Repeatability of Diffusion-Weighted MRI Parameters in a Paediatric Oncology Population

Neil P Jerome[1], Keiko Miyazaki[1], David J Collins[1], Matthew R Orton[1], James d'Arcy[1], Lucas Moreno[2], Andrew D J Pearson[2], Lynley V Marshall[2], Fernando Carcellar[2], Martin O Leach[1], Stergios Zacharoulis[2], and Dow-Mu Koh[3]

[1]CR-UK and EPSRC Cancer Imaging Centre, The Institute of Cancer Research, Sutton, Surrey, United Kingdom, [2]Paediatric Drug Development Team, Cancer Therapeutics and Clinical Studies, The Institute of Cancer Research, Sutton, Surrey, United Kingdom, [3]Department of Radiology, Royal Marsden Hospital, Sutton, Surrey, United Kingdom

Introduction: DWI provides a sensitive way of detecting functional changes that may precede changes in tumour size and in response to cytostatic effects arising from targeting specific biological pathways; thus there is an increasing need for non-invasive biomarkers reporting on drug action and tumour response for early phase clinical trials, providing more sensitive early markers of targeted anti-tumour effects and accelerating the decision-making processes in drug development. Diffusion-weighted MR imaging (DWI), providing information on tissue cellularity, integrity of cellular membranes and tortuosity of the extracellular space, is widely used in adult clinical trials of novel anti-cancer therapeutics, but there is little experience in children. A paediatric cohort is likely to have different vascular physiology and metabolism to an adult population, and so it is necessary to establish the repeatability of functional imaging biomarkers, particularly where the relative rarity of specific pathologies calls for multicentre trials.

Purpose: The aim of this present study is to evaluate the performance of DWI in children with solid tumours, and specifically the repeatability of the quantitative markers derived from the mono-exponential ADC and bi-exponential IVIM diffusion models.

Methods: ***Patient Cohort:*** This prospective study was approved by the institutional review board; written consent was obtained prior to patient inclusion in the study. Inclusion criteria were: patients less than 16 years with confirmed diagnosis of a solid tumour, with a measurable target lesion ≥ 2 cm and requiring MRI within routine care. Patients requiring general anaesthesia, with renal function impairment, contrast agent allergy, any contraindications to MRI, lung metastases only, or disease at sites that may introduce artefacts were excluded. ***MRI studies:*** Imaging was performed with a 1.5T MR system (Avanto; Siemens Medical Systems, Erlangen, Germany) using a phased-array head coil (intra-cranial) or a phased-array body coil (extra-cranial studies). DWI was performed during routine MRI and repeated after 24 hours, with the following parameters: free-breathing DW-MRI using a multi-slice 2D EPI with TE = 75 ms; TR= 3500 ms; matrix size 128 × 128 (interpolated to 256 × 256); 24 slices of 5 mm; generalized autocalibrating partially parallel acquisition acceleration factor 2; spectral adiabatic inversion-recovery fat suppression; signal averages 3. Diffusion three-scan trace-weighting was with b-values of 0, 50, 100, 300, 600 and 1000 $mm^{-2}s$. The field of view and slice positioning were transverse, 220 × 220 mm^2 (intra-cranial) and coronal, 300 × 300 mm^2 (extra-cranial), with the imaging volume positioned through the centre of the tumour. ***Data Analysis:*** DWI image analysis was performed offline using ADEPT software (The Institute of Cancer Research, London, UK). Regions-of-interest (ROIs) were manually drawn around the tumour by an expert radiologist in the three central slices of the initial imaging study, with matching ROIs in the second. Apparent diffusion coefficient values (ADC, 10^{-5} mm^2s^{-1}) were calculated by performing Levenberg-Marquardt mono-exponential fitting using signal intensities of (i) all b-values, (ADC_{all}), (ii) b-values ≥100 $mm^{-2}s$ (ADC_{100}), and (iii) b-values ≥300 $mm^{-2}s$ (ADC_{300}) on a pixel-by-pixel basis. IVIM parameters were calculated using an MCMC method as a robust least-squares estimator, with initial conditions set by linear fitting for D using b≥200 $mm^{-2}s$ and extrapolating back to b=0 to provide initial estimates of the pseudodiffusion and perfusion fraction (f and D*). Results from the ROIs were combined and the corresponding median value was used in the subsequent analysis of repeatability.

Results: The study cohort comprised 17 patients, median age 11 years (range 6 to 15 years). All patients were co-operative and tolerated the MR protocol; one patient was unable to return, and one dataset suffered technical failure, giving repeatability within 15 repeated measurements (seven intra-, eight extra-cranial solid tumours). The coefficient of variation (CV) and 95% confidence interval limits for DWI parameters are given in **Table 1**. Of the mono-exponential fittings, the most reproducible DWI parameters for the full cohort were ADC_{300} (CV = 3.2%), whilst including small b-value data increased the CV across both intra- and extra-cranial tumours. In general, extra-cranial tumours exhibited smaller CV, though all mono-exponential DWI parameters showed good repeatability (<5%). Of the IVIM parameters, the true diffusion coefficient D had a CV less than 3%, lower than the corresponding mono-exponential ADC using the higher b-values. Parameters associated with flow had much higher values, exceeding 40% for f in the full cohort and for fD* in the extra-cranial group.

Table 1: Coefficient of Variation and 95% confidence limits for DWI parameters from a paediatric cohort of solid tumours

	Intra-cranial	Extra-cranial	Full cohort
ADC_{all}	3.9 (-7.4, 8.0)	2.8 (-5.3, 5.6)	3.7 (-7.1, 7.6)
ADC_{100}	4.1 (-7.7, 8.4)	2.4 (-4.6, 4.8)	3.3 (-6.2, 6.6)
ADC_{300}	3.9 (-7.3, 7.9)	2.7 (-5.2, 5.5)	3.2 (-6.1, 6.5)
f	37.6 (-51.0, 104.1)	42.3 (-54.9, 121.7)	41.0 (-53.8, 116.3)
D	2.0 (-3.8, 3.9)	3.0 (-5.6, 6.0)	2.5 (-4.8, 5.0)
D*	34.1 (-47.8, 91.7)	37.7 (-51.1, 104.3)	35.1 (-48.8, 95.1)
fD*	26.9 (-40.5, 68.0)	46.9 (-58.2, 139.5)	38.1 (-51.4, 105.9)

Discussion: Added logistical and physiological challenges involved when scanning children require high repeatability of functional parameters; repeatability of DWI parameters in this cohort were comparable to those in adult cohorts (1). ADC reproducibility for the entire cohort appears to be excellent, as well as demonstrating that a mono-exponential DWI model may be biased by inclusion of lower b-value data, removed in bi-exponential IVIM fitting. The higher CV seen in more complex diffusion models may reflect instability in the model fitting process, or sensitivity to physiology varying on a 24 hour timescale, and indicates that interpretation requires caution.

Conclusion: DWI has potential as a non-invasive marker for treatment response and tumour differentiation (2,3); we demonstrate that a free-breathing DWI protocol in children aged between 6 and 15 is feasible and well tolerated, and that functional parameters with repeatability comparable to adult cohorts can be obtained. This pilot study will support the incorporation of DWI as part of functional imaging in paediatric phase I-II clinical trials of new molecularly targeted agents.

Acknowledgements: CRUK and EPSRC Cancer Imaging Centre in association with MRC and Department of Health (England; grant C1060/A103334, C7809/A10342), NIHR funding to the Clinical Research Facility in Imaging and the Biomedical Research Centre. Lucas Moreno and Lynley Marshall are funded by the Oak Foundation. ADJP is supported by Cancer Research UK (programme grant C1178/A10294) – Chair in Paediatric Oncology. We acknowledge Experimental Cancer Medicine Centre (ECMC) Network funding for support to early clinical trials.

References: 1. Koh D-M, Blackledge M, Collins DJ, Padhani AR, Wallace T, Wilton B, et al, *European Radiology* 19:2728 (2009) **2.** Rodriguez Gutierrez D, Manita M, Jaspan T, Dineen RA, Grundy RG, Auer DP, *Neuro Oncol*. 15:981 (2013) **3.** Gahr N, Darge K, Hahn G, Kreher BW, Von Buiren M, Uhl M, *European journal of radiology* 79:443 (2011)