The feasibility of evaluating treatment response of bone metastases by segmenting tumor diffusion volumes to estimate total disease burden on whole body diffusion-weighted imaging

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Introduction: There are currently many oncologic clinical trials evaluating the efficacy of novel radical and palliative therapies for the treatment of malignant bone disease. However, a major limitation of conducting these studies has been the lack of a reliable biomarker for monitoring and quantifying treatment effects. Standard 'RECIST' imaging response criteria using tumor size measurement regard bone tumours without significant soft tissue component as unmeasurable [1]. However, metastatic bone disease confined to the marrow cavity is common and this poses a significant challenge to the development of new, targeted therapies for malignant bone disease. A relatively recent development for visualizing bone involvement is whole-body diffusion weighted imaging (WB-DWI) [2, 3]. Using fat-suppressed WB-DWI at high b-values (~1000 s/mm^2), enhances the detection of bone metastases by improving the contrast between diseased and background tissues. Lesion detection can be further enhanced by applying the computed DWI (cDWI) technique, which allows higher b-value images with optimal lesion conspicuity and background signal suppression, calculated from images acquired at lower b-values [4, 5]. Semi-automatic techniques can be applied to these images for tumour segmentation [6]. By using similar thresholds, tumour segmentation allows the total volumetric tumour burden and tumour ADC to be calculated on a whole body basis, thus providing two potentially useful quantitative biomarkers using one examination. However, to our knowledge, no study has investigated the clinical utility of total tumour diffusion volume and global tumour ADC to assess treatment response in patients with metastatic bone disease. We present the findings of a feasibility study to assess the utility of diffusion tumour volume and global ADC for assessing treatment response in patients with metastatic bone disease.

Methods: WB-DWI images were acquired in six patients with metastatic bone disease before and after antitumour treatment. A summary of the patient diagnosis and treatment administered is given in **Table 1.** For each patient, an optimum computed b-value was visually determined on the pre-treatment data by a radiologist with 7 years clinical experience in body diffusion weighted MRI to maximize the contrast between disease and background tissue. The computed data were then segmented using the method proposed in [6]. The post-treatment data were then registered to the pre-treatment data using a marker-based registration technique and segmented using the same computed b-value and applied threshold. After segmentation, normal soft-tissues were removed if still included in the final segmentation mask: testes, kidneys, spleen, spinal cord, nerve endings, residual fat and any tissues above the C4 vertebral body. Using the final segmentation mask the median global ADC values and total tumour volume were calculated, and the change in these values after treatment was compared to the clinical assessment determined by clinical, biochemical and/or other imaging tests. An example of the final computed images and segmentation mask is demonstrated in **Figure 1** for patient 3.

Results: Table 1 displays the changes in median global ADC and total volumetric tumour burden as a percentage of the pre-treatment values. In this initial study cohort, the total tumour burden estimates were negatively correlated with patient response, i.e. an increase in tumour burden (+38 to 310%) was observed in non-responders, whereas a decrease (-40 to -71%) was observed amongst responders. The inverse was true of the median ADC values where a decrease in ADC (-14 to -20%) was seen in 3 of 4 non-responders, whereas an ADC increase (+34 to 128%) was observed in the responders. One patient that demonstrated a small increase in the median ADC initially progressed with treatment (patient 1), but there was subsequent clinical response at 10.5 weeks following a change in chemotherapy treatment.

Figure 1: Example WB-DWI coronal, 3D MIP images (inverted gray scale) of patient 3 shown before (top row) and after (bottom row) treatment with hormone therapy. Images computed at a b-value of 1011 s/mm^2 are shown on the left and the results of automatic segmentation are shown on the right in red. Pre-therapy tumour volume = 118 ml, median ADC = 0.87 x 10^{-3} mm^2/s; post treatment volume = 34 ml, median ADC = 1.16 x 10^{-3} mm^2/s
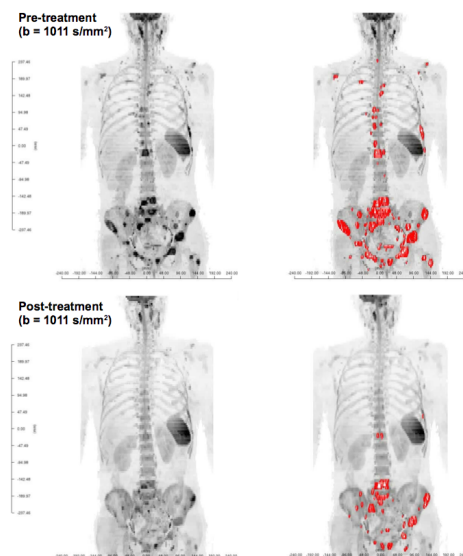
Table 1: Summary of patient details including final clinical outcomes and changes in both the median total body ADC and tumour burden estimates derived from the automatic segmentation methodology.

Patient number	Patient diagnosis	Treatment administered[†]	Time between scans (weeks)	Clinical outcome[‡] (Marker used[§])	Change in median ADC	Change in tumour burden
Patient 1	Metastatic breast cancer	C	13	+ (Cl, MRI)	+23.7%	+14.2%
Patient 2	Multiple Myeloma	HT	11.5	+ (Cl, MRI, PP)	-20.4%	+235.2%
Patient 3	Metastatic breast cancer	HT	17.5	- (Cl, MRI)	+34.2%	-71.2%
Patient 4	Metastatic breast cancer	APD, C, E/R	16	+ (Cl, MRI)	-2.8%	+310.4%
Patient 5	Metastatic breast cancer	APD, C	9	- (Cl, MRI)	+127.7%	-39.7%
Patient 6	Metastatic prostate cancer	C	15.5	+ (Cl, CT, MRI, PSA)	-13.8%	+37.8%

[†] APD = Bisphosphonates, C = Chemotherapy, E/R = Excision and radiotherapy of the primary breast tumour, HT = Hormone Therapy.
[‡] + = progressor, - = responder, o = stable.
[§] Cl = Clinical assessment, CT = Computed tomogrphy, MRI = Morphological MRI, PP = Plasma Proteins, PSA = Prostate Specific Antigen.

Discussion: In this preliminary study, whole body estimates of global tumour ADC and volumetric tumour burden, as determined using a semi-automatic registration method, provide two quantitative imaging response biomarkers, which appear promising for the evaluation of metastatic bone disease. The total tumour burden after treatment decreased, while global ADC values increased in responders after treatment. We are currently evaluating these indices as response biomarkers in prospective WB-DWI studies. Clearly, the clinical utility of such an approach requires evaluation in larger prospective trials to determine its robustness; and thresholds ascertained for significant changes to specific diseases and therapies.

Conclusions: WB-DWI can provide dual quantitative response biomarkers of global tumour ADC and total tumour diffusion volume, which appear promising for the evaluation of metastatic bone disease. These biomarkers maybe able to overcome the inherent limitations of size measurement criteria and be could prove useful for the conduct of future clinical trials.

References: [1] Jaffe, J Clin Oncol 2006; 24:2382-92, [2] Takahara et al., Radiat Med 2004; 22(4):275-82, [3] Ballon et al., NMR Biomed 2000; 13:321-28, [3] Li et al., J Magn Reson Imaging 2007; 26(4):1139-44, [4] Blackledge et al., Proc 19th Annual Meeting ISMRM 2011, 2979, [5] Blackledge et al., Radiology 2011; 261(2):573-81, [6] Blackledge et al., Proc 19th Annual Meeting ISMRM 2011, 2560