Assessing response in bone metastases in prostate cancer with diffusion weighted MRI

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Introduction: DW-MRI has potential to provide new and previously unobtainable quantitative measures in response of metastatic bone lesions. The purpose of this study was to determine whether changes in ADC in patients with metastatic bone disease secondary to carcinoma of the prostate are significantly different in responders compared to progressors following chemotherapy.

Methods: ***Subjects:*** 38 patients age range 50-83 years (mean age 65.6 years) with histology proven carcinoma of the prostate and prior anti-androgen treatment were recruited. Metastatic bone disease was confirmed on bone scintigraphy / conventional T1W and T2W MRI. ***Imaging protocols:*** Patients were imaged at baseline (within 7 days prior to commencement of therapy) and 12 weeks +/-7 days following commencement of chemotherapy. 26 patients were evaluable having completed follow up MRI studies at 12 weeks**.** MRI was performed on a 1.5 T Siemens Avanto using an external coil array with subjects positioned supine. Sagittal T1W (590/11msec TR/TE; 400mmm FOV, 4mm slice thickness) and T2W (2690/93msec TR/TE; 400mm FOV; 4mm slice thickness) images of the spine and axial T1W (607/19msec TR/TE; 340mm FOV; 5mm slice thickness) and T2W (5340/127msec TR/TE; 340 mm FOV; 5mm slice thickness) images of the pelvis were acquired. Axial single shot twice refocused diffusion weighted spin echo planar images[1] were acquired covering the lumbar spine and pelvis with the following parameters: 3000/80msec TR/TE; FOV 350 mm, slice thickness 5mm, 4 averages, 3 orthogonal directions and b values of 0, 50, 100, 250, 500 and 750 smm^{-2} with SPAIR fat saturation. ***Data Analysis***: Monoexponential ADC maps using all 6 b values (0, 50,100, 250, 500, 750 smm^{-2}) were generated using system software taking an average value for the 3 directions of diffusion sensitisation. ADC maps were also generated using b 100, 250, 500, 750 smm^{-2} (ADCslow). Using T1W MR sequences to aid ROI placement up to 5 regions of interest (ROIs) were drawn around lesions on ADC maps avoiding artefacts. ROIs were copied onto ADCslow maps. A combination of PSA and RECIST assessment of soft tissue disease on CT were used to classify overall disease status as responding, progressing or stable [2]. ***Statistics***: Data were analysed using SPSS (v15) and tested for normality using the Kolmogorov-Smirnov test. Unpaired t tests were used to identify differences in baseline ADC and ADCslow between lesions in patients that subsequently responded versus those who progressed. A paired student t-test compared changes in ADC and ADCslow pre and post treatment. **Results:** A total of 100 lesions were analysed: 33 in responding patients (n=8), 59 in progressing patients (n=15) and 8 in stable patients (n=3). There was a significant increase in ROI area in progressors (p=0.003) but no significant change in responders or stable patients (p=0.644 and 0.351 respectively). Both ADC and ADCslow in lesions from responders showed a significant increase after treatment (p= 0.0002 and p=0.0005 respectively). Also mean ADC and ADCslow from lesions in progressors was significantly higher after treatment (p=0.001 and p=0.001 respectively). There was no significant change in the mean values of ADC or ADCslow in lesions from stable patients (p=0.65 and p=0.55 respectively).

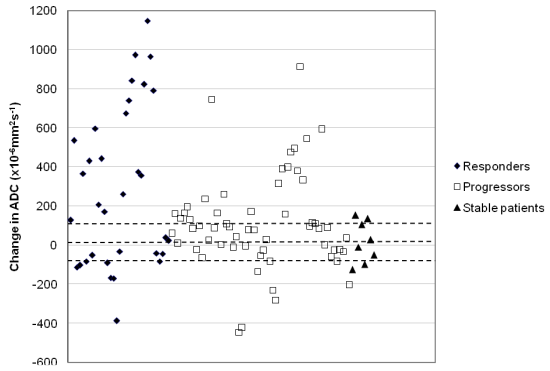

Figure 1. Per lesion changes in ADC of metastatic bone lesions. Bland Altman limits derived from reproducibility studies on normal volunteers are represented dashed lines[3].

Although an overall increase in ADC and ADCslow was demonstrated by paired student t tests, scatterplots revealed that some lesions in responding and progressing patients demonstrated a fall in ADC while other lesions in the same patients showed an ADC rise (Fig 1 and 2). Bland Altman limits of reproducibility of ADC derived from normal volunteer studies[3] (19.6 +/- 85.8 x 10^{-6} mm^{2}s^{-1}) applied to scatterplots of changes in ADC post treatment indicated that 58% of lesions in responding patients showed a rise in ADC above reproducibility of normal marrow compared to 37% in progressing patients with 47% of lesions (47%) not showing changes outside the limits of reproducibility in the latter group.

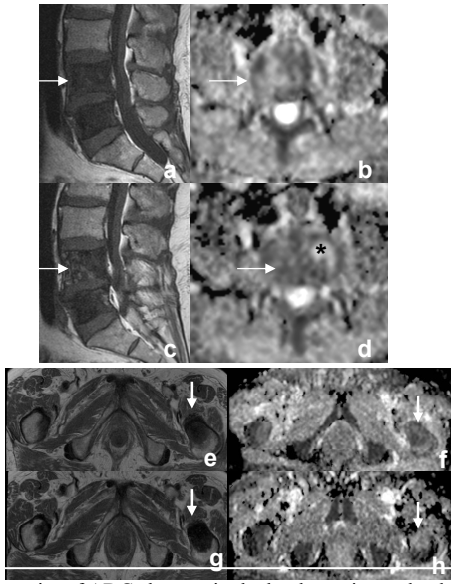

Figure 2. Heterogeneity of ADC changes in the lumbar spine and pelvis of a patient with bone metastases secondary to prostate carcinoma responding to treatment. Sagittal T1W MRI lumbar spine before (a and b) and 12 weeks after treatment with chemotherapy (c and d). A return of high signal within L4 from fat is seen (c) (arrows) with an associated fall in mean ADC from 1150 to 1083 mm^{2}s^{-1}x 10^{-6} (b and d arrows). There is also a new focal area of increased ADC (d, *) likely to represent oedema or necrosis. In the pelvis, axial T1W imaging (e), ADC map (f), and corresponding sequences and slices after chemotherapy (g and h) show no change in volume of disease. An ADC rise within the lesion from 1122 to 1190 mm^{2}s^{-1}x 10^{-6} (f and h arrows) indicates a response with a change in ADC opposite to that observed in L4.

Discussion: This is the first clinical series demonstrating ADC changes in bone metastases in patients undergoing treatment who are responding, progressing and in those who remain stable. Uniquely we have also applied limits of reproducibility derived from bone marrow specific studies. The results demonstrate that both ADC and ADCslow increase significantly in responders and progressors. No significant change in ADC in all stable patients agreed fully with PSA/RECIST criteria of stable disease. The heterogeneity of ADC change revealed by scatterplots after 12 weeks of treatment is likely to be related to the composition of bone marrow and histopathological changes which have opposing effects on ADC. This study has shown that rising ADC in bone metastases is common in both responding and progressing patients. Case studies within this series indicate that this is due to necrosis and bone lysis respectively. A fall in ADC is also encountered due to returning marrow fat in responders and tumour repopulation of lytic lesions in progressors. Therefore ADC alone cannot be used as a measure of response. We have previously defined an ADC threshold of 655 x10^{-6} mm^{2}s^{-1} which separates normal from diseased marrow with 90% sensitivity and 93% specificity[4]. The application of thresholds to ADC histogram analysis to identify proportions of normal and diseased marrow may be a better indicator of response or progression and allow wider separation of responding and progressing patients[4]. Prospective studies applying a histogram approach could also incorporate a quantitative metabolic marker of disease activity such as FDG PET for correlation as a next best alternative to histopathological validation. **References** 1.Reese et al. MRM 2003; 49: 177-182 5; 2.Bubley GJ et al JCO 1999:17(11); 3461-7; 3.Messiou et al ISMRM 2010 155.5; 4.Messiou et al ISMRM 2010 4843.