A Practical Approach to Pharmacokinetic Modelling in monitoring Neoadjuvant Chemotherapy in Breast Cancer

Reem Bedair[1], Andrew Patterson[2], Mary McLean[3], Roie Manavaki[1], Scott Reid[4], John Griffiths[3], Martin Graves[2], and Fiona Gilbert[1]

[1]University of Cambridge, Department of Radiology, Cambridge, Cambridgeshire, United Kingdom, [2]Department of Radiology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, Cambridgeshire, United Kingdom, [3]Cancer Research UK Cambridge Research Institute, Cambridge, Cambridgeshire, United Kingdom, [4]GE Healthcare, Diagnostic Imaging, Buckingham, Buckinghamshire, United Kingdom

Target Audience: Radiologists, oncologists and MRI Scientists with an interest in quantitative DCE imaging.

Purpose:

Neoadjuvant chemotherapy (NACT) has now become the standard for down-staging locally advanced breast cancer and facilitating breast-conserving surgery[1,2]. Standard dynamic contrast-enhanced MRI (DCE-MRI) has been used to monitor the therapeutic response based on Response Evaluation Criteria In Solid Tumours (RECIST). However, quantitative DCE-MRI, together with pharmacokinetic modelling (PK) has the potential to provide earlier response indicators for the prediction of the final treatment outcome[3]. This carries the potential to intervene during treatment to spare patients the associated morbidities of ineffective regimens. The choice of analysis approach has been one of much controversy; with the hotspot region of interest (ROI) method commonly suggested for diagnostic purposes and the voxel-wise assessment of the entire lesion for therapy monitoring[4]. Practically, the most commonly used method is to calculate the PK parameters within a single ROI encompassing either the whole tumour or the largest section of the tumour[2,3]. In this work, we compare the early changes in the PK-derived parameter (K^{trans}) using both a voxel-wise histogram analysis across the whole tumour and the average K^{trans} from the largest section. The study was performed in a cohort of breast cancer patients undergoing NACT.

Methods:

In this prospective ethically approved study, eleven patients with locally advanced breast cancer underwent DCE-MRI at three time points along their course of chemotherapy. All patients underwent 6 cycles of chemotherapy followed by surgery. MRI was preformed a) prior to the start of therapy (t0), b) after the third cycle (t1) and c) after NACT completion (t2). DCE-MRI was preformed using a 3.0T MR system (MR750, GE Healthcare, Waukesha, WI), and an 8-channel receive breast coil with transmission on the body coil. The DCE series employed a 3D segmented *k*-space acquisition (TR/TE/α=7.1/3.8mm/12°, 256x256 matrix) with spatial resolution of 1x1x1.4mm. Total acquisition time was 8 minutes with a 9s temporal resolution. Data was collected at 48 time points before and after intravenous injection of 0.1mmol/kg of Gd-DTPA (Magnevist, BayerSchering, Berlin, Germany). Native T_{10} maps were calculated using 3D SPGR at multiple flip angles. B1 mapping was performed using the Bloch-Siegert shift sequence. Quantitative analysis of the tumour tissue time course data was preformed using DCETool[5] in OsiriX (Pixmeo, Bernex, Switzerland). ROIs were drawn on all consecutive enhancing sections of the tumour. K^{trans} maps were computed using the two-compartment Tofts model[6] and a population-based input function. A voxel-wise histogram analysis was performed over the entire tumour using in-house developed in MATLAB (The MathWorks, Inc., Natick, MA). The mean, median, and 95th percentile were derived as they have previously been investigated to measure tumour response[7]. ROIs were drawn on the parametric maps of the section of the tumour with the largest dimension (LD) and greatest contrast uptake through visual assessment, and the mean of $K^{trans}_{(LD)}$ was calculated. Changes across visits were assessed using repeated measures analysis of variance (ANOVA) with Bonferroni corrections. Pairwise comparisons were made between each visit. Response to NACT for each patient was determined by pathological analysis of post-therapy surgical specimens.

Results:

Five patients achieved complete pathological response while 6 were non-responders. Figure 1 shows the parametric maps of an example responder and non-responder. A significant reduction of mean ($p<0.001$), median ($p<0.05$) and 95th percentile ($p<0.05$) K^{trans} was found on the pixel-wise analysis across all visits. A pair-wise *t*-test showed the greatest change in all three parameters between t0 and t1 ($p<0.05$, $p<0.05$, $p=0.01$ respectively). A significant decrease of mean $K^{trans}_{(LD)}$ was also found across the visits for all patients ($p=0.01$) with statistical significance between t0 and t1 ($p<0.05$). Figure 2 shows the distributions of mean K^{trans} obtained from pixel-wise analysis and over the largest slice of the tumor. No significant differences were found for mean, median and 95th percentile K^{trans} or mean $K^{trans}_{(LD)}$ between t1 and t2.

Discussion/Conclusion:

Whole tumour pixel-based histogram analysis demonstrates significant differences in the distribution of the K^{trans} values of responders compared with non-responders. However, due to the complexity of performing pixel-wise assessments, the calculation of the average K^{trans} from the single largest section provides statistically similar results and is much quicker to perform. It may therefore be more easily incorporated into routine clinical practice, and may provide earlier therapeutic response indicators.

References:[1]Ah-See *et al*.Clin can Res. 2008;14:6580-9 [2]Kuhl *et al.* Radiol 2007;3:672-91 [3]Padhani *et al.* Radiol. 2006;2:361-74 [4]Su *et al*. JMRI 2003;18:467-477 [5]Sung *et al*. RSNA 2011 [6]Tofts *et al.* JMRI 1999;10:223-232 [7]Patankar *et al.* AJNR 2005;26:2455-2465.

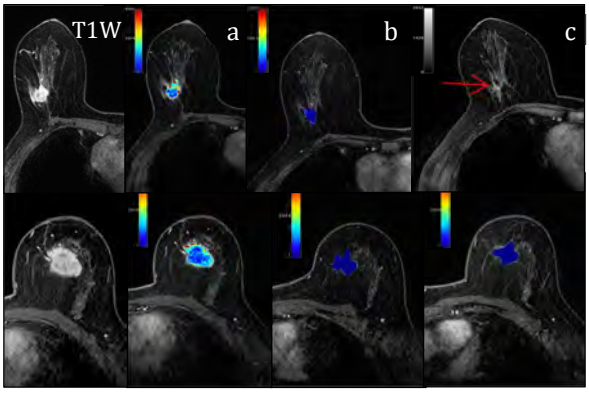

Figure 1 shows an example of a complete responder (top row) and non-responder (bottom row) to NACT: T_1W image a)K^{trans} map at t0 b)K^{trans} map at t1 c)K^{trans} map at t2. Note the complete resolution of the known malignant lesion in the top right corner (red arrow).

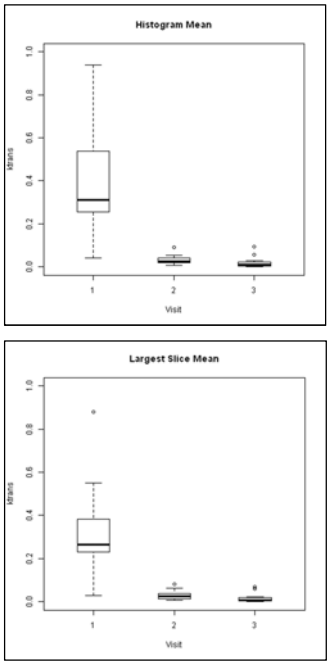

Figure 2 shows the distribution of the K^{trans} calculated from the pixel-wise analysis (top) and over the largest tumour slice (bottom).