

Pharmacokinetic analysis of DCE-MRI in invasive breast carcinomas: correlation with tumour grade

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Introduction Dynamic contrast enhanced MRI (DCE-MRI) has almost unequivocally demonstrated high sensitivity for detection of breast cancer [1]. Analysis of the correlation between quantitative DCE-MRI findings and prognostic factors (such as histological tumour grade) is important for defining the role of this technique in the diagnosis of breast cancer as well as the monitoring of neo-adjuvant therapies. Several animal model studies of breast cancer have demonstrated a strong relationship between tumour grade and capillary permeability using macro-molecular contrast media but were unable to demonstrate an increase in permeability to the smaller Gd-DTPA molecule in higher-grade tumours [2]. Previous clinical studies where prognostic factors were compared to DCE-MRI reported contradictory results and did not include pharmacokinetic modelling of contrast uptake. In this study, we performed pharmacokinetic analysis of DCE-MRI (Gd-DTPA) in patients with histologically confirmed and graded invasive breast carcinomas.

Patients and methods Quantitative analysis of DCE-MRI was performed retrospectively in 59 lesions (in 52 patients). All patients were female with a median age of 55 (32 - 80). Tumour grading was performed using the Nottingham Prognostic Index for primary breast cancer. Twelve lesions were found to be Grade 1 tumours, twenty-nine, Grade 2 and eighteen, Grade 3 tumours. DCE-MRI acquisition was performed on a 1.5 T MRI scanner (Gyrosan ACS NT, Philips Medical Systems). The MR signal detection was performed with a standard bilateral breast coil and the patients were positioned prone. A 2D multislice, T1-weighted gradient echo sequence was used (TR/TE/ ϕ = 213/4.6/90°, FOV = 300mm, 25 slices, 4mm slice thickness, 12 dynamic scans at 32.5 seconds intervals, 154 × 256 image matrix, reconstructed to 256 × 256). The imaging was performed in the transverse plane, with the imaging volume encompassing both breasts in all three dimensions. A standard dose of 0.1 mmol per kilogram body weight of gadopentetate dimeglumine Gd-DTPA was used, followed by a 10 ml saline flush.



Figure 1. Parametric maps of ME, IRE and WOS

Individual lesions were identified using parametric maps of maximal enhancement (ME), initial rate of enhancement (IRE) and the wash-out-slope (WOS) which were computed on a voxel-by-voxel basis and displayed superimposed on grey-scale anatomical images (Figure 1.). All three images (ME, IRE and WOS) were examined simultaneously by a trained radiologist who identified a single circular 16-voxel ROI close to the lesion rim and away from the necrotic, central areas (if present). Resulting SI/time curves were analysed using a two-compartment pharmacokinetic model [3].

Results Three pharmacokinetic variables (f_{ex} , k_{ep} , and K^{trans}) were extracted in 59 lesions: fractional volume of the extracellular extravascular space (f_{ex}) and two capillary permeability related variables (k_{ep} , and K^{trans}) [3]. A constant pre-contrast value of T1 (T_{1_0}) was assumed in all lesions (T_{1_0} = 876 ms, the mean value of T_{1_0} in invasive breast carcinomas [4]). Results of the measurements performed in three histological grade groups are summarised in Table 1. Regression analysis was performed on logarithmically transformed values of variables f_{ex} , k_{ep} , and K^{trans} against the tumour grade.

Table 1. Pharmacokinetic variables f_{ex} and K^{trans} in three histological groups

	f_{ex}		K^{trans} [1/min]	
	Mean	SD	Mean	SD
grade 1 (n = 12)	.389	.126	.606	.276
grade 2 (n = 29)	.459	.144	.913	.725
grade 3 (n = 18)	.459	.107	1.409	.689

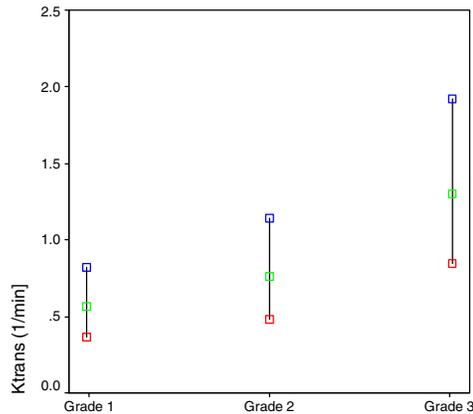


Figure 2. 95% CI for K^{trans} [min^{-1}]

All statistical tests were performed at α = 0.05 confidence level. Regression coefficients for k_{ep} (R = 0.43, p = 0.003) and K^{trans} (R = 0.44, p = 0.001) were statistically significant. The confidence intervals (CI) of the regression coefficients were used to estimate the location of the means of transformed variables in each of the tumour grade subgroups. Inverse transformation yielded the estimates of the variable means in three tumour grade subgroups, expressed in original units. The estimated 95% confidence interval limits for K^{trans} are presented graphically in Figure 2. The displayed p -value represents the overall regression model significance. Red and blue squares represent lower and upper CI limits, and green squares represent geometric mean of variable K^{trans} in each of the subgroups.

Discussion In this study a significant correlation between permeability-related pharmacokinetic variables (k_{ep} , and K^{trans}) and tumour grade in invasive breast cancer was found. None of the measured pharmacokinetic variables varied significantly between Grade 1 and Grade 2 tumours. However, k_{ep} , and K^{trans} were significantly higher in Grade 3 tumours compared to low grade (Grade 1 and 2) tumours. This method might therefore be used to monitor the effectiveness of neo-adjuvant treatment of high grade tumours, but is unlikely to resolve the changes in tissue microcirculation in low grade tumours.

The lack of correlation between tumour grade and Gd-DTPA capillary permeability reported previously in animal studies [2] may be a result of higher overall rate of permeability in experimental tumours. The improved spatial and temporal sampling of DCE-MRI together with accurate pre-contrast mapping of native longitudinal relaxation time may enable better differentiation between Grade 1 and Grade 2 tumours.

References: 1. JMRI, 2000. 12(6): p. 965-974. 2. JMRI, 1999. 9(2): p. 177-86. 3. JMRI, 1999. 10(3): p. 223-232. 4. Acta Radiologica, 1993. 34(4): p. 356-361.