Neoadjuvant Chemotherapy in Breast Cancer: Prediction of Post-Surgery Disease-Free Survival Using DCE-MRI, Water ADC Mapping And Proton Spectroscopic Imaging

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Introduction: Breast cancer is one of the most prevalent and serious forms of cancer in the UK, accounting for more than 1 in 4 of female cancer cases and demonstrating age standardised incidence and mortality rates of 117 and 31 per 100,000, respectively [1]. Some primary breast cancers are considered inoperable at diagnosis due to their problematical location and size, with tumours greater than 3 cm in diameter being associated with an increased risk of disseminated disease. In such cases neoadjuvant chemotherapy is routinely used prior to surgery to increase the chances of a successful outcome. Decrease in tumour volume at the end of chemotherapy can be determined using contrast-enhanced MRI and has been shown to have value in predicting the length of time that patients remain disease-free after surgery [2]. Quantitative data obtained from dynamic contrast-enhanced MRI (DCE-MRI) [3], Water apparent diffusion coefficient (ADC) mapping [4] and proton MR spectroscopy [5] can be used to detect early response to chemotherapy and a study was undertaken to determine if these techniques can also demonstrate utility in predicting disease-free survival.

Methods: Longitudinal MRI was carried out at 1.5 T (IGE Signa Advantage) in 16 women; all of whom underwent a standard dosage chemotherapy regime (5-Fluorouracil, Epirubicin and Cyclophosphamide) followed by appropriate surgery. MRI and MRS were carried out prior to chemotherapy (TP0) and after the final, usually sixth, course (TPF). **Water ADC** was measured using EPI with 8 diffusion gradient weightings from 0 to 680 s/mm^2. Microvascularity was assessed using a multi-slice, 2D, T_1-weighted dynamic contrast-enhanced (DCE-) MRI: fast spoiled gradient echo (FSPGR), 13s temporal resolution, 7.5 minute duration. A three-compartment pharmacokinetic model was used to calculate microvessel transfer constant (**K^{trans}**), exchange rate (**K_{ep}**) and extracellular-extravascular tissue volume fraction (**V_e** = K^{trans}/K_{ep}). The proportion of signal arising from water was measured using a 1D STEAM spectroscopic imaging sequence with seven 0.25 ml voxels in a column passing through each tumour (%W = water signal / sum of water and fat signals, only analysing those voxels wholly within tumour tissue). Echo times of 30 and 135 ms were used (**%W135** and **%W30**) with a TR of 3 s. **Water T_2** was also estimated from MRS data. **Tumour volume** was measured using manually traced regions-of-interest drawn on high resolution 3D, post-contrast, fat-suppressed FSPGR images. Changes in parameter values between TP0 and TPF were calculated either as absolute differences, D(x), or percentage change, PC(x), as deemed most appropriate. The ability of each MRI parameter to predict disease-free survival, as determined by reviewing patients' notes, was assessed by splitting data into >median and <median groups then using Kaplan-Meier survival curves and log-rank tests. Clinical prognostic markers were also obtained from patients' notes (**tumour type** and **grade**, **oestrogen** and **progesterone** receptor status, and axillary lymph **node status**) and underwent survival analysis.

Results: Thirteen women were deemed well at their most recent clinic appointment (median time from surgery = 3.0 years, range = 1.4 to 4.0 years) whilst three women had developed metastases since surgery (after 1.3, 1.5 & 1.9 years). Survival analysis indicated that nine of the 24 MRI variables (**eight parameters** with two time-points and one change each) and one of the **five clinical variables** were significantly correlated with the length of disease-free survival (log-rank p = 0.049, see table).

Parameter	*Median (Range)*	*All three cases of recurrence displayed values*
K_{ep} at TP0	3.49 (1.11 to 7.44) /unit time	> median
$D(K_{ep})$	-2.30 (-5.74 to 0.41) /unit time	< median
%W135 at TPF	74.8% (34.9% to 100.0%)	< median
PC(%W135)	-17.9% (-45.9% to 19.1%)	< median
%W30 at TP0	96.7% (78.6% to 100.0%)	< median
%W30 at TPF	84.0% (51.4% to 100.0%)	< median
PC(%W30)	-9.2% (-35.8% to 7.9%)	< median
T_{2W} at TP0	61.9 (47.2 to 94.4) ms	< median
D(ADC)	0.16 (-2.64 to 3.06) mm^2/s	< median
Node status	All three cases had nodal metastases at surgery	

Discussion: Whilst the number of cases in this study (hence statistical power) is relatively low, it has been demonstrated that quantitative DCE-MRI, ADC and proton MRS data all have significant power to predict disease-free survival in women following breast cancer treatment. Whilst multiple individual statistical tests have been undertaken, the number of significant results far exceeds that expected by chance alone (29 x 0.05 = 1.45). A follow-up study with an increased number of cases would be desirable (preferably in a multi-centre setting to determine reproducibility) and would also permit statistical (e.g. logistic regression) modelling to determine if a combination of MRI and traditional clinical parameters could lead to a synergistic increase in prognostic accuracy.

References:

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