ADC changes with time in focal and diffuse myeloma bone disease as indicators of disease response and progression.

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Introduction The predominance of fat in adult marrow demands a systematic approach to interpretation of diffusion weighted (DW) magnetic resonance imaging (MRI) in bone. In marrow disease return of normal fatty marrow following treatment results in increased restriction of water diffusion[1] and leads to an ADC fall. Focal necrosis however results in a conflicting ADC rise. This study examines the time course of ADC changes in bone with treatment comparing progressors and responders in order to establish changes associated with response on DW MRI.

Methods DW MRI of lumbar spine and pelvis of 5 patients with active disease embarking on therapy and 7 patients undergoing surveillance (5 patients in remission/2 monoclonal gammopathy of uncertain significance, MGUS) was performed at baseline, 4 and 20-24 weeks (mean patient age 59.4 years): Siemens Avanto 1.5T, axial plane, slice thickness 5mm, TR 3600ms, TE 70ms, 7 averages, 3 orthogonal directions and b values of 0, 50, 250,750, 1300, 1400 smm^{-2} with SPAIR. Corresponding T1 and T2W imaging was also performed to guide ROI placement. Monoexponential ADC maps were generated using system software. Regions of interest (ROIs) (up to 5 per patient) were drawn around lesions or whole bone if disease was diffuse. For patients under surveillance with no obvious marrow abnormality or diffuse abnormality on T1W/DW MRI a $2.3cm^2$ ROI was drawn in L5 and left and right iliac bones. Serum paraproteins and bone marrow trephine samples taken at comparable time points were used as markers as disease activity for correlation with imaging.

Results 20 ROIs from patients responding to treatment (2 focal lesions, 18 diffuse disease at baseline T1W and DW MRI), 18 from patients with stable disease (2 focal lesions, 16 little or no abnormality visible at baseline T1W/DW MRI) and 5 from a single patient who progressed on surveillance (little or no abnormality visible at baseline T1W/DW MRI) were available over the 3 timepoints.

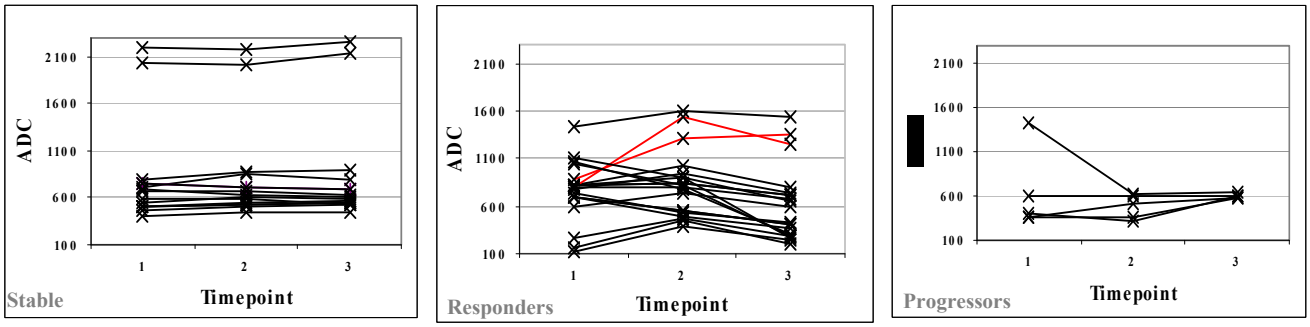
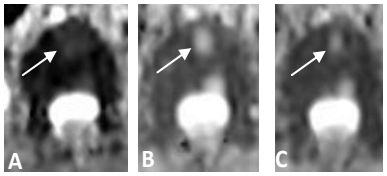


Figure 1. Mean ADCs ($mm^2s^{-1}x\ 10^{-6}$) of bone marrow from patients with stable, responding (focal lesions shown in red) and progressing myeloma at baseline, 4 and 20-24 weeks. The mean coefficient of variation (CV) of marrow in stable patients (patients in remission or with low grade MGUS undergoing surveillance) was 5.8% suggesting that changes in ADC of 11.5% (1.96 x CV) are needed to reflect changes in disease activity. In responders, 11/20 lesions showed a rise in ADC and 9/20 showed a fall after 4 weeks of treatment. This heterogeneity in direction of ADC change was intra and interpatient. Between 4 and 24 weeks, 19/20 responding lesions showed an ADC fall although not significant ($p>0.05$)ANOVA with Bonferroni correction). In the patient who progressed there was a mixed change in ADC between 0 and 4 weeks and following this ADCs either changed little or rose.



Patterns of response.
Figure 2. ADC maps at baseline (A), 4 (B) and 24 weeks(C) of the L1 vertebral body in a patient with focal myeloma deposits responding to treatment. A rise in ADC at 4 weeks reflects necrosis (B). At 24 weeks a reduction in size of lesions and a return of normal fatty marrow causes ADC to fall (C).

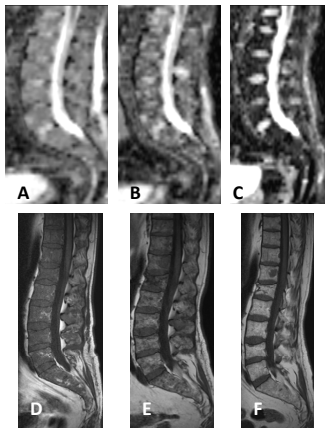


Figure 3. ADC maps of the lumbar spine at baseline (A), 4 (B) and 24 weeks(C) in a patient with diffuse myeloma disease responding to treatment. ADC maps show a gradual fall in ADC due to replacement of disease with normal fatty marrow. The return of normal fatty marrow is confirmed on corresponding T1W imaging (D, E, and F).

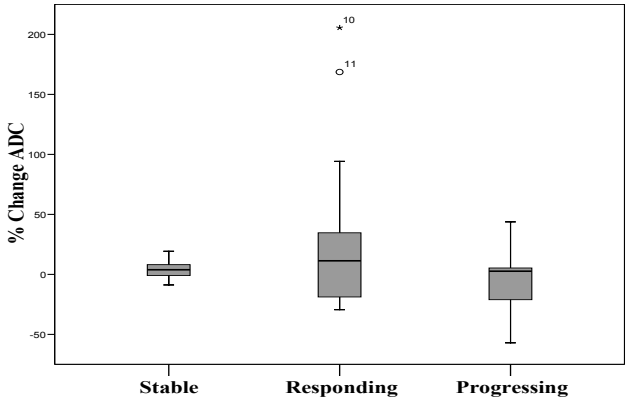


Figure 4. Boxplot of % change in ADC following 4 weeks of treatment illustrates the heterogeneity in direction of ADC change in responders.

Conclusion

ADC changes in excess of 11.5% are needed to detect changes in ADC of bone marrow that are within the limits of reproducibility. There are possible trends in ADC change between 4 and 20-24 weeks in responding patients as most lesions showed a fall in ADC although this was not significant in this small series. Inter and intrapatient heterogeneity of ADC changes in response to treatment within the first 4 weeks are likely related to return of fat and necrosis. The timing of necrosis/ return of normal fatty marrow may relate to treatment type and efficacy and may vary in focal vs diffuse disease. Because of heterogeneity, changes in mean ADCs are insufficient for predicting response vs progression and segmentation of ROIs is warranted.

References 1.Messiou C, Collins DJ, Morgan VA and de Souza NM et al, Abstract 3943.ISMRM 2009.