COMPARING THE EFFECTS OF DIFFERENT POOLED ARTERIAL INPUT FUNCTIONS ON DCE-MRI MEASUREMENT ERROR ANALYSIS ACROSS ANATOMICAL LOCATIONS

N. Tunariu[1], J. Taylor[1], J. Stirling[1], J. d'Arcy[2], D. J. Collins[2], S. Walker-Samuel[2], and A. R. Padhani[1]

[1]Paul Strickland Scanner Centre, Mount Vernon Cancer Centre, Northwood, Middlesex, United Kingdom, [2]CR-UK Clinical MR Research Group, Institute of Cancer Research, Sutton, Surrey, United Kingdom

Background: Dynamic contrast-enhanced MRI (DCE-MRI) is a recognized *in-vivo* biomarker of the angiogenic status of tumour vasculature with widespread clinical uses. Optimization of DCE-MRI is an intrinsic part of the qualification process for it to be used as a predictive functional imaging biomarker. We have previously shown that measurement error of DCE-MRI is markedly improved in patients with breast cancer by using arterial input functions (AIFs) appropriate to the sampling rates used clinically [1]. In this study we examine generalizing this observation for tumours at other anatomical sites (liver and pelvis). Thus the purposes of this study was to examine the effects of different population arterial input functions (AIFs) on transfer constant (K^{trans}) estimates, measurement error, and on model fitting in liver and pelvis tumours, and to compare these with our previously reported breast data [1].

Methods: Three cohorts of patients were examined: (1) 13 patients with liver metastases, (2) 21 patients with pelvic tumours (all gynaecological), and (3) 11 patients with breast cancer [1]. All patients were examined on a 1.5T Siemens Symphony scanner using appropriate coils. All patients were studied twice within 1 week in order to determine measurement error prior to any therapy.

Following anatomical images done for lesion localization, T_1-weighted DCE-MRI studies were obtained using spoiled 2D GRE [FLASH] sequences (TE 4.7ms, TR 11ms, $\alpha=35^o$, 3-4 slices) acquired before and after the bolus administration of 0.1 mmol/kg bw of Gd-DTPA with 40 time points over 8 min, through the centre of tumours. Images were registered to proton-density weighted images to enable the calculation of changing tissue T_1-relaxivities and contrast agent concentrations. Whole tumour ROIs were outlined and pixel-by-pixel values of K^{trans} (min^{-1}) were calculated using the methods of Tofts [2] in MRIW software [3]. The pharmacokinetic analysis was performed by specifying 4 pooled bi-exponential input plasma clearance coefficients in accordance with data reported by Weinmann [4], Fritz-Hansen [5], by combining Weinmann and Fritz-Hansen data (modified Fritz-Hansen) [6] and Just [7] (femoral artery – internal data obtained from 20 men using a dual gradient echo sequence for bolus tracking studies). Data were analyzed pixel-by-pixel using the four AIFs in turn, keeping all other variables constant.

Pixels (% of all pixels), which failed to fit, were counted for each AIF and removed from any further analyses. Kinetic parameter values for each fitted tumour pixel were obtained including $\chi 2$ (goodness-of-fit). The Bland-Altman approach was used to assess the measurement error of K^{trans} for the 4 AIFs using the procedures of Galbraith [8 and references therein]. For each lesion, the difference d between the two pre-treatment measurements of a parameter was calculated. Data were transformed using natural logarithms if the variability of d was found to depend on its mean value (significant two-tailed Kendall's tau test). The following statistics were generated: overall mean for averaged data from the 2 examinations, repeatability coefficient (r) in % which represents the range beyond which differences are considered statistically significant, within patient coefficient of variability (wCV).

Results: The table shows reductions in mean K^{trans} values (noted in individual tumours and for the cohorts) with improvements in measurement error when non-Weinmann input functions are used. In general, no differences in $\chi 2$ values for goodness-of-fit are seen for the different AIFs in any given organ. Liver data fitting was always worse. Importantly, it can be seen that the % of pixels failures is also variable across tumour sites (most in the liver and least in the breast) and that the modified Fritz-Hansen AIF always gives the least number of pixel failures regardless of tumour location.

Plasma input function coefficient	**K^{trans} mean (min^{-1})**			**K^{trans} r% of mean**			**K^{trans} wCV (%)**			**Goodness of fit ($\chi 2$) / % fitting failures**		
	liver	***pelvis***	***breast***	***liver***	***pelvis***	***breast***	***liver***	***pelvis***	***breast***	***liver***	***pelvis***	***breast***
Weinmann	1.503	0.433	0.774	±92.7	-39.2 to 64.7	-54.0 to +117.4	33.5	19.7	32.4	0.21 / 42.0%	0.08 / 28.2%	0.03 / 5.1%
Fritz-Hansen	0.448	0.116	0.323	±70.0	±28.9	±43.6	25.3	10.4	15.7	0.19/ 53.4%	0.07 / 33.6%	0.03 / 10.6%
Modified Fritz-Hansen	0.388	0.149	0.228	±50.7	±34.3	±45.2	18.3	12.4	16.3	0.27 / 24.0%	0.08 / 23.1%	0.03 / 3.3%
Femoral artery	0.240	0.218	0.171	±43.6	±23.9	±35.7	15.7	8.6	12.9	0.22 / 53.6%	0.08 / 37.8%	0.03 / 17.1%

Conclusions: Our analyses indicate that previous observations in breast cancer patients are valid for tumours at other anatomical sites such as in the pelvis and liver. That is, that there is an improvement in reproducibility by using "more physiological" (non-Weinmann) arterial input functions. New observations when comparing tumours at different anatomical locations include variability of pixel failures and goodness of kinetic model fitting (most in the liver and least in the breast). We recommend that the pooled modified Fritz-Hansen AIF be used in DCE-MRI analyses particularly for multicentre studies because of its ability to minimise fit failures while maintaining good reproducibility.

References

(1)Tunariu N, ISMRM 2007; (2) Tofts, PS and Kermode, AG. JMRI 1997; 7:91; (3) d'Arcy JA, Radiographics 2006; 26:621; (4) Weinmann HJ, Physiol Chem Phys Med NMR 1984; 16:16; (5) Fritz-Hansen T, Magn Reson Med 1996; 36:225; (6) Walker-Samuel S, Phys. Med. Biol. 2006; 51: 3593; (7) Just, N, Proc. I.S.M.R.M.2002, (8) Galbraith SM, NMR Biomed 2002 15:132.