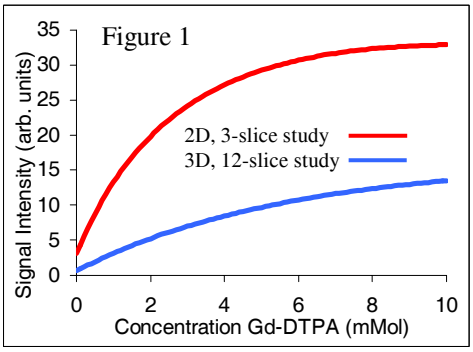
Methodological improvements in multi-centre Phase I DCE-MRI studies of novel antivascular drug treatments: Implications for reproducibility and quality assurance

N. J. Taylor[1], D. J. Collins[2], J. A. d'Arcy[2], J. J. Stirling[1], T. Wallace[2], D-M. Koh[2], and A. R. Padhani[1]

[1]Paul Strickland Scanner Centre, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, United Kingdom, [2]CRUK Clinical MR Research Group, Royal Marsden Hospital, Sutton, Surrey SM2 5PT, United Kingdom

Introduction: DCE-MRI has become the method of choice in monitoring the early effects of antivascular anticancer agents in Phase I trials. Methodologies adopted in the past have shown several deficiencies, such as lack of tumour coverage (limited number of slices available to obtain a usable time resolution), poor slice registration and quality control (QC), quantification assumptions (such as linearity of sequences and inappropriate arterial input functions (AIFs))[1]. The use of different vendor equipment or scanners with different capabilities, together with different people performing the imaging makes the reproducibility poorer for the multi-site trials than for single sites[2]. Good reproducibility of DCE-MRI is crucial to being able to able to detect drug induced changes in vascularisation, and all the above problems have the potential to make the reproducibility sufficiently poor to prevent studies coming to meaningful conclusions. With such concerns in mind, a protocol was designed for a novel combination vascular disruptive agent (VDA) and antiangiogenesis trial, which was intended to improve reproducibility and overall trial results[3], and the interim results of the reproducibility section of this study are presented here.

Methods: The sequence and protocol design[3] was carried out by physicists at two sites, using non-identical Siemens 1.5T MRI scanners (Siemens, Erlangen, Germany). Site one uses a TIM Symphony and site two uses an Avanto, with a higher gradient specification. Care was taken to match the sequence measurement parameters to a common denominator because of the different gradient performances. Parameters were optimised for a 3D breathhold navigator-echo VIBE, acquiring 12 slices in six seconds of breathholding (on expiration), followed by breathing for a further six seconds. Three edge slices on each side were discarded due to slice profile effects, leaving the middle six to cover more tumour than previously with the 2D technique despite using thinner slices. Quantification of T_1 values was achieved by a two-point Wang calculation[3,4] and all sequence parameters optimised by phantom and modelling studies for as linear a response to contrast concentration as possible[3]. Final sequence values were TE 1.45ms, TR 4.36ms and flip angle 24°. Figure 1 (blue line) shows the signal:Gd-DTPA relationship, compared with that of a previous 2D study (red line). Base relaxation times for the modelling were 1000ms (T_1) and 60ms (T_2).



Quality control at both sites was achieved by use of common checksheets, and radiographic staff were trained to fill these out during scanning to prevent missed measurements. In relatively complex procedures, missed sequences can null the entire scanning session. Radiographers were also carefully trained to look for similar anatomical landmarks to ensure slice registration, and the sites encouraged to communicate with each other. Data analysis of the study occurred at one study site. This ensured consistency of methods and software for analysis as well as for ROI placement criteria. Quantitative parameters calculated were the transfer coefficient K^{trans}, the interstitial space volume v_e, the rate constant k_{ep} and the integrated area under the gadolinium curve's first minute $IAUGC_{60}$. The model used was that of Tofts[5], with a modified Fritz-Hansen (MFH) assumed AIF[6,7]. Reproducibility was carried out using the methods described by Galbraith[8] with natural log transformation if required. Patients were enrolled in a Phase I trial of a new VDA combination, the majority having colorectal tumours with liver metastases; the liver is known to be a difficult area to image due to motion and patient compliance[8]. Multiple lesions from each patient were separately analysed, giving 13 measurements from 9 patients. The table shows the reproducibility values for Site 1, and values for both sites which can be compared with a previous 2D-DCE-MRI study with single lesion analysis using an unmodified Fritz-Hansen AIF[6,9].

r%	Site 1 n=10	Sites 1+2 n=13	Sites 1+2, 2D study, n=32
K^{trans}	±22.5	±18.1	-48.7 to +95.1
v_e	±20.7	±19.7	±46.4
k_{ep}	±34.9	±28.4	-32.7 to +48.5
$IAUGC_{60}$	±28.8	±24. 7	±55.2

Results and discussion: Reproducibility values for kinetic parameters are shown in the Table. Reproducibility, r (given as a percentage of the mean) illustrates the innate variability of the technique, and is the minimal change required to be 95% confident of a real change in a parameter for an individual lesion/patient that is due to any treatment effects. The smaller the range of r%, the more reproducible is the technique. The Table shows that the r% values for the current 3D study compare very favourably with previous work[2,10-11], and are markedly improved when compared with a previous 2D DCE-MRI trial performed at the same two sites (but with the Fritz-Hansen AIF)[9]. Comparing our two-site 3D navigator study with the previous 2D study shows a 30% improvement in overall K^{trans} reproducibility[9]. This study also shows that multi-site trials may not necessarily have inferior reproducibility to single-site trials, with differences being due to intrinsic patient variability rather than due to methodological variability. These results indicate that provided that multicentre studies are undertaken with great care and planning, tight reproducibility of DCE-MRI can be achieved. This should translate into better test performance for assessing novel antivascular therapy response for both individual patients and cohorts. We anticipate that with further developments such as cohort or individually-derived AIFs, or ones including first pass terms, may result in further improvements in reproducibility.

References:

1. O'Connor, J.P.B. *et al*., Brit. J. Cancer 2007; **96**(2): 189-195
2. Taylor, N.J. *et al*, *Proc. I.S.M.R.M. 14th Ann. Meet*. 2006 #766
3. Miyazaki, K. *et al*., *Proc I.S.M.R.M. 14th Ann Meet*. 2006 #2979
4. Wang, H.Z. *et al*., *Magn Res Med* 1987; **5**: 399-416
5. Tofts, PS and Kermode, A.G. *Magn Reson Med*. 1991; **17**: 357
6. Fritz-Hansen, T. *et al*., *Magn Res Med* 1996; **36**: 225-231
7. Walker-Samuel S. *et al*, Phys. Med. Biol. 2006; 51: 3593
8. Galbraith, S.M. *et al*., NMR Biomed 2002; **15**(2) 132-142
9. Padhani, A.R. *et al*., *Proc. I.S.M.R.M. 14th Ann. Meet.* 2006 #765
10. Tunariu, N. *et al., Proc. I.S.M.R.M. 14th Ann. Meet*. 2006 #2828
11. Taylor, N.J. *et al*., *Proc. I.S.M.R.M. 15th Ann. Meet.* 2007 #2819