# Repeatability of DCE-MRI Parameters in a Paediatric Oncology Population

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**Introduction:** Conventional radiologic assessment of tumour response based on changes in tumour size can be relatively insensitive to cytostatic treatment effects arising from drugs targeting specific biological pathways; thus there is an increasing need for non-invasive early markers that are sensitive to targeted anti-tumour effects, helping to accelerate decision-making in drug development. Modelling of dynamic contrast-enhanced (DCE) MRI data enables assessment of parameters that describe tumour vasculature *in vivo*. These include the volume transfer and efflux rate constant between extracellular extravascular space and plasma ($K^{trans}$ and $k_{ep}$), fractional volumes of extracellular extravascular space ($v_e$) and blood plasma ($v_p$). Model independent parameters such as initial area under the gadolinium curve over 60 seconds (IAUGC60) and the native longitudinal relaxation time (native $T_1$) can also be obtained. DCE-MRI is widely used in adult clinical trials of novel anti-cancer therapeutics, but a paucity of experience in children, likely to have different vascular physiology and metabolism, makes it necessary to establish the repeatability of DCE-MRI functional biomarkers, particularly where the relative rarity of specific pathologies calls for multicentre trials.

**Purpose:** The aim of this present study is to examine the feasibility of performing DCE-MRI in children with solid tumours, and specifically the repeatability of the quantitative markers, model-derived and model-independent, available from the DCE-MRI data.

**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. Patients were imaged twice with a separation of 24hrs, with no treatment intervention. ***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). 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. The free-breathing DCE-MR imaging protocol comprised: i) proton density–weighted 3D spoiled gradient-echo sequence with TE 0.95 ms, TR 3 ms, 128×128 matrix (interpolated to 256 × 256), 14 partitions with 5 mm thickness, GRAPPA acceleration factor 2, flip angle 3°, 10 signal averages. ii) Dynamic $T_1$-weighted acquisition using the same parameters and positioning, except with a flip angle of 16° and one signal average. Eighty volumes at 3.23 s each were acquired in approximately 4 minutes; at the fifth acquisition, a single dose of gadolinium-based contrast agent (0.1 mmol/kg, Magnevist® or Dotarem®) was injected followed by 10 ml of saline. Where patients had a Hickman-type central line in place (n = 4), the injections were performed manually by an expert radiologist; injections were otherwise performed using a power injector through a peripherally-inserted intra-venous cannula. Flow rate was appropriate to the size of the inserted cannula (1 – 3 ml/s). iii) A repeat of the proton density-weighted sequence following the dynamic acquisition, used for the subsequent conversion of the DCE signal intensity to contrast agent concentration (18,19). ***Data Analysis:*** Analysis was performed on a voxel-by-voxel basis using MRIW 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, and matched in the second. Contrast agent concentrations were calculated using the dynamic $T_1$- and proton density-weighted images acquired at the end of the DCE-MR examination (18,19). IAUGC60 and native $T_1$ were calculated, as well as compartmental pharmacokinetic (PK) model analysis using an extended Tofts model and a population-averaged arterial input function (AIF), containing components describing the first pass, second pass and equilibrium phases, derived from a subset of children in this study cohort (1,2). The model-dependent parameters evaluated were $K^{trans}$, $k_{ep}$, $v_e$, $v_p$. Results from the three analysed slices 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 the tumour in four patients did not exhibit uptake of contrast agent, giving repeatability within 12 repeated measurements (five intra-, seven extra-cranial solid tumours); the population AIF was derived from individual AIFs of nine cases (1). The coefficient of variation (CV) and 95% confidence interval limits for derived parameters are given in **Table 1**, and show for the full cohort the imaging parameters with lowest CV were native $T_1$ (6.21%), IAUGC60 (12.77%), and $K^{trans}$ (CV = 15.23%), and that all parameters in the extra-cranial group had CV < 20%.

**Table 1:** Coefficient of Variation and 95% confidence limits for DCE-MRI parameters from a paediatric cohort of solid tumours

| | Intra-cranial | Extra-cranial | Full cohort |
|---|---|---|---|
| Native $T_1$ | 7.99 (-14.5, 16.9) | 5.19 (-9.7, 10.7) | 6.21 (-11.5, 12.9) |
| IAUGC60 | 9.38 (-16.8, 20.1) | 11.71 (-20.5, 25.7) | 12.77 (-22.1, 28.3) |
| $K^{trans}$ | 13.58 (-23.3, 30.3) | 16.79 (-27.9, 38.7) | 15.23 (-25.7, 34.5) |
| $k_{ep}$ | 21.74 (-34.4, 52.4) | 19.74 (-31.8, 46.7) | 19.60 (-31.7, 46.3) |
| $v_e$ | 20.05 (-32.2, 47.6) | 17.48 (-28.8, 40.5) | 18.56 (-30.3, 43.4) |
| $v_p$ | 50.73 (-60.9, 155.5) | 16.29 (-27.2, 37.3) | 36.24 (-49.8, 99.1) |

**Discussion:** The added logistical and physiological challenges when scanning children require high repeatability of functional parameters; the coefficients of variation for DCE-MRI parameters assessed in this cohort appear comparable to those achieved in adult cohorts (3,4). It is notable that the model-independent parameters displayed a greater repeatability than those derived from the PK model, indicating caution should be used when modelling DCE-MRI data.

**Conclusion:** This pilot study shows the repeatability of DCE-MRI metrics in a paediatric cohort with both intra- and extra-cranial tumours, and will support the incorporation of DCE-MRI 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.

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