

Multiparametric whole body MRI in castrate resistant prostate cancer bone metastases – total tumour volume, ADC and fat fraction parameters reproducibility

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Target audience: Radiologists and physicists with an interest in metastatic prostate cancer imaging and metastatic bone imaging.

Purpose: The medical management metastatic castration-resistant prostate cancer (mCRPC) has changed dramatically, with several new targeted agents showing increases in overall survival¹. More than 70% of these patients have bone only disease and the only imaging criteria available for assessing therapeutic benefit relate to disease progression on bone scans², with no validated imaging criteria to positively assess therapy benefit. Whole body diffusion weighted imaging (WB-DWI) is emerging as a promising tool for therapy monitoring of bone metastases³. Bone marrow fat fraction (FF) may also provide additional information⁴. In view of the nature of mCRPC (large volume, intra and inter tumour heterogeneity related to prior therapies), it is imperative that response assessments tools include total tumour (TT) burden metrics. Currently, there are no published data documenting the reproducibility of TT bone disease apparent diffusion coefficient (ADC) or FF values. The aim of this study was to document the reproducibility of total TT volume defined on DWI, TT ADC and FF using histograms methods.

ADC ($10^{-6} \text{ mm}^2/\text{s}$)				Fat Fraction (%)		
	Average value	Range	r%	Average value	Range	r%
Mean	960.8	773.5-1200.2	-12.4 +6.4	28	13-54.1	-26.5 +19.2
Median	927.6	723-1202	-6.6 +6	23.6	11-61	-32.2 +21.9
25 th percentile	763.4	625-927	-9- +8.9	14.3	7-42	-30.2 +32.7
75 th percentile	1118.7	825-1469	-3.6 +5.9	37.8	19-74	-26.5 +18
Inter Quartile Range	355.3	200-542	-25.7 +32.9	23.5	11-41	-35 20.6
Standard Deviation	296	167.12-380.51	-17.2 +26.1	19.3	10.7-25.6	-25.6 +17.4
Skewness	1.1	-0.25-2.76	-125.7 +97.5	1.1	-0.5-2	-13.5 +28
Kurtosis	3.5	-0.98-12.59	-115.3 +152.5	1.4	-1-5.7	-151.3 +212.3
Tumour Volume	218 ml	5-590 ml	-12.4 +6.4			

Table 1. Average, Range and Bland Altman reproducibility coefficient (r %) for total tumour burden ADC and FF maps parameters

calculated fat & water images using an in-house Osirix plug-in that calculated the relation $FF = 100\% \times S_{\text{fat}}/(S_{\text{fat}} + S_{\text{water}})$ at every voxel location. The FF map was resampled to match the slice thickness of ADC maps. Voxel by voxel values of ADC and FF for the delineated VOIs were analysed using histogram measures of central tendency (mean, median), data spread (standard deviation, centile values and interquartile ranges) and histogram shape descriptors (skewness, kurtosis). Bland Altman analyses (MedCalc Software v12.7) was performed to obtain the reproducibility coefficient r%.

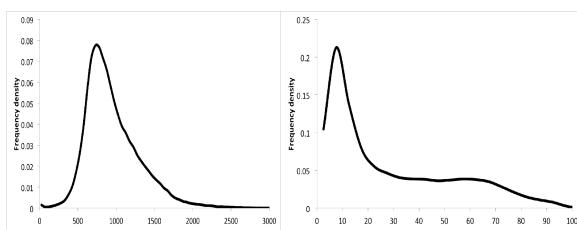


Figure 1. Histograms showing the population distribution of the ADC and FF(%) values for the 10 patients at their 1st visit.

Methods: 10 patients with mCRPC were randomly selected to undergo paired studies regardless of their therapy status. Evaluations were done on a 1.5T Aera scanner (Siemens, Erlangen, Germany); 9 patients were scanned with a 30 min break; 1 patient was scanned after a 10 day interval. The MRI protocol consisted of axial, single-shot twice-refocused DW echo planar images (upper cervical spine to proximal thighs) with the following parameters: 11300/69/180ms TR/TE/TI; 420mm FOV, Grappa 2, 6mm slice thickness, three orthogonal diffusion directions; b-values of 50, 600 and 900 s/mm^2 with Inversion Recovery fat saturation, 3 averages for b50 and b600 s/mm^2 and 5 averages for b900 s/mm^2 . Mono-exponential ADC maps were automatically generated. Matching volume axial CAIPIRINHA (Controlled Aliasing In Parallel Imaging Results IN Higher Acceleration) with 2-point DIXON reconstruction were acquired in order to calculate fat fraction images with the following parameters: 7.63/2.39/4.78ms TR/TE1/TE2; 5mm slice thickness. An experienced radiologist (NT) delineated volumes of interest (VOIs) twice encompassing the metastatic bone involvement based on b900 s/mm^2 images and ADC maps, using semi-automated segmentation provided by Osirix v5.8 software. Fat fraction maps were generated from the Dixon

Results: Figure 1 illustrates the cumulative histogram of the data acquired at visit 1 and the Table 1 shows the reproducibility coefficient (%) for ADC and FF parameters. Measures of central tendency for ADC (in particular median values) and the total tumour volume are highly reproducible (-6.6 to +6% and -12.4 to +6.4% respectively). Higher order histogram descriptors (kurtosis and skewness) had very poor reproducibility.

Discussion and conclusion: Documenting response of metastatic bone disease is an unmet clinical need. With the increasing use of whole body MRI for therapy assessment, total tumour burden analysis remains a considerable challenge. The high reproducibility of total tumour volume and total tumor median ADC suggests that these parameters could be to judge the effectiveness of therapy in clinical trials. Automated segmentation methods may

allow more reproducible tumour delineations so as to improve histogram assessments of tumour heterogeneity and response to treatment.

References: ¹de Bono JS Future Oncol. 2012; ²Scher HI et al JCO 2011; ³Padhani AR et al JMRI 2013; ⁴Vanel N et al Eur Radiol. 2000. **Acknowledgements:** CRUK and EPSRC Cancer Imaging Centre in association with the MRC and Department of Health grant C1060/A10334; NHS funding to the NIHR Biomedical Research Centre, the NIHR Clinical Research Facility and post-doctoral fellowship funding by the NIHR (NHR011X); An Experimental Cancer Medicine Centre Network award (C51/A7401 & C12540/A15573); MOL is a NIHR Senior Investigator.