Prediction of Neoadjuvant Chemotherapy response of breast cancer with changes of MR perfusion and diffusion characteristics in early chemotherapy by using neural network algorithm

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Introduction

Neoadjuvant Chemotherapy (NAC), locally enforced before the surgery, plays a significant role in the multimodality therapy of breast cancer. To predict whether a patient will have a complete response after the early NAC in-vivo is critical for the therapy plan. Diffusion-weighted MRI (DW-MRI) and dynamic contrast-enhanced MRI (DCE-MRI) have been reported great potential to predict NAC responder[1-4]. However, most studies used the diffusion or perfusion imaging alone for prediction[1-4]. Multivariate analysis method to combine diffusion and perfusion imaging together, such as neural network or logistic regression, should generate better prediction model. In this study, we employed neural network and logistic regression to predict the final treatment response by using the changes of DW-MRI and DCE-MRI parameters after the early NAC cycles.

Methods and Materials

Population: After institutional ethics approval and informed consent were obtained, 36 patients with breast cancer were recruited. All patients underwent four NAC cycles with subsequent mastectomy. DW-MRI and DCE-MRI were performed before NAC and after the second NAC cycle.

MR Imaging: MR imaging was performed using a 1.5T MRI system (GE Medical System, Signa Excite, HD) and a phased-array bilateral breast coil. The MRI protocol included 3D axial DCE-MRI and DW-MRI. DW-MRI was acquired using b-values of 0 and 1000 s/mm^2. Scan parameters were TR/TE=5000/59ms, FOV=30mm*30mm, matrix=256*256, slice thickness=4mm, spacing=1.0 mm. DCE-MRI was acquired every 58s to scan 124 slices. A total of 9 time points were obtained, wherein a bolus of Gd-DTPA at 0.1 mmol/kg was injected at the second time point with the rate of 3 ml/s. Scan parameters were TR/TE=6/2.6ms, FOV=32mm*32mm, matrix=324*288, slice thickness=2.4mm and spacing=-1.2 mm.

Image Analysis: For DW-MRI, region of interest (ROI) was drawn by a semi-automatic segmentation method. Firstly, we manually chose all slices that saw lesions for each acquisition. Then the segmentation was done using the maximum entropy thresholding segmentation algorithm by grouping those select slices. Fig 1 shows an example of our semi-automatic segmentation result. After the segmentation, mean apparent diffusion coefficient (ADC) of ROI was calculated by using a mono-exponential function[2]:

$$ADC = -\frac{1}{b_i}\ln\frac{S_i}{S_0}$$

where S_i and S_0 are signal intensities with and without diffusion-sensitizing gradients, respectively; and in this case, b_i=1000.For DCE-MRI, the intensity curve for each exam was extracted from manually selected ROI. Then a non-physical model was used to extract the wash-in rate (W_i) which reflects the most important contrast kinetics in breast cancer[3,4]:

$$S_p(t) = S_{\max}[1 - e^{-W_i(t-t_0)}]e^{-W_0(t-t_0)}$$

where W_o represents contrast wash-out rate, and S_{max} maximum enhancement, S_p the percentage change in image intensity enhancement: $S_p=(I_{post}-I_{pre})/I_{pre}$ and t_0 is the time of contrast agent injection. Area under the time-intensity curve (AUC) is another meaningful parameter in DCE-MRI[4]. In this study, AUC of 300s after bolus injection was used, which reflects the entire enhancement process. To eliminate the possible intensity bias introduced by different coil positioning and coil sensitivity among patients, we utilize a reference-region (RR) to calibrate the AUC. The muscle clinging to ribs was chosen as RR. The ratio of AUC of ROI to RR was used and presented as AUC_r.

Histological analysis: Treatment response was determined by the histological examination of the post-operation specimen, with comparison of the pre-operation biopsy. Responders were defined as reduction of tumor cell density by more than 90% or completely diminishment of the tumor cells, and microscopically no infiltrative cancer of cancer in situ, while non-responders defined as reduction of tumor cell density by less than 90%.

Data analysis: The changes of the ADC, W_i, and AUC_r after the second NAC cycle in responders and non-responders were compared by independent-samples t-test. To predict the responder from the outcome of the early two NAC cycles, logistic regression (LR) model and neural network (NN) model were used. The sensitivity and specificity to predict responders were also calculated.

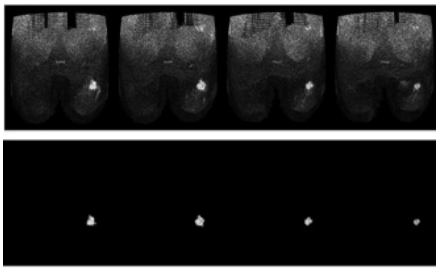

Fig 1. A typical segmentation (bottom row) of lesions in DW images.

Table 1. Comparison of parameter changes after the early two NAC cycles between responders and non-responders

	change of non-responders	change of responders	P
ADC (10^{-3} mm^2/s)	0.0504±0.1536	0.1322±0.1371	0.150
W_i	0.0008±0.0032	-0.0013±0.0039	0.090
AUC_r	0.0551±0.1950	-0.0889±0.1652	0.047*

Table 2. Prediction Result of NN, responder prediction sensitivity = 80%, specificity = 100%

		Histology	
		Nonresponder	Responder
NN	Nonresponder	26	2
	Responder	0	8

Table 3. Prediction Result of LR, responder prediction sensitivity = 30%, specificity = 84.6%

		Histology	
		Nonresponder	Responder
LR	Nonresponder	22	7
	Responder	4	3

Results

According to the histological results, 10 patients were classified as responders while 26 patients were non-responders. The calculated parameters and their t-test results are shown in table 1. AUC_r change was found significantly different between responder and non-responder group. While the difference of mean ADC and W_i change between two groups were nearly significant. The performances of the NN and LR models are shown in table 2 and 3, respectively. NN model has 80% sensitivity and 100% specificity to predict responder, much better than LR model, which has 30% sensitivity and 84.6% specificity.

Discussion and Conclusion

Our research has found that the outcome of early NAC evaluated by DW-MRI and DCE-MRI can predict the final treatment response. More significantly, combining image biomarkers from both diffusion and perfusion MRI produces good predication sensitivity and specificity. Comparison of neural network and logistic regression multivariate analysis methods shows that neural network technique is better. In conclusion, monitoring the early NAC by using DW and DCE MRI together with neural network method can be used to differentiate NAC responders and non-responders, which facilitate personalized therapy and better outcome.

References:

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