Inter- and intra-observer variability of DCE-MRI in breast cancer

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Background: Dynamic contrast MRI (DCE-MRI) can be used to assess breast cancer microvasculature in response to neoadjuvant chemotherapy. We have previously shown that changes in T_1-weighted DCE-MRI kinetic parameters after 2 cycles of chemotherapy (5-fluorouracil, epirubicin and cyclophosphamide) are successfully able to predict pathological response following 6 cycles of treatment [1]. Changes in median transfer constant (K^{trans}) is the best predictor for response with a sensitivity of 100% and specificity of 72%; tumour size failed to predict for eventual pathological response. Integral to the success of this technique is accurate definition of the tumour region of interest (ROI); guidelines on ROI placement appear in the literature[2]. The purpose of the current study is to quantify variations in kinetic parameter estimates between observers and within the same observers ascribable to ROI placement in patients with breast cancers. We are not aware of other DCE-MRI literature data addressing inter- and intra-observer variability.

Methods: 30 untreated patients with primary breast cancers were studied using a 1.5T Siemens Symphony scanner. T_1 weighted DCE-MRI studies were obtained using methods previously described. Briefly, spoiled GRE [FLASH] sequences (TE 4.7ms, TR 11ms, α=35°, 4 slices) were 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 their breast cancers.

Two observers (**ap** – a radiologist with 7 years of DCE-MRI experience and **mb** - a clinical oncologist with no prior DCE-MRI experience) independently outlined ROIs on the same central image slice of each tumour on two separate occasions, 2 weeks apart. Prior to outlining, a period of training (3 hours) for **mb** was conducted by **ap** on 10 other patients to ensure compatibility in the placement of tumour outlines. Lesion morphology was classified according to Esserman et al[3] into circumscribed (18 lesions), nodular (7), diffuse infiltrative (1), septal (2) or patchy (2) by mutual agreement between observers. For homogeneous and well-defined lesions the entire lesion was outlined around its outer border. For infiltrating or septal spreading lesions, the dominant enhancing nodule was outlined. Areas of obvious necrosis and adjacent blood vessels were ignored.

ROI so placed were used to calculate pixel-by-pixel values of transfer constant (K^{trans}), leakage space (v_e) and rate constant (k_{ep}) using the Tofts methods of Tofts[4] on software designed for purpose (MRI Workbench, Institute of Cancer Research, London). The median values of each parameter and of area under the Gd-DTPA concentration curve at 60 seconds ($IAUGC_{90}$) were recorded for each ROI. Descriptive and reproducibility statistics were calculated using Bland-Altman statistics[5]: observer repeatability, 95% limits of agreement and within patient coefficients of variance (wCV). Natural logarithm transformation (due to the error being proportional to the mean) of K^{trans} and k_{ep} data was performed.

DCE-MRI parameter		**ap1/ap2 (intra)**	**mb1/mb2 (intra)**	**ap2/mb2 (inter)**
K^{trans} (min^{-1})	Observer repeatability	-13.3 to +15.4%	-22.7 to +29.3%	-18.0 to +21.9%
	95% LOA	-0.14 to +0.15	-0.29 to +0.17	-0.18 to +0.22
	wCV (%)	5.3	9.7	7.4
v_e (%)	Observer repeatability	± 5.5%	± 11.0%	± 7.1%
	95% LOA	-0.3 to +0.2	-0.6 to +0.4	-0.3 to +0.4
	wCV (%)	2.0	4.0	2.6
k_{ep} (min^{-1})	Observer repeatability	-11.2 to +12.6%	-17.2 to +20.8%	-15.0 to +17.6%
	95% LOA	-0.12 to +0.13	-0.22 to +0.13	-0.16 to +0.17
	wCV (%)	4.4	7.1	6.0
$IAUGC_{90}$ (mmol.sec)	Observer repeatability	± 14.3%	± 22.7%	± 13.4%
	95% LOA	-2.52 to +1.92	-3.94 to +2.43	-1.75 to +2.37
	wCV (%)	5.2	8.2	4.8
ROI size (number of pixels)	Observer repeatability	± 17.2%	± 29.6%	± 29.0%
	95% LOA	-159 to +220	-189 to +404	-288 to +367
	wCV (%)	6.2	10.7	10.5
	95% LOA = 95% limits of agreement; wCV coefficient of variation			

Results: the table shows observer repeatability statistics and 95% limits of agreement by observers **ap** and **mb**. Agreement plots showing the 95% limits of agreement for K^{trans} are also shown.

Conclusions:

- Intra-observer variability is better for the experienced observer and inter-observer variability (for the second examination) is not worse than intra-observer variability.
- K^{trans} (the best predictor of response in previous studies of chemotherapy[1]) is the most variable of the kinetic parameters - even for an experienced observer; values vary by ± 15%.
- The data indicate that about a quarter of the previously documented single slice repeatability of K^{trans} (-51 to +105%) can be accounted for by intra-observer variability; stressing the need for the same observer to draw all ROIs in a given patient at the same time/sitting.
- The effects of inter- and intra-observer variability in ROI placement needs to be taken into account when DCE-MRI is used to assess treatment responses.

References: [1]Ah-See et al (poster presentation ASCO 2004). [2]Leach et al (*Br J Radiol* 2003; 76: S87-91. [3]Esserman et al *Ann Surg Onc* 2001; 8(6):549-559. [4]Tofts, PS and Kermode, AG. *JMRI* 1997;7:91. [5] Bland JM and Altman DG. *BMJ* 1996; 313: 7059

Scatter plots showing variation, with 95% confidence intervals (for K^{trans} values transformed by natural log).