly different in those responding to treatment from those with progressive disease as defined by serum paraproteins and marrow histology. Segmentation of ADC histograms was used to quantify changes in the fat component of marrow related to treatment response.

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Materials and methods

This was a prospective, single-institution study with institutional approval from the local research ethics committee. Written informed consent was obtained from each subject.

Patient population

20 patients with histology-proven myeloma were recruited. Group 1 comprised 8 with active myeloma (age range 45–75 years, mean 59.5 years, 5 female, 3 male) and Group 2 comprised 12 patients in disease remission (age range 43–76 years, mean 58.1 years, 6 female, 6 male). The diagnosis of symptomatic myeloma was made according to the International Myeloma Working Group Criteria [7], and the diagnosis of remission was made according to the European Group for Blood and Marrow Transplant Guidelines [8].

Patients with active disease received treatment with a standard haemato-oncology regimen at our institution consisting of: cyclophosphamide 500 mg on days 1, 8 and 5; thalidomide 100–200 mg continuously; dexamethasone 40 mg on days 1–4 and 12–15, cycle duration 21 days, duration 3–6 cycles.

Five responders received granulocyte colony-stimulating factor receptor (GCSF) prior to the 4- to 6-week MRI and four responders received GCSF prior to the 20-week MRI. Time between the last dose of GCSF and MRI scan ranged between 7 and 85 days with a mean of 30 days. The number of 300-μg doses between scans varied between 1 and 5, with a mean number of doses of 2.2.

Imaging

Patients were imaged at baseline (within 1 week prior to commencement of therapy), at 4–6 weeks and at 20 weeks following treatment. Patients in remission had imaging at identical time points. MRI was performed on a 1.5-T Siemens Avanto (Siemens, Forchheim, Germany) using surface coils placed anteriorly and posteriorly on patients positioned supine. Sagittal T_1W [590/11 ms repetition time/echo time (TR/TE); 400 mm field of view (FOV), 4 mm slice thickness], T_2W (2690/93 ms TR/TE; 400 mm FOV; 4 mm slice thickness) and short tau inversion-recovery (STIR) (7670/81 ms TR/TE; 400 mm FOV, 4 mm slice thickness) images of the spine and axial T_1W (607/19 ms TR/TE; 340 mm FOV; 5 mm slice thickness), T_2W (5340/127 ms TR/TE; 340 mm FOV; 5 mm slice thickness) and STIR (3680/78 TR/TE; 340 mm FOV; 5 mm slice thickness) images of the pelvis were acquired.

Single-shot twice-refocused diffusion-weighted echo planar images [9] in a transverse plane were acquired covering the lumbar spine and pelvis with the following parameters: 3000/80 ms TR/TE; FOV 350 mm, slice thickness 5 mm, four averages, three orthogonal directions and *b*-values of 0, 50, 750, 1300 and 1400 s mm^{-2} with SPAIR (spectral selection attenuated inversion recovery) fat saturation. A maximum *b*-value of 1400 s mm^{-2} has previously been shown to be optimal for imaging malignant bone disease [6].

Two-point Dixon images through the lumbar spine and pelvis in a transverse plane were obtained in order to obtain fat fraction and water fraction images with the following parameters: TR 6.88 ms, TE 2.38 and 4.76 ms, FOV 380 mm, slice thickness 5 mm, one average.

Data analysis

Disease was classified in Group 1 as responding, stable or progressing at 4–6 weeks and 20 weeks, and in Group 2 as stable or progressing at these time points. Response criteria were based on paraproteins measured at baseline (within 1 week prior to commencement of therapy if applicable), 4–6 weeks and 20 weeks in all cases (50% reduction of serum M protein and reduction in 24-h urinary M protein by 90% or to 200 mg per 24 h. If serum and urine M protein were unmeasureable, a 50% decrease in the difference between involved free light chain levels was required in place of the M-protein criteria. If serum and urine M protein were unmeasureable and serum free light assay was also unmeasureable, a 50% reduction in plasma cells was required in place of M protein [1, 8]). Marrow sampling was performed at all time points in one case of non-secretory myeloma to assess response.

Image analysis

Monoexponential ADC maps using all five *b*-values (0, 50, 750, 1300, 1400 s mm^{-2}) were generated using system software, using T_1W and STIR MR sequences to aid region of interest (ROI) placement. Up to five ROIs were drawn on ADC maps, avoiding areas of artefact. Sites of marrow biopsy identified by imaging appearances/patient notes were avoided. In cases of extensive diffuse disease or if bone marrow appeared normal, 2.3 cm^2 ROIs were placed in right and left iliac bones and in L4–S1. ROIs were visually transferred onto the same regions on follow-up studies. Mean ADC was documented at baseline and at follow-up.

ADC histograms were generated from individual ROIs and the number of pixels with an ADC value of $\leq$655 mm^2 s$^{-1}\times10^{-6}$ likely to represent normal marrow fat were calculated for each time point. Previous work has shown that an ADC value of 655×10^{-6} mm^2 s^{-1} differentiates normal and pathological marrow with a sensitivity of 90% and specificity of 93% [6].

Fat fraction maps (fat/fat+water) were generated from slice-matched two-point Dixon images using DiffusionView. ROIs within L5 at all time points were transferred from the ADC maps onto these fat fraction maps and the fraction of fat within each ROI was documented.

Statistical analysis

Data were analysed using SPSS® v. 15 (SPSS Inc., Chicago, IL) and tested for normality using the Kolmogorov–Smirnov test. An independent samples *t*-test was used to identify differences in baseline marrow ADCs between patients in both groups and the percentage of pixels representing fat in both groups.

Table 1. Numbers of patients and lesions

Time of imaging following treatment	Group 1: 8 patients with active myeloma (n=35)			Group 2: 12 patients in remission (n=47)		
4–6 weeks	7 patients responding (n=28)		1 patient missed scan	8 patients stable (n=29)	4 patients missed scan	
20 weeks	6 patients responding (n=25)	1 patient missed scan	1 patient progressing (n=5)	8 patients stable (n=29)	2 patients progressing (n=10)	2 patients missed scan

Paired t-tests were used to interrogate changes in mean ADC before and after treatment in responding, progressing and stable patients. Bland–Altman limits derived from normal volunteer studies [6] were applied to scatter plots of ADC changes in all patients with time.

Percentage changes in the number of pixels with an ADC of $\leq 655\,mm^2\,s^{-1}\times10^{-6}$ representing the fat fraction on the ADC maps were correlated with percentage changes in fat fraction acquired from two-point Dixon MRI using Pearson's correlation coefficient.

Results

Comparison of ADC values and fat fraction between groups at baseline

ADC values of lesions from patients in Group 1 (n=35, mean $761.2\pm255\times10^{-6}\,mm^2\,s^{-1}$) were significantly higher (p=0.047) than those in Group 2 (n=47, mean $601.8\pm459\times10^{-6}\,mm^2\,s^{-1}$). Baseline ADC histograms showed a significant difference in the percentage of pixels with an ADC of $\leq655\times10^{-6}\,mm^2\,s^{-1}$ in Group 1 *vs* Group 2 (27.2% *vs* 83.0%, respectively, $p\leq0.001$).

Comparison of ADC values in responders, progressors and stable disease

At 4–6 weeks, response to treatment was seen in seven patients in Group 1 while eight patients in Group 2 were stable (five patients did not have a scan at 4–6 weeks). At 20 weeks, six patients were responding to treatment, eight remained stable (in Group 2), whereas three (one in Group 1 and two in Group 2) had progressive disease. Follow-up of two ROIs was lost at 4–6 weeks because of artefacts, and one patient who was responding at 4–6 weeks did not undergo a further MRI at 20 weeks. Numbers of patients responding, stable and progressing and number of lesions measured at each time point are given in Table 1.

Per lesion analysis

Changes in ADC in 28 lesions in 7 responders showed a significant increase at 4–6 weeks (p=0.005) but no significant change between baseline and 20 weeks (p=0.733) or between 4–6 and 20 weeks (p=0.065). ADCs in progressing and stable patients did not change significantly between either time point (Table 2).

The percentage change in ADC for paired lesions in responders between (i) baseline and 4–6 weeks, (ii) 4–6 weeks and 20 weeks and (iii) baseline and 20 weeks was 33.1%, −19.5% and −3.7%, respectively; in stable patients changes were −2.4%, −5.9% and −4.6%, respectively, at these time points. The percentage change for lesions in progressors at 20 weeks was 10.3%.

Bland–Altman limits of ADC reproducibility derived from previous normal volunteer studies [6] ($19.6\pm85.8\times10^{-6}\,mm^2\,s^{-1}$) applied to scatterplots of changes in all categories of patients showed that 60.7% of lesions in responding patients (17 out of 28) increased in ADC above these limits at 4–6 weeks and 82.6% (19 out of 23) reduced in ADC below these limits at 20 weeks (Figure 1a). In stable patients, 70.0% (20 out of 29) and 72.4% (21 out of 29) of lesions were within stable limits at 4–6 weeks and 20 weeks, respectively. In progressing patients, 53.3% of lesions (8 out of 15) remained within Bland–Altman limits at 20 weeks, 20.0% of lesions (3 out of 15) showed an ADC decrease and 26.7% (4 out of 15) showed a rise.

Changes in the percentage of pixels representing fatty marrow in responders and progressors did not reach significance at 4–6 or 20 weeks (Table 3). However, the

Table 2. Per lesion analysis: mean apparent diffusion coefficient (ADC) values of lesions in responding, progressing and stable patients from both groups at baseline, 4–6 and 20 weeks

Patients	Baseline mean ADC ($\times10^{-6}\,mm^2\,s^{-1}$)	4–6 week mean ADC ($\times10^{-6}\,mm^2\,s^{-1}$)	20 week mean ADC ($\times10^{-6}\,mm^2\,s^{-1}$)
Responders	n=30	n=28	n=25
	782 ± 260	960 ± 402	721 ± 451
Change from baseline (p-value)		0.005	0.733
Change from 4–6 weeks (p-value)			0.065
Progressors	n=15		n=15
	537 ± 154	N/A	574 ± 168
Change from baseline (p-value)			0.315
Stable patients	n=29	n=29	n=29
	709 ± 514	703 ± 5090.74	675 ± 486
Change from baseline (p-value)		0.74	0.06
Change from 4–6 weeks (p-value)			0.07

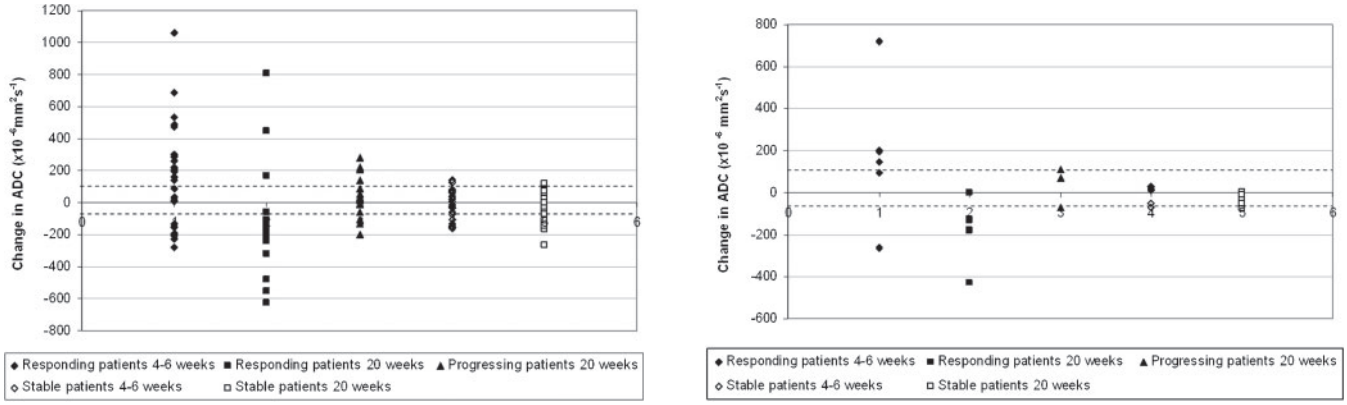

Figure 1. (a) Per lesion changes in apparent diffusion coefficient (ADC) values of bone marrow in patients with myeloma responding to treatment, progressing patients and stable patients in remission with monoclonal gammopathy of uncertain significance (MGUS). Bland–Altman limits derived from reproducibility studies on normal volunteers [6] are shown by dotted lines. (b) Per patient changes in ADC of bone marrow in responders, progressors on treatment and stable patients in remission/MGUS. Bland–Altman limits derived from reproducibility studies on normal volunteers [6] are shown by dotted lines.

percentage of pixels representative of fatty marrow showed a consistent decrease in progressors. In responding patients there was heterogeneity of changes in the fatty component at 4–6 weeks and 20 weeks.

Per patient analysis

A single mean ADC from all measured lesions was determined for each patient at baseline, 4–6 weeks and 20 weeks. In responders, ADC showed a significant increase at 4–6 weeks ($p=0.046$) and a significant decrease between 4–6 and 20 weeks ($p=0.029$) (Table 4).

The percentage change in ADC for responders between (i) baseline and 4–6 weeks, (ii) 4–6 weeks and 20 weeks and (iii) baseline and 20 weeks was 31.6%, −16.3% and 6.2%, respectively. Stable patients showed a −1.9%, −5.5% and 5.5% change, respectively, at these time points.

The percentage change for progressors at 20 weeks was 6.3%.

Bland–Altman limits of reproducibility of ADC derived from normal volunteer studies ($19.6 \pm 85.8 \times 10^{-6}\,mm^2\,s^{-1}$) applied to scatterplots of changes in ADC (Figure 1b) showed that ADC increased in 66.7% of responding patients (four out of six) at 4–6 weeks and decreased in 83.3% (five out of six) at 20 weeks (Figure 2). At 4–6 weeks and 20 weeks, 87.5% (7 out of 8) of patients with stable disease were within Bland–Altman limits. Of the small number of progressors (three), one showed ADC changes within Bland–Altman limits, one showed an ADC rise and one an ADC fall.

Receiver operating characteristic (ROC) analysis of percentage ADC changes between stable and responding patients at 4–6 weeks gives a significant area under the curve (AUC) of 0.682 ($p=0.012$), with an ADC change of 3.3%, distinguishing responders with 65% sensitivity and 59% specificity. ROC analysis of percentage changes of responders *vs* stable patients between 4–6 and 20 weeks and 0 and 20 weeks produced poor ROC curves (AUC=0.228 and 0.415, respectively). ROC analysis of percentage change in ADC of progressors *vs* stable patients and progressors *vs* responders at 20 weeks produced AUCs of 0.637 ($p=0.118$) and 0.345 ($p=0.118$), respectively.

Correlation of fat fraction from ADC with two-point Dixon techniques

Fat fraction was measured by two-point Dixon and by ADC histogram segmentation at baseline and at 4–6 weeks of follow-up in nine cases. Pearson's correlation coefficient between percentage change in fat fraction measured by two-point Dixon and percentage change in the number of pixels with an ADC of $\leq 655 \times 10^{-6}\,mm^2\,s^{-1}$ was 0.924, indicating a significant correlation ($p<0.001$).

Table 3. Per lesion analysis: percentage of pixels with apparent diffusion coefficient (ADC)$\leq 655 \times 10^{-6}\,mm^2\,s^{-1}$ from matched regions of interest at baseline, 4–6 and 20 weeks in responders, progressors and stable patients

Number of patients	Baseline percentage of pixels with an ADC of $\leq 655 \times 10^{-6}\,mm^2\,s^{-1}$ (%)	4–6 weeks percentage of pixels with an ADC of $\leq 655 \times 10^{-6}\,mm^2\,s^{-1}$ (%)	20 weeks percentage of pixels with an ADC of $\leq 655 \times 10^{-6}\,mm^2\,s^{-1}$ (%)
Responders (*n*=6)	28.8 ± 40	36.5 ± 43	61.3 ± 47
Change from baseline (*p*-value)		0.33	0.09
Change from 4–6 weeks (*p*-value)			0.07
Progressors (*n*=3)	65.0 ± 18		49.7 ± 15
Change from baseline (*p*-value)			0.10
Stable (*n*=8)	72.6 ± 27	67.3 ± 33	74.4 ± 25
Change from baseline (*p*-value)		0.07	0.36
Change from 4–6 weeks (*p*-value)			0.11

Table 4. Per patient analysis: mean total apparent diffusion coefficient (ADC) values for responding, progressing and stable patients in both groups at baseline, 4–6 weeks and 20 weeks

Number of patients	Baseline mean ADC ($\times 10^{-6}$ mm^2 s^{-1})	4–6 week mean ADC ($\times 10^{-6}$ mm^2 s^{-1})	20 week mean ADC ($\times 10^{-6}$ mm^2 s^{-1})
Responders (n=6)	719 ± 314	778 ± 244	602 ± 255
Change from baseline (p-value)		0.046	0.355
Change from 4–6 weeks (p-value)			0.029
Progressors (n=3)	537 ± 88	N/A	573 ± 147
Change from baseline (p-value)			0.578
Stable (n=8)	650 ± 352	644 ± 347	614 ± 334
Change from baseline (p-value)		0.657	0.104
Change from 4–6 weeks (p-value)			0.170

Discussion

This study has documented ADC values in active myeloma and in myeloma marrow in remission and shown that values in the former are significantly higher, indicating the potential for DWI to quantify the transition from active disease to remission and *vice versa*.

Both per lesion and per patient scatterplots showed an increase in ADC at 4–6 weeks and a fall in ADC at 20 weeks in responders. These ADC changes may reflect necrosis/oedema at 4–6 weeks followed by return of normal marrow fat at 20 weeks. The heterogeneity in direction of ADC change at both time points particularly in the per lesion analysis may be related to timing of oedema/necrosis and return of marrow fat in individual lesions. A rise in marrow ADC in responders at 3 weeks has been described by Horger et al [10] and a fall in ADC after treatment at an unspecified time point was found by Hillengas et al [11]. The use of two time points in this study gives new insight into the temporal changes in ADC in patients responding to treatment. Clearly, judicious timing for DWI follow up will be necessary in future studies. Although we have not interrogated the relationship between magnitude of paraprotein and ADC changes, there is preliminary evidence for a relationship between ADC and serum paraproteins. Sommer et al [12] found higher ADCs and T_2 signal in patients with a serum M component $<20\,g\,l^{-1}$ *vs* those with $>20\,g\,l^{-1}$.

The linear relationship between changes in fat fraction in bone marrow as measured by two-point Dixon and ADC histogram segmentation provides indirect evidence that the presence of fat in normal marrow is a major contributing factor to restricted diffusion in normal

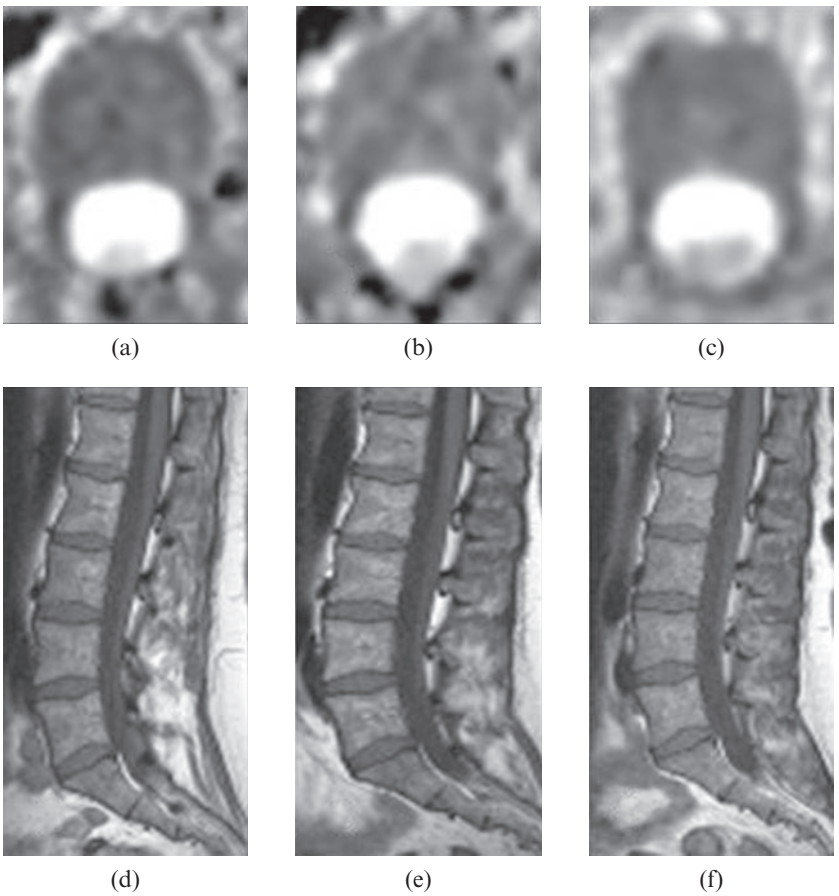

Figure 2. Apparent diffusion coefficient (ADC) maps of the lumbar spine at baseline (a), 4–6 weeks (b) and 20 weeks (c), and corresponding sagittal T_1 weighted (T_1W) MRIs (d,e,f) in a patient with diffuse myeloma disease responding to treatment show diffuse increase in ADC at 4–6 weeks followed by a reduction in ADC at 20 weeks. This was the most common pattern of ADC change in responders. Serum paraproteins fell from $39\,g\,dl^{-1}$ at baseline, to $32\,g\,dl^{-1}$ at 4–6 weeks and $3\,g\,dl^{-1}$ at 20 weeks. Despite significant ADC changes, the T_1W marrow signal remained unchanged over time.

marrow. Whether marrow fat acts as a barrier to diffusion or simply displaces extracellular matrix reducing measureable signal from free water remains to be determined.

Following on from this, although changes in the fraction of normal marrow fat measured by ADC histogram segmentation did not reach significance in this small series, the proportion of marrow fat in the majority of responders decreased at 4–6 weeks and increased at 20 weeks, which is in keeping with early necrosis/oedema followed by the return of normal marrow fat indicated by mean ADC data. The percentage of normal marrow as defined by ADC decreased in all progressors. Although mean ADC, ADC histogram segmentation and two-point Dixon as markers of disease status may all prove useful, this study has shown that because normal fatty marrow can be replaced both by tumour in progressors and necrosis/oedema in responders, more complex ADC histogram interrogation may prove to be the most sensitive method of quantification. If the ADC of necrosis/oedema which is likely to be higher than that of tumour can be defined, DWI could be used to measure changing proportions of normal marrow fat, tumour and necrosis/oedema.

The effects of GCSF on ADC were not formally examined in this study as numbers were too small to draw conclusions. GCSF has the potential to increase diffusivity in bone marrow as the increase in cellular marrow with its associated extracellular matrix displaces fatty marrow. The ADC of cellular marrow induced by GCSF may not differ significantly from diseased marrow, hence the lack of a consistent effect in this series. GCSF effects also are likely to be dependent on multiple factors such as dose, timing and status of bone marrow at the time of administration. In this study, length of time between GCSF administration and MRI scan as well as the number of doses administered was variable.

This study confirms significant changes in ADC in patients responding to treatment, and indirect evidence from two-point Dixon MRI suggests that these changes are influenced by changes in marrow fat. Vascularity may also have an effect on ADC [13], as there is positive correlation between vascular density and marrow infiltration [11]. Unfortunately the protocol employed in this study did not include sufficient low *b*-value data to extract this information. These data using spine and pelvic coverage provide good evidence and groundwork to justify a prospective study of whole-body DWI assessment of tumour, vascularity, fat and necrosis over time and their effect on ADC in a larger patient cohort. Semi-automated techniques must also be developed to enable use of whole data sets, as lesion selection is likely to be a source of bias and undersampling. Optimum timing of DWI follow-up and the relationship between ADC changes and magnitude of response will require documenting compared with conventional imaging methodologies. Early identification of non-responders would have major clinical implications, allowing timely alterations in treatment. Comparisons with other markers of disease activity such as 18-fludeoxyglucose positron emission tomography/CT may also allow correlation on a lesion-by-lesion basis to interrogate heterogeneity of response.

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