Associations with Disease Free Survival and Pre treatment Texture Features Obtained From Dynamic Contrast Enhanced Breast Images

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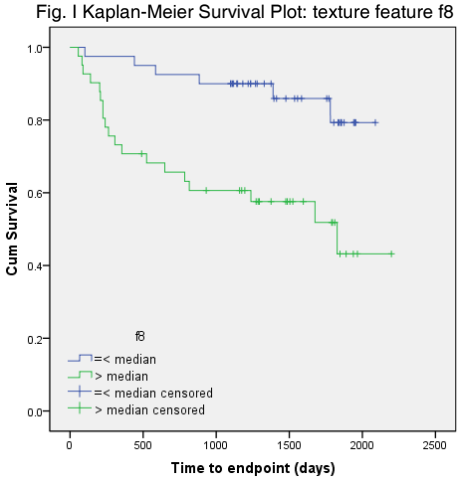
Target audience: MR researchers, oncologists, breast clinicians, breast radiologists,

Purpose: Neoadjuvant chemotherapy (NAC) is now considered the standard treatment for locally advanced breast cancer. An overall survival rate of 82% and progression free survival of 65% at four years have been reported[1] for patients who have undergone NAC. Consequently, for a significant minority of patients some form of relapse can be anticipated. Biomarkers of reduced survival intervals could potentially impact upon treatment management. If a reduced survival interval could be predicted prior to treatment then alterative treatment strategies could be considered. Texture analysis (TA) results in the quantification of gray 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[2] and linked with traditional breast cancer prognostic indicators[3].
The aim of this work was twofold. Firstly, to determine if there were any associations between pre-treatment MR derived TA features and disease free survival (DFS) in a cohort of biopsy proven breast cancer patients who underwent NAC, and secondly, to compare the results of TA features with DCE-MRI parameters, MR derived tumour size and traditional pre treatment prognostic parameters such as histological grade.

Methods: Ninety-eight patients were scanned prior to NAC on a 3.0T HDx scanner (GE Healthcare). In each case a 3D dynamic dataset was acquired utilising VIBRANT. Texture and empirical vascular parameters were acquired. Semi-automated ROI's were generated on each slice that demonstrated malignant tissue throughout the breast from an early arterial phase. For vascular analysis the signal intensities from the individual ROI's were averaged for each individual phase prior to analysis. Texture analysis was undertaken purely from the early arterial phase. For the texture analysis multiple 2D datasets were averaged to provide pseudo 3D texture features, f1 to f16.
For all MRI parameters ≤median values were compared to >median for statistical analysis of survival. Pre treatment biopsy samples provided the following traditional survival indicators: human epidermal growth factor receptor 2 (HER2) status (negative or positive), oestrogen receptor (ER) status (negative or positive), progesterone (PR) status (negative or positive), tumour type (special type or no special type) and grade (I and II or III). Treatment failure (critical event) was defined as tumour remission and/or metastasis, whilst data from patients without treatment failure were treated as censored. Patient status, critical or censored, was determined by reviewing patient notes. For univariate analysis Kaplan-Meier survival plots were generated for each parameter, group comparisons were made utilising logrank tests. A Cox's proportional hazards model was used for multivariate survival analysis.

Fig. I Kaplan-Meier Survival Plot: texture feature f8



Results: Seventeen patients were excluded from the final analysis (did not proceed to surgery, 11; <4 cycles of NAC, 2; no radiotherapy in the adjuvant setting, 3; new lesion of unknown origin at time of analysis, 1), consequently, results are presented for 81 patients. Twenty-five patients suffered a treatment failure and 56 patients were censored. The median follow-up time for patients with recurrence was 354 days, range 56 to 1827 days, while for censored patients median follow-up time was 1495 days, range 490 to 2199 days. Table I presents those parameters demonstrating a significant difference in univariate DFS analysis, note that no DCE-MRI parameters reached the significant level ($p<0.05$). Kaplan-Meier survival plots for f8, is illustrated in Figure I. Only f8 and MR longest diameter (LD) were retained by the Cox's proportional hazards model, with f8 having the highest hazards ratio, see Table II.

Parameter	Dichotomise	95% CI mean survival (days)	p value
MR Vol.	≤median	1748 - 2058	<0.001
	>median	1062 - 1610	
MR LD	≤median	1641 - 2070	0.049
	>median	1124 - 1593	
f7	≤median	1594 - 1976	0.050
	>median	1205 - 1752	
f8	≤median	1722 - 2041	0.001
	>median	1092 - 1648	
ER	+ve	1681 - 2031	0.010
	-ve	849 - 1534	

Table I. Significant Kaplan-Meier results

Discussion: The results of the univariate test demonstrate that texture features (f7 and f8), MR lesion size and ER status obtained prior to treatment can all provide an insight into longer term DFS. However, when interactions between variables are considered via the Cox's proportional hazards model only two variables are retained, f8 and MR LD. Sum entropy is denoted by f8 (measure of randomness of the sum of the grey levels of neighbouring pixels). Therefore lesions demonstrating high levels of heterogeneity would have high f8 values. A hazard ratio of 2.028 (95% CI 1.051 – 3.913), as noted with f8, indicates a doubling of the risk of a critical event for every unit increase in f8. However, the real increase in risk maybe as low as 5% as evident by the 95% confidence interval.

Parameter	Hazard ratio (95% CI)	p value
f8	2.028 (1.051 – 3.913)	0.035
MR LD	1.018 (0.998 – 1.038)	0.078

Table II. Cox's proportional hazards model results

Conclusions: Not only can texture features provide an insight into longer term DFS but for this cohort texture features out performed DCE-MRI parameters and traditional prognostic indicators.

References: [1]van de Hage et al. J. Clin Oncol 2001, [2] Haralick et al. IEEE 1973 [3]Pickles et al. ISMRM 19th, 1010. 2011,