Artificial Neuronal Network Analysis of Neoadjuvant Chemotherapy Response using Quantitative Morphological, Texture and Enhancement Kinetic Parameters

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Purpose: The morphological appearance and the contrast enhancement kinetics of breast lesions are two key elements in the interpretation of breast MRI. Not only that they can be used in differential diagnosis, they may also be used to predict response to neoadjuvant chemotherapy [1-2]. In this study, we investigated whether the lesion morphology or texture, or its enhancement kinetic parameters can be used to predict which lesion will respond well to the AC neoadjuvant chemotherapy. We performed quantitative analysis to obtain parameters using 8 morphological parameters and two sets of texture parameters, Gray Level Co-occurrence Matrix (GLCM) and LAWS' texture energy features. In the contrast enhancement kinetic analysis, we applied both ROI and pixel-by-pixel approaches, using the raw descriptor (wash-in rate, maximum enhancement, wash-out slope) as well as pharmacokinetic analysis to obtain quantitative Ktrans and kep parameters. According to tumor shrinkage, the lesions were separated into responders and non-responders. An artificial neuronal network (ANN) analysis was employed to investigate what subset of parameters may be used to predict response, and also we investigated the changes in the parameter after 1-2 cycles therapy between responder and non-responder groups.

Methods: Thirty-three patients received neoadjuvant chemotherapy with AC regimen (doxorubicin and cyclophosphamide) were included in the analysis. All of them had a baseline MRI and an early F/U study after 1-2 cycles AC. Depending on the 1-D size change after 1-2 cycles, those showing less than 15% reduction was classified as non-responders. Of 33 subjects, 17 were responders and 16 were non-responders. In each patient, the cancer ROI on each imaging slice was manually outlined, and all ROI's were combined to obtain a 3D representation of the lesion. Eight morphological features including volume, surface, NRL (Normalized Radial Length) Mean, NRL Entropy, NRL Ratio, Sphericity, Compactness, and Roughness were calculated to describe the morphological properties for each case. Ten GLCM texture features (energy, maximum probability, contrast, homogeneity, entropy, correlation, sum average, sum variance, difference average, and difference variance) and 14 LAWS' texture energy features were obtained to describe the texture properties for each case. The enhancement kinetics from each lesion was analyzed using ROI analysis and pixel-by-pixel (90%-50%) analysis, and the raw descriptors and Ktrans and kep pharmacokinetic parameters analyzed using Toft's model with and without vascular compartment were obtained. All together there were 27 kinetic features, which made up a total of 59 features. Many features in the data set are usually irrelevant to the chemotherapy response and redundant with each other, which will increase the computational complexity and reduce the recognition rate. A wrapper algorithm was used here to choose the optimal feature subset, utilizing the classification algorithm to score each subset according to its predictive power. The multiple layer perceptron (MLP) neural network was used as classification method and due to the limited sample size the leave-one-out cross validation was used to evaluate the generated classifier. The baseline features of all patients were used for classification into responders and non-responders. MLP neural network used here consists of three layers with 7 input nodes, 5 hidden nodes and 2 output nodes. The number of hidden units in the ANN strongly determines the level of complexity. To retain sufficient complexity but meanwhile to restrict a meaningful number of degree of freedom, the best structure determined from our data set is to choose 7 input nodes and 5 hidden nodes. Each parameter set was normalized to have the zero mean and unit variance before training. Forward search strategy was applied to find the optimal feature subset, which was obtained when the MLP classifier produce the least error rate. The ANN analysis was performed separately using (1) morphology/texture features, (2) enhancement kinetic features, and (3) all (1)+(2) features, and the classification accuracy was compared using the ROC analysis.

Results: The ANN classification based on 32 morphology/texture features (8 morphological features, 10 GLCM texture, 14 Laws' texture) can achieve 76% accuracy, as shown in the ROC curves in Fig. 1. The analysis based on 27 kinetic features achieved 51% accuracy, which was only slightly better than random guess. However, if all parameters were combined, it can achieve up to 85% accuracy, with the selected parameter set including 1 morphological (roughness), 2 GLCM (difference average, difference variance), 2 Laws' (LAW_EE, LAW_LE) and 2 kinetic (ROI-washout, and 50% kep) features. In search of the best topologic structure, we found that 3 parameters (2 GLCM and ROI_washout) were consistently selected during topologic structure testing, suggesting that they were strongly associated with response prediction. The value of 3 parameters between responder(R) and non-responder (NR) groups, one from each category, are shown in Fig. 2. Also plotted on the figure are their values measured in F/U study after 1-2 AC. It can be seen that in the texture feature "LAW_EE" (related to sharp edge), it was significantly lower in the baseline of R than NR, and after therapy the values in the R group increased significantly, in a direction approaching to the NR. In the morphological feature "roughness", it has a significantly higher mean value in the baseline of R, but no significant changes after therapy. In the kinetic parameter 'ROI_washout", i.e. the wash-out rate measured from the ROI enhancement kinetics, the value in the baseline of R was lower (i.e. with faster wash-out) but not quite significant compared to NR (p=0.06). After therapy the wash-out slope increased significantly (i.e. from a wash-out pattern to a plateau pattern, which was commonly reported). Although the kinetic parameters did not performed well by themselves, however, they can be combined with morphology/texture parameters to improve the classification accuracy from 76% to 85%.

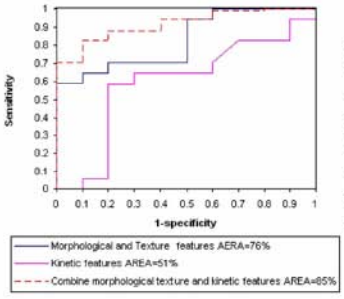

Fig. 1: The ROC curves from ANN analysis.

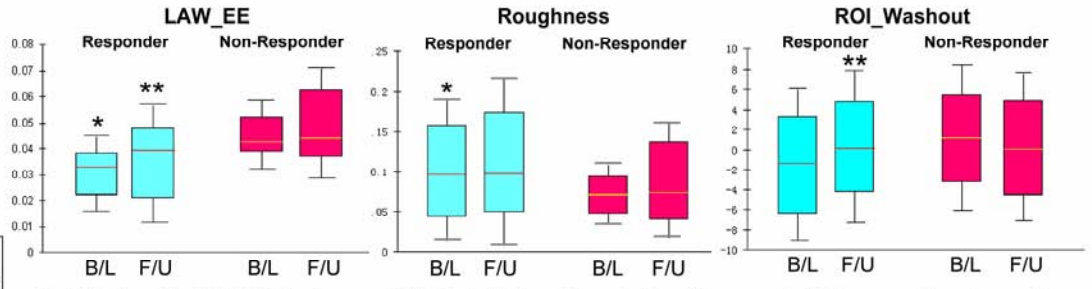

Fig. 2: The box plot of LAW_EE, Roughness, and ROI_Washout between Responder(R) and Non-responder(NR) groups, and in each group the changes between B/L and F/U MRI after 1-2 cycles AC. *- significant between R and NR B/L studies, **- significant between B/L and F/U in R.

Discussion: Since there are 59 features in our study, the size of the feature subset is 2^{59}. It is impossible to exhaustively examine all subsets, and furthermore it may not be easy to find the best feature subset by forward search strategy. A feature selection algorithm is needed to select a subset of parameters. Due to the limited sample size (only 33 cases), the training result was not stable with different selected seeds, also the results varied a lot in different topologic structure. After many testing sessions we chose to fix the number of input parameters as 7, and these were applied in 3 analyses using morphology/texture, kinetic, and all features, respectively. Since the 27 kinetics features were not independent, rather they were parameters measured using different analysis approaches, and that might explain why the training result was not good (51%). However, when they were combined with morphology/texture features, 2 kinetic parameters were selected, and that contributed to improved classification from 76% to 85%. In summary, we have demonstrated that quantitative analysis of morphology and texture in breast cancer are feasible, and artificial neuronal network may be applied to find an optimized subset for diagnosis, or therapy response prediction as demonstrated in this work. To further improve this method, genetic search strategy combined with neural network may be considered in the future.

References [1] Gibbs et al. Magn. Res. Med. 2003; 50:92-98. [2] Esserman et al. Ann Surg Oncol. 2001 8(6):549-559.

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