Significant increases in contrast arrival time measured with DCE-MRI are seen after treatment with an anti-VEGF agent

Matthew R Orton[1], Matthew Gwilliam[1], Christina Messiou[2], David J Collins[1], Veronica Morgan[2], Helen Young[3], Nandita de Souza[1], and Martin O Leach[1]

[1]CR-UK and EPSRC Cancer Imaging Centre, Institute of Cancer Research, Sutton, Surrey, United Kingdom, [2]Radiology Department, Royal Marsden NHS Foundation Trust, Sutton, Surrey, United Kingdom, [3]AstraZeneca, Macclesfield, Cheshire, United Kingdom

Introduction Quantitative analysis of dynamic contrast enhanced MRI data involves curve-fitting of noisy measurements, and when the model is physically derived, some or all of the estimated parameters will have a defined relationship with the underlying tissue properties, for example K^{trans}. For data with sampling intervals less than around 10 seconds it is typically necessary to include the arrival time of the contrast medium in the tissues of interest (TOI) in the parameters to be estimated. For faster sampling a separate arrival time may be needed for each voxel in the image to allow for variations across the TOI. The arrival time is not usually reported in its own right in DCE-MRI studies since the hypotheses being tested are usually focused on tissue properties. Variations in the arrival time are more likely to be related to a systemic effect of some kind, as it is the contrast delivery via the vascular network that will have the largest effect on the arrival time in the TOI. This observational report describes statistically significant increases in the contrast arrival time in a cohort of patients with liver metastases after 1 week and 4 weeks of treatment with an anti-VEGF agent. This result highlights the importance of adequate temporal sampling rates, and the use of robust methods of arrival time estimation, such as that presented in [1].

Data Acquisition and Processing With appropriate ethical approval 15 patients with metastatic liver disease were enrolled and received daily treatment with an anti-VEGF agent. Repeat baseline DCE-MRI measurements were performed 1 week apart prior to starting treatment, and follow-up measurements were acquired after 1 week and 4 weeks of treatment. The DCE-MRI protocol was as follows: 3D FFE sequence with TR/TE = 3.05/0.89 ms, FA = 16°, 14×5mm slices, NSA = 1, GRAPPA factor = 2, FOV = 308×320 mm, 208×256 matrix. A calibration scan with FA = 3° and NSA = 8 (other parameters as above) was included prior to the dynamic scan to enable conversion of the image intensities to contrast agent concentration. A sequential breath-hold protocol was used [3] and two image volumes were acquired during sequential 6 sec breath-holds, each followed by a 6 sec breathing gap, and 40 volumes were acquired over a 4 minute period. A single dose of contrast (0.2 ml/kg Magnevist) was administered at 3ml/sec using a power injector, followed by 20ml of saline – the injection was initialised at the start of the third breath-hold. Regions of interest were drawn by an experienced radiologist on four central slices and the extended-Kety model fitted voxel-wise using a population averaged arterial input function [2]. The arrival time was also estimated voxel-wise and was constrained in the fitting to a 10 second time interval – the temporal location of this interval was adjusted for each data set based on a visual inspection of the median uptake curve from the volume of interest. The median arrival time for each volume was recorded and paired t-tests performed between: i) the two baseline measures, ii) mean baseline measure and 1 week post-treatment, iii) the same at 4 weeks.

Results and Discussion The figure shows ladder plots to visualize the above comparisons. The mean difference (baseline 2 – baseline 1) is -0.7 sec (p = 0.25), the increase after 1 week on treatment is 4.9 sec (p = 0.0014) and at 4 weeks it is 5.6 sec (p = 0.0018). A feasible driver for changes in arrival time is changes in cardiac output – familiarity of the patient with an imaging protocol (particularly involving contrast administration) could feasibly have an impact on the measured arrival time, but this is unlikely here since the baseline data are not significantly different. It is therefore likely that these changes are due to the treatment itself, but it is not possible to infer a specific mechanism from these data.

Conclusions These data show that an increase in the cohort arrival time of around 5 seconds is seen after 1 week of treatment with an anti-VEGF agent. To avoid the potential for bias when model fitting DCE-MRI data it is necessary to acquire the data with sufficient temporal resolution – ideally faster than 1 volume every 5 sec – to enable such changes to be estimated accurately, and to ensure any onset estimation methods used are robust to noise.
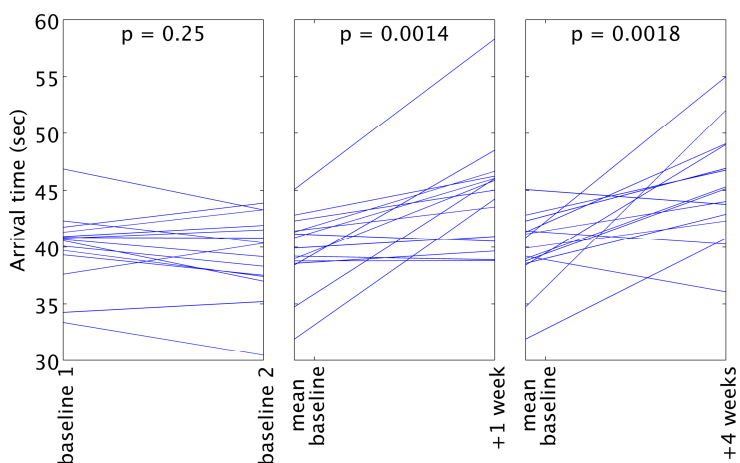
Ladder plots showing arrival times for 15 patients. Left is for repeat baseline measures, middle compares baseline with +1 week, right with +4 weeks, p-values are for paired t-tests.

[1] Orton MR, et al., Phys Med Biol. 2007; 52(9):2393-2408.   [2] Parker GJ, et al., Magn Reson Med. 2006; 56(5):993-1000.