Prognostic value of Pre-Treatment DCE-MRI in Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy: a Comparison with Traditional Clinical Prognostic Parameters

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Target audience: MR researchers, oncologists, breast clinicians, breast radiologists,

Purpose: A number of authors[1-7] have reported the prognostic value of MR parameters in predicting survival internals [both disease free (DFS) and overall (OS)] for breast cancer patients who have undergone neoadjuvant chemotherapy (NAC). However, the cohort size is generally small with short follow up intervals. Only two studies[2,7] have a sample size ≥50 combined with a ≥60 months median follow up period. The aims of this study was to 1) provide data on a large (≥50) cohort with a long median follow up interval (≥60 months); 2) determine if any associations were noted between MR parameters and survival intervals; and 3) assess the prognostic value of the MR parameters against traditional clinical survival indicators.

Methods: Vascular DCE-MRI parameters (pharmacokinetic modelled and empirical) along with MR lesion volume were obtained prior to and post 2nd NAC cycle. Pharmacokinetic parameters were derived from an open two compartment model. For both PK and empirical parameters ROIs were drawn on the slice with the largest cross sectional tumour area, then data was obtained from a 3x3 pixel hot spot from within that ROI. Pre NAC absolute values and percentage differences were obtained. For all MRI parameters ≤median values were compared to >median for statistical analysis of survival. Pre NAC biopsy samples and clinical examination provided the following traditional pre NAC survival indicators: T stage (≤T2, ≤50mm or ≥T3, >50mm), axillary lymph node (ALN) status (negative or positive), oestrogen receptor (ER) status (negative or positive), progesterone receptor (PR) status (negative or positive), tumour type (special type or no special type) and grade (I and II or III). Age was dichotomised as follows, ≤40 or >40 years.

To demonstrate which parameters were associated with survival intervals a multivariate Cox's proportional hazards model (CPHM) was employed. However, to streamline the number of variables entered into this model the univariate Kaplan-Meier analysis was utilised. Only those MR parameters with at least a borderline significant ($p<0.1$) logrank test result were entered into the CPHM. To allow a comparison with MR parameters all traditional survival indicators were entered into the CPHM. Treatment failure (critical event) was defined as tumour remission and/or distant metastasis (DFS) or cancer related death (OS), whilst data from patients without treatment failure were treated as censored. Time to event was defined from surgery to event. Patient status, critical or censored, was determined by reviewing patient notes.

Event	n	Median (min – max) survival (days)
DFS critical event	38	634 (52 - 3247)
DFS censored	49	2771 (1700 – 4058)
OS critical event	32	568.5 (133 – 3263)
OS censored	55	2800 (1700 - 4058)

Table I. DFS and OS events and intervals

Disease Free Survival				Overall Survival			
Parameter	KM logrank	Hazard ratio (95% CI)	p value	Parameter	KM logrank	Hazard ratio (95% CI)	p value
v_e	0.047			v_e	0.066		
Max EI	0.069			Max EI	0.078	16.297 (1.924 – 138.056)	0.010
EI@30sec	0.099	6.870 (1.297 – 36.387)	0.023	AUC@90sec	0.038		
AUC@90sec	0.033			MR volume	0.098		
MR volume	0.033			% v_e	0.058	1.066 (1.032 – 1.102)	<0.001
%MaxEI	0.069	1.022 (1.008 – 1.036)	0.002	%MaxEI	0.025		
% Rise Time	0.035			% nMITR	0.046	0.981 (0.968 – 0.994)	0.005
Grade				% AUC@90sec	0.082		
Type				Grade			
ER status				Type			
PR status		6.505 (2.031 – 20.833)	0.002	ER status			
T stage				PR status		11.802 (2.206 – 63.143)	0.004
ALN status		5.374 (1.751 – 16.494)	0.003	T stage		6.728 (1.305 – 34.676)	0.023
Age		0.950 (0.908 – 0.994)	0.025	ALN status		6.248 (1.136 – 34.371)	0.035
				Age			

Table II. Kaplan-Meier logrank results for MR parameters and CPHM retained variables with associated hazard ratios, 95% CI and significance levels. v_e - extracellular extravascular space, EI - enhancement index, Rise time – time to reach half max EI, nMITR – normalised max intensity time ratio.

Results: Patients underwent surgery between August 2000 and June 2005. Final review of patient's notes took place in March 2012. DFS and OS data from 87 patients are presented in Table I. Overall median follow up intervals were 66 months (DFS) and 78 months (OS). All patients underwent pre NAC MR examinations and 66 patients had post 2nd NAC cycle MR data. Kaplan-Meier logrank test results ($p<0.1$) for MR parameters are presented in Table II along with retained parameters from the CPHM undertaken in the 51 patients with full data sets.

Discussion: Empirical vascular parameters were retained in the CPHM for both DFS and OS. Further, enhancement index at 30 seconds and maximum enhancement index provided the variables with the highest hazards ratio (HR) for DFS and OS respectively. Both Li et al.[2] and Bone et al.[7] demonstrated the importance of vascular parameters in their results with signal enhancement ratio (SER) and K^{trans}, respectively, retained by the studies CPHM. Enhancement index, SER and K^{trans} all reflect perfusion and vessel permeability and as such are surrogates for tumour neoangiogenesis. Survival failure in breast cancer patients results from metastasis spread. Elevated levels of neoangiogenesis enhance the dissemination of tumour cells via the circulation and in turn the likelihood of metastatic failure.

Conclusions: Elevated DCE-MRI parameters that reflect perfusion and vessel permeability are associated with shorter survival intervals and in this cohort provided prognostic information superior to traditional clinical survival indicators as evident from the higher hazard ratios.

References: [1]Tuncbilek N, et al. European Journal of Radiology. 2012;81(5):863-867. [2]Li S, et al. Radiology. 2011;260(1):68-78. [3]Heldahl M, et al. Acta radiologica. 2010;51(6):604-612. [4]Pickles MD, et al. European Journal of Radiology. 2009;71(3):498-505. [5]Johansen R, et al. JMRI. 2009;29(6):1300-1307. [6]Partridge SC, et al. American Journal of Roentgenology. 2005;184(6):1774-1781. [7]Bone B, et al. Acta Radiologica. 2003;44(4):373-378.