Prognostic Value of MR Parameters Obtained Prior to the Initiation of Neoadjuvant Chemotherapy: A Comparison with Traditinal Prognostic Indicators

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

Purpose: Neoadjuvant chemotherapy (NAC) is frequently utilised to treat patients with locally advanced breast cancer (LABC) prior to surgery and adjuvant therapies [1]. Five year survival rates for stage III breast cancer patients are reported to be 72% [2]. Consequently, there is a pressing need to improve treatment outcomes. Currently, treatment stratification is based on traditional prognostic indicators such as disease stage and lesion descriptors [1]. However, using such stratification, both the initial treatment response and the longer term survival outcomes can be quite varied. If a pre-treatment MR biomarker could predict survival outcomes then alternative treatment strategies could be considered.
Dynamic contrast enhanced MRI (DCE-MRI) allows a non-invasive, *in-vivo* characterisation of tumour vascular kinetics. DCE-MRI derived parameters reflect blood flow, vascular density and vessel permeability [3], which have been shown to correlate with traditional prognostic indicators [4]. Texture analysis (TA) results in the quantification of grey tone spatial variation thereby providing textural features that characterise the underlying structure of the object under investigation. MR based TA features have been previously described [5] and have also been linked with traditional breast cancer prognostic indicators [6]. Likewise tumour shape has been associated with prognostic indicators [7].
The aims of this study were to determine if any associations exist between MR parameters and survival intervals [disease free (DFS) and overall survival (OS)], additionally, to compare the prognostic value of MR parameters against traditional survival indicators.

Methods: All MR imaging was undertaken on a 3.0T HDx scanner (GE Healthcare) prior to NAC. In each case a 3D dynamic dataset was acquired utilising VIBRANT with a temporal resolution of ~30secs. Semi-automated 2D ROI's were generated on each slice that demonstrated malignant tissue throughout the breast from an early arterial phase to generate a pseudo 3D volume of interest (VOI). For DCE-MRI analysis the signal intensity time course was assessed in a pixel-by-pixel manner across all dynamic phases. Texture analysis was undertaken purely from the early arterial phase (~1min post injection) resulting in texture features f1 to f16. A 2D approach was adopted for shape analysis whereby only the ROI with the largest cross sectional area was interrogated. Finally, MRI based size parameters, longest dimension (LD) and volume were also analysed. For all MRI parameters ≤median values were compared to >median for statistical analysis of survival.
Clinical records provided the following traditional survival indicators: age (≤45years or >45 years), grade (I and II or III), histological type (special type or no special type), oestrogen receptor (ER) status (negative or positive), progesterone (PR) status (negative or positive), human epidermal growth factor receptor 2 (HER2) status (negative or positive), molecular subtype (triple negative or all other), T stage (≤T2 or >T2), and N stage (N0 or ≥N1).
Patients were categorised as having a critical survival event or censored. Critical events were defined as local tumour recurrence and/or metastasis (DFS) or a cancer related death (OS). Patients without critical events, but known to be well at their most recent follow-up, were censored. The DFS and OS time interval was defined as the time from initiation of NAC to critical or censored event. Univariate Kaplan-Meier (KM) survival plots were generated for each MR parameter, group comparisons were made utilising logrank tests. A Cox's proportional hazards model (CPHM) was used for multivariate survival analysis. To avoid over-parameterisation, while allowing a comparison against traditional prognostic indicators, only significant (KM logrank $p<0.05$) MR parameters were entered into the CPHM along with all traditional parameters.

Results: Eighty-one patients underwent NAC, surgery, and adjuvant radiotherapy ± hormonal therapy. The number of critical and censored events along with median follow-up intervals is presented in Table I. When considering DFS the following MR parameters demonstrated significant KM logrank results: volume, f8, complexity, circularity, percentage maximum enhancement index at 30secs (PC30). With regards to OS volume, f8, maximum intensity time ratio and PC30 all demonstrated significant KM survival plot results. Final Cox's proportional hazards models are presented in Table II for both DFS and OS.

Group	Disease Free Survival		Overall Survival	
	Median (min. max.) days	n	Median (min. max.) days	n
Whole cohort	2078 (271-2934)	81	2204 (368-2934)	81
Censored	2349 (686-2934)	50	2332 (658-2934)	59
Critical event	767 (271-2569)	31	836 (368-2457)	22

Table I. Survival follow up intervals

Parameter	DFS Hazard ratio (95% CI)	p value
N stage$_{(+ve)}$	3.187 (1.455 – 6.981)	0.004
complexity	1.008 (1.001 – 1.016)	0.028
f8	1.592 (0.963 – 2.631)	0.070
	OS Hazard ratio (95% CI)	
N stage$_{(+ve)}$	5.016 (1.739 – 14.466)	0.003
Age$_{(\leq 45)}$	2.375 (0.856 – 6.588)	0.097
f8	1.810 (0.950 – 3.448)	0.071

Table II. Cox's proportional hazards model results

Discussion: The results of the univariate KM survival analysis reveal that vascular, textural, shape and size are all MR features associated with DFS. Further when interactions between variables are considered via a CPHM shape and texture parameters are retained along with nodal status. The same analysis for OS revealed vascular, textural, and size to be once again associated with survival. However, texture represented the only MR parameter class retained by the overall survival CPHM along with nodal status and age. Sum entropy is denoted by f8, lesions demonstrating high levels of heterogeneity have high f8 values. Complexity refers to the irregularity of the lesions border with higher values indicating a more irregular boundary. The results of this study indicate that shorter disease free survival intervals can be expected for node positive, heterogeneous, irregular bordered tumours while a shorter overall survival can be expected in node positive, heterogeneous lesions in younger women.

Conclusions: This work has demonstrated in a large cohort with a long median follow up interval via a CPHM that MR parameters (textural and shape) can provide independent prognostic information that can complement traditional prognostic indicators. Further it seems that MR parameters may have a role to play in treatment stratification for patients diagnosed with LABC since these survival associations are evident prior to the initiation of NAC treatment.

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