Quantitative Analysis of MRI Tumor Characteristics for Neoadjuvant Chemotherapy Response Prediction in Breast Cancer to the First-line Doxorubicin-Cyclophosphamide Regimen and the AC Followed By Taxane Regimen

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Purpose:

Neoadjuvant chemotherapy has become increasingly used in breast-cancer treatment and management. At our institution an aggressive neoadjuvant chemotherapy protocol is been used. Patients receive 2-4 cycles Doxorubicin-Cyclophosphamide (AC), then are switched to taxane which included paclitaxel (or Nab-paclitaxel) combined with Carboplatin and Herceptin for HER-2 positive patient. In this study all patients received a baseline MRI before treatment, several follow-ups during the course of treatment to monitor the response to each regimen, then a final MRI before surgery. In our previous work, we have successfully demonstrated that MRI has been very helpful to provide response monitoring information for timely adjustment of protocol. In this current study, we will take the role of MRI one step further beyond therapy response monitoring, to quantitatively investigate whether the pre-treatment tumor morphology appearance can be used as predictors of final treatment outcome. The response to the first line AC regimen was first determined, then the final response after completing AC+taxane was also assessed. The analyzed MRI parameters include 8 morphological parameters and two sets of texture features, Gray Level Co-occurrence Matrix (GLCM) and LAWs' energy texture features. An artificial neural network training algorithm was used to select features to predict AC response and the overall response.

Methods:

61 subjects who received 2-4 cycles of AC followed by Taxane regimen were included in this study. When a patient was determined not showing a good response to AC, the regimen was switched to Taxane after 2 cycles AC instead of completing all 4 cycles. By pooling all the patients together, we investigated the patients' response to AC regimen alone, and the response to full course treatment after completing AC followed by Taxane regimen. The clinical response assessment was based on MRI, ultrasound, and the clinical examinations. Of 61 patients, 33 were AC Responders (AC_R), 24 were AC non-responders (AC_NR); 36 were AC+T responders (AC+T_R, without residual diseases on MRI), and 11 appeared as AC+T partial or non-responders (AC+T_NR) with residual disease after all treatments. Only the lesion in the baseline MRI study was analyzed. Each lesion was automatically segmented using a fuzzy C-mean algorithm, then 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. 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, all together 32 morphological/texture features. The artificial neural network (ANN) analysis was performed to select a subset of optimal features which could differentiate between responders and non-responders, 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 88% accuracy (area under the curve) for AC response prediction. For AC followed by Taxane regimen response prediction, the selected features could only reached 66% accuracy, as shown in Fig.1. The selected parameter set for AC response prediction included 3 morphological (compactness, circularity, roughness), 1 GLCM (entropy), and 1 Laws' (LAW_LE) features. Unpaired t-tests were utilized to evaluate each individually selected parameter. Compactness is significant lower (p=0.008) in baseline of AC_R than AC_NR. Two cases with relatively low/high compactness were shown in Fig 2. The compactness defines as the ratio of surface area to the volume, so spherical-like pattern has lower compactness index than an irregular nodular pattern. Gray level entropy was also found to be significant higher (p=0.01) for AC_R than AC_NR. The entropy illustrated the stabilization of a system, so it reflected the homogeneity of a lesion. Two cases with relatively low/high gray level entropy index were shown in Fig.3. Regardless of their AC responses, 3 illustrated cases appeared to achieve a final clinical response after AC+T. Therefore, although the Compactness and Gray level entropy appeared to predict AC response, they failed to predict the final response after AC+T, resulting in a lower accuracy.

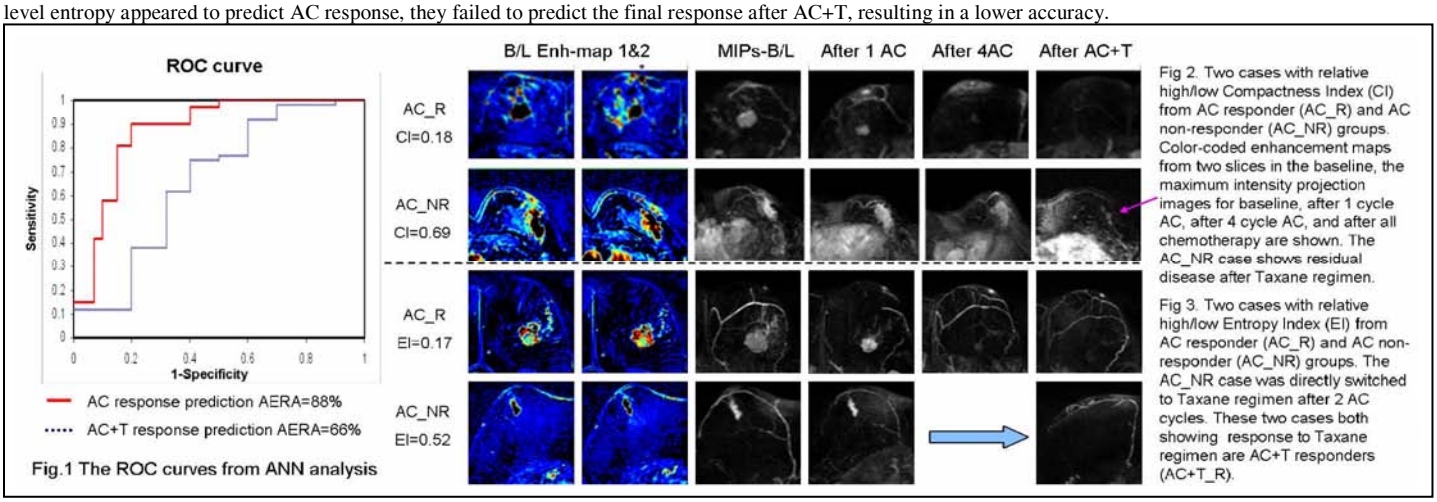

Fig.1 The ROC curves from ANN analysis

Fig 2. Two cases with relative high/low Compactness Index (CI) from AC responder (AC_R) and AC non-responder (AC_NR) groups. Color-coded enhancement maps from two slices in the baseline, the maximum intensity projection images for baseline, after 1 cycle AC, after 4 cycle AC, and after all chemotherapy are shown. The AC_NR case shows residual disease after Taxane regimen.

Fig 3. Two cases with relative high/low Entropy Index (EI) from AC responder (AC_R) and AC non-responder (AC_NR) groups. The AC_NR case was directly switched to Taxane regimen after 2 AC cycles. These two cases both showing response to Taxane regimen are AC+T responders (AC+T_R).

Discussion:

In this study, we investigated the association of baseline characteristic features of breast lesions to chemotherapy response. Three morphological features and 2 texture features could predict AC response with a high accuracy (88%). The prediction of the final response to the full course treatment after completing AC followed by Taxane regimen only reached to 66%. The results suggested that the baseline feature of breast lesions may be analyzed quantitatively, and that may be useful to predict the response to the first line therapy regimen (AC in this work). It may be used to select patients who are more likely to respond to AC and give them all 4 cycles. For those who are not likely to show a good response, AC treatment can be cut down to 2 cycles to spare them from ineffective treatment, and also to allow earlier switch to the second line Taxane regimen. Our results also showed that after completing both regimens, the baseline lesion features could not predict final responses well. This was encouraging, suggesting that the cocktail treatment approaches (combining many drugs) could treat various types of lesions with different clones, and that diminishes the selective sensitivity of different lesions to a specific drug. Therefore many lesions, regardless of their baseline features, might respond well.

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