Value of Machine Learning with CE-MRI Radiomics for Early Prediction of Pathological Complete Response to Neoadjuvant Therapy in HER2-positive Invasive Breast Cancer

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Abstract

Backgrounds To assess the value of radiomics based on multiphases contrast-enhanced magnetic resonance imaging(CE-MRI) for early prediction of pathological complete response(pCR) to neoadjuvant therapy(NAT) in patients with human epithelial growth factor receptor 2(HER2) positive invasive breast cancer.

Methods A total of 127 patients with newly diagnosed primary HER2 positive invasive breast cancer underwent CE-MRI before NAT and performed surgery after NAT. Radiomic features were extracted from the 1st postcontrast CE-MRI phase(CE₁) and multi-phases CE-MRI(CE_m). With selected features using a forward stepwise regression, 23 machine learning classifiers based on CE₁ and CE_m were constructed respectively. The performance of classifiers were assessed and compared.

Results For the task of pCR classification, 6 radiomic features from CE₁ and 6 from CE_m were selected for the final machine learning models respectively. The linear SVM based on CE_m outperformed the Logistic regression model using CE₁ with an AUC of 0.84 vers 0.69. In mass and non-mass enhancement groups, the accuracy of linear SVM achieved 76% and 84%. Whereas in unifocal and unilateral multifocal cases, 79% and 75% accuracy were achieved by linear SVM.

Conclusion Multiphases CE-MRI imaging may offer more heterogeneity information in the tumor and provide a non-invasive approach for early prediction of pCR to NAT in patients with HER2 positive invasive breast cancer.

Backgrounds

HER2 positive breast cancer(non-luminal) is defined as HER2-positive and hormone receptor (HR)-negative tumor. It has high malignancy, more recurrence and metastasis, poor prognosis, but is sensitive to neoadjuvant therapy (NAT, Neoadjuvant chemotherapy and anti-HER2 therapy) [1, 2]which is widely used to treat HER2 positive breast cancer[3–5]. NAT could improve the disease-free and overall survival, therefore the pathologic complete response (pCR) to NAT has been proposed as a surrogate endpoint for long-term survival in HER2 positive breast cancer patients[6–9]. Nevertheless, only about 40% of the patients could achieve pCR after the completion of NAT. Predicting pCR before NAT is desirable for identifying patients who do not benefit from NAT. Identification of pCR can only be conformed by histopathological specimens which is traumatic and does not reflect the heterogeneity of the entire tumor. Thus, a method to predict pCR early and noninvasively remains a major challenge.

Compared with mammography and ultrasound, breast magnetic resonance imaging (MRI) was conformed as the most reliable imaging tool for evaluating the response of tumor to chemotherapy[10, 11]. Many imaging modality of MRI, such as T2WI, DWI and CE-MRI, had been proposed to evaluate the response to NAT in patients with breast cancer[12, 13]. However, CE-MRI is sensitive to perfusion, permeability of tissue microvessels and angiogenic changes and has been identified as the most

sensitive method for prediction of treatment response to NAT[14–22]. While clinical MRI images of predicting pCR to NAT depend on naked eyes, radiomics can translate medical images into high-dimensional datas which reflect not only macroscopic but also the cellular and molecular properties of tissues[23, 24]. Radiomics is the bridge to combine medical imaging and personalized medicine. The purpose of radiomic analysis is to generate image-driven biomarkers which can provide a deeper understanding of microenvironment and spatial heterogeneity in tumor noninvasively.

To date, previous studies have indicated that radiomics model can detect the pCR to NAT in breast cancer[13, 14, 21, 25]. However, there are no studies published that specifically assess the performance of MRI radiomics in detecting pCR to NAT in HRE2 positive subtype. In addition, these studies demonstrated the feasibility and potential benefits of radiomics in pCR prediction in breast cancer only using CE₁ which only reflects the spatial heterogeneity of the tumor. Nevertheless, features derived from multi-phases of contrast enhanced MRI images can imply much information changing over time points[26].

In the present study, the MRI scan and treatment protocol for all patients were consistent. We utilized all phases of contrast enhanced MRI images calculating new sequential texture features changing over time points and compared the predictive ability of features from CE₁ and CE_m. We aimed to construct a radiomics model for personalized pCR evaluation after NAT in HER2 positive invasive breast cancer.

Materials And Methods

Patient Population

This retrospective study was approved by our institutional review board, which waived informed consent. In total, 127 female patients who underwent conserving breast surgery or radical mastectomy between January 2012 and December 2018 were consecutively enrolled in the study according to the inclusion and exclusion criteria. The flowchart of the study is shown in Fig. 1.

Inclusion criteria were as follows: (1) patients had primary invasive HER2-positive breast cancers ($\geq$ T2, and/or positive nodal status) confirmed by biopsy; (2) patients received complete standard treatment(4 ~ 6 cycles of PCH) with no prior treatment before NAT; (3) pretreatment MRI data obtained using the 1.5-T MR scanner (Aurora Dedicated Breast MRI System; USA; Aurora); (4) the course of NAT need to be monitored with MRI; (5) underwent modified radical mastectomy or breast conservation within one month after completion of NAT; (6) available clinicopathologic data (age, menopausal status, tumor size, Ki-67 index, MRI-reported T stage, N stage, surgery type, FGT, BPE, numbers of lesion, enhancement pattern).

Exclusion criteria were as follows: (1) Metastasis elsewhere in the body; (2) not complete standard treatment; (3) cancelled surgery or not undergo surgery at our hospital; (4) poor MR image quality resulting from poor contrast injection or motion artefacts; (5) Occult breast cancer.

Magnetic Resonance Imaging and Imaging Analysis

For all patients, axial breast CE-MR were performed before NAT on a 1.5-T MR scan (Aurora Dedicated Breast MRI System; USA; Aurora) using a breast unique transmit/receive coil in the prone position. The CE-MRI protocol included: (a) T1-weighted fat-saturated precontrast sequence, (b) multiple (3 phases) T1-weighted fat-saturated postcontrast sequences that were acquired after intravenous administration of a 0.1 mmol/kg dose of Gd-DTPA (Magnevist; Bayer-Schering Pharma, Berlin, Germany). Scan parameters were TR/TE = 29.0/4.8 ms; FOV = 36 cm × 36 cm; matrix = 360 × 360; 108 slices; slice thickness = 1.5 mm. The scanning time of each phase was about 3 minutes, and the number of single-phase scanning layers was 108.

Treatment regimen and criteria for pCR

All patients received 4 ~ 6 cycles of PCH regimen (paclitaxel + carboplatin + trastuzumab; paclitaxel: 80 mg/m², carboplatin: AUC = 2, herceptin was initially measured at 4 mg/kg and maintained at 2 mg/kg; Once a week, 3 times is a cycle of treatment) and then underwent radical mastectomy or breast conservation.

Pathological response was determined by pathologist. pCR was defined as the absence of residual invasive tumor cells in the breast and axillary lymph nodes (ypT0/is + ypN0), as determined microscopically, in surgical specimens.

Tumor Masking and Inter-Observer Reproducibility Evaluation

When drawing the outline of the tumor, we obey the following principles. First, regardless of whether the lesion presented mass or non-mass enhancement, tumour regions of interest (ROI) were delineated along the contour of the tumor on the 1st postcontrast CE-MRI scan (the peak enhanced phase of the multiphase CE-MRI where the border of lesion was the most obvious). Second, the ROIs of breast cancer were drawn manually on each slice including the necrosis and blood areas to get the 3D segmentation of the whole tumor. Last, if the tumor is unilateral multifocal lesion, the largest one will be selected as the object. And then the 3D segmented contouring based on the 1st postcontrast images were propagated to pre-contrast and the other two post-contrast phases of CE images. The segmentation of whole tumour was performed on the 3D-Slicer software(version 4.10.2, <https://www.slicer.org>).

Inter-observer reproducibility of ROI detection and radiomic feature extraction were measured using CE₁ of 30 randomly chosen samples. Two experienced radiologists(QL and QX) performed the ROI delineation independently, and then radiomic features extracted from the above two ROIs were compared to get the inter-class correlation coefficient. An ICC score greater than 0.8 was interpreted to reach satisfactory agreement. ICC for radiomic features was defined as high (ICC ≥ 0.8), medium(0.8 > ICC ≥ 0.5), or low (ICC < 0.5).

Feature extraction

Radiomic shape and texture features were calculated with PyRadiomics package(<https://pyradiomics.readthedocs.io/en/latest/index.html>) in the Python software (v. 3.7, Python Software Foundation, <https://www.python.org/>). In total, three groups of imaging features(Supplementary material 1) for each patient were extracted from normalized pretreatment CE-MRI scans: Group 1(CE_{shape}) consisted of 14 shape-based features derived from the 1st postcontrast CE images; Group 2($CE_{texture}$) comprised 93 texture features based on each phase CE-MRI independently, yielding 372 features; Group 3($CE_{sequential}$) comprised of 930 sequential features, which were calculated from 93 texture features to characterize the textural changes over time points. In group 3, ten new sequential features from each texture feature were calculated (Algorithms for the ten new sequential features were shown in **Supplementary material 2**). The first six features, including mean, variance, kurtosis, skewness, energy and entropy, were extracted from each individual subject. The other four features, including Kendall-tau-b, conservation, stability, and dispersion, were calculated from the interactive information between the current subject and the remainder of the subjects. All these features have been used in previous radiomic studies[26].

Feature selection method and machine learning-based classification construction

To avoid severe multicollinearity or overfitting, a forward stepwise regression was used to select potential important features(stepwisefit function in Matlab 2016,The MathWorks, Natick, MA). And then, the number of selected features was determined by AIC(Akaike information criterion).

With useful features, radiomic machine learning models based on the 1st postcontrast CE-MRI scan individually and multi-phases CE-MRI scans were constructed respectively. Twenty-three classifiers were constructed to discriminate whether a patient achieved pCR: including three decision tree classifiers(fine tree, medium tree, and coarse tree), two discriminant analysis classifiers(Linear Discriminant Analysis LDA and quadratic discriminant analysis QDA), six SVM classifiers(linear, quadratic, cubic, fine gaussian, medium gaussian, and coarse gaussian), four k nearest neighbor (KNN) classifiers(fine KNN, medium KNN, coarse KNN, and weighted KNN), and five ensemble learning classifiers(subspace discriminant, subspace KNN, the AdaBoost algorithm with decision tree, the bootstrap-aggregated (bagged) tree algorithm with decision tree, and the RUSBoost algorithm with decision tree). All the models were conducted using the 5-fold cross validation, whereby 80% of cases as training set while 20% as testing set. The procedure was repeated for ten rounds to average the estimates of performance.

The feature selection and machine learning classification were achieved using the Statistics and Machine Learning Toolbox in MatLab (v. R2018a; The MathWorks, Natick, MA).

Performance of optical model in different types of carcinoma

The performance of the machine learning-based classification were assessed by their accuracy, sensitivity, specificity, and AUC. The optical machine learning classification was used to discriminate pCR vs. non-pCR in mass and non-mass groups, uni-focal and unilateral multi-focal groups respectively. The AUC values was calculated to assess the performance of the model.

Radiomics signature building

The Rad-score of each patient was calculated via a linear combination of potential features, weighted by their respective coefficients. The formula of Rad-score were shown in **Supplementary material 3 and 4**.

Statistical analysis

Descriptive statistics were summarized as mean $\pm$ standard deviation (SD). Comparisons between pCR and non-pCR groups were made with the *t* test or *Mann-Whitney U* test for quantitative variables and with the χ^2 test or *Fisher's* test for qualitative variables. All statistical analysis and statistical drawing were performed by MATLAB 2018a software and python3.6. *p* less than 0.05 was considered statistically significant.

Results

Clinical characteristics

A total of 127 lesions from 127 women (mean age, 51.2 years; age range, 24–84 years) were ultimately evaluated. Fifty-four of 127 patients (42.52%) achieved pCR in the study. Among the 127 cases of HER2 positive breast cancer, 89 cases presented mass enhancement and 38 cases presented non-mass enhancement, while 96 patients were with uni-focal cancers and 31 patients had unilateral multi-focal lesions. There were no significant difference in clinical features and MRI morphology between pCR and non-pCR groups (shown in **Table 1**).

ICC

ICC for radiomic features was from 0.9522 to 0.9762 between the two radiologists QL and QX.

Selected features

For the CE₁ and CE_m, 6 features from CE_{texture} and 6 features from CE_{sequential} were selected for the final machine learning models respectively. The potential features were shown in **Supplementary material 5 and 6**.

Performance of the machine learning-based classification

With the selected six features from CE₁, the accuracy of 23 classifiers ranged from 57.5–68.5% (**Table 2**). The optimal model was Logistic regression yielding the highest accuracy of 68.5%, with an AUC of 0.69.

With the selected six features from CE_m, the accuracy of 23 classifiers ranged from 40.9–79.5% (**Table 3**). The best accuracy was achieved based on linear support vector machine (SVM) in conjunction with 6 sequential features based on CE time points, with an AUC of 0.84.

The linear SVM based on CE_m showed an improved performance, with an AUC of 0.84(**Fig. 2**) over Logistic regression using CE_1 (AUC = 0.69, **Fig. 3**).

In mass and non-mass enhancement groups, the accuracy of linear SVM achieved 76% and 84%. Whereas in uni-focal and unilateral multi-focal cases, the accuracy of linear SVM achieved 79% and 75%.

Rad-score building

The Rad-score caculated from the two optical models were significantly higher in the pCR group compared to the non-pCR group (**Fig. 4**). However, the liner SVM based on multiphase CE-MRI outperformed the Logistic Regression using the single 1st post-contrast CE-MRI sequence according to the boxplot.

Discussion

In the study, we investigated the ability of machine learning models based on pretreatment CE-MRI to predict pCR to NAT in patients with HER2 positive invasive breast cancer. Sequential texture features changing over time points of pretreatment CE-MRI were proposed with better performance compared with traditional texture features based on the single 1st phase of postcontrast T1-weighted imaging at CE-MRI imaging. The outperformance of sequential texture features indicated that combining multiphases of pretreatment CE-MRI could be helpful for the early prediction of pCR to NAT in HER2 positive invasive breast cancer.

In order to predict response to chemotherapy in patients with breast cancer, previous studies[13–15] utilize texture measures extracted from CE_1 . Herein, our study made full use of all phases of CE-MRI images and compared the prediction ability of machine learning models based on CE_1 and CE_m . For the 1st phase, the 6 radiomic features selected for the final models comprised 2 features from first order, 1 from GLCM, 2 from GLSZM and 1 from GLRLM. The potential model based on CE_1 yielded the highest accuracy of 68.5% with an AUC of 0.69, which was similar to the results of recent reports in HER2 positive subgroups[13–15]. For multiphases, all the selected 6 radiomic features were obtained from $CE_{\text{sequential}}$, comprising 2 features caculated from kurtosis, 2 from entropy, 1 from dispersion and 1 from stability. Among them, kurtosis and entropy had been identified as biomarkers of response to neoadjuvant chemotherapy in previous reviews[13][27]. The optical model was able to perform robustly. Specifically, the AUC of the final model was 0.84, which was significantly higher than that of previous reports[12, 25] based on the 1st phase. The result revealed that sequential texture features captured more detailed information of tumor complexity and heterogeneity that indistinguishable to the 1st phase. Besides, the sequential texture features changing over time points had been identified to be useful in the subtype classification of breast cancer[26]. Specially, the optical model linear SVM performed well in predicting pCR to NAT in HER2 positive patients stratified by breast cancer enhancement pattern and number. In mass and non-mass enhancement groups, the accuracy achieved 76% and 84%. Whereas in uni-focal and unilateral multi-focal cases, the accuracy were 79% and 75% respectively. While in many studies[12,

14, 24, 25], non-mass enhancement and unilateral multifocal cases were excluded, our model performed well without regarding to tumor morphology and number. Several studies suggested that non-mass enhancement and multifocal or multicentric[28–30] tumors were more frequently present in HER2-positive subtype. For patients with non-mass enhancement and multifocal breast carcinoma, neoadjuvant therapy was more recommended to downstage and improve prognosis[31, 32]. In our study, the rates of non-mass enhancement and multifocal lesions were 28.35% (38/127) and 25.20%(32/127), respectively. So it is more scientific to include non-mass enhancement and multifocal cases in the study of predicting the response to NAT in HER2 positive breast cancer.

In our research, all patients underwent MRI examination with the same scanner and treated with the consistent regimens of 4–6 cycles of PCH. The linear support vector machine (SVM) was the optimal model with an AUC of 0.84. The prediction performance was greater than a recent study[12] on HER2 positive subgroup in which the corresponding AUCs was 0.70. A possible explanation is that the treatment regions for training set and validation are not uniform. Another study[25] combining the HER2 positive and TN breast cancers as one subgroup concluded that the AUCs of model of predicting pCR to NAC were less than 0.80 not only in the training sets but also in the validation sets. Nevertheless, analysis suggested that there was a difference in pCR rates after NAC for HER2-positive and triple-negative breast cancers. To the end, a study [14]concluded that a model using intratumoral and peritumoral radiomics was able to predict pCR with an AUC of 0.80 in HER2 positive breast cancers which was similar to our result. Previous studies [33–35] have shown that radiological characteristics may be affected by differences in MRI magnetic intensity. So the same scanner and uniform treatment regions can enhance robustness of the omics and were beneficial to the establishment of a better prediction model.

Rad-score were calculated for each patient with equation of the optical model. Our results indicated that the Rad-score in the pCR group was significantly higher compared to the non-pCR group. This was successfully conformed in treatment evaluation in patients with locally advanced rectal cancer[36].

The work presented in our study had several limitations. First, this was a retrospective study and all patients were recruited from a single center. Second, we compared the performance of machine learning models based on radiomic of pretreatment the 1st postcontrast sequence and multiphases CE-MRI imaging. However, the study lacked an independent validation cohorts, external validation of our results pending adequate patient follow-up will be entailed in the future work.

Conclusion

Multiphases CE-MRI imaging may offer more heterogeneity information in the tumor and provide a non-invasive approach for early prediction of pCR to NAC in patients with HER2 positive invasive breast cancer.

Abbreviations

AUC Area under the receiver operating characteristic curve

CE Contrast enhanced

NAT Neoadjuvant therapy

GLCM Gray-level co-occurrence matrix

GLRLM Gray-level run length matrix

GLSZM Gray-level size zone matrix

GLDM Gray level dependence matrix

ICC Intraclass correlation coefficient

ROC Receiver operating characteristic curve

ROI Region of interest SVM Support vector machine

PCR Pathological complete response

RUS Random undersampling

Declarations

Ethics approval and consent to participate

Written informed consents were waived due to the study design. The medical ethics committee of Fudan university cancer hospital approved this retrospective study and confirmed that the data was anonymized and maintained with confidentiality.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conception and design: LQ and XQ. Acquisition of data: LQ,XQ, LJW. Analysis and interpretation of data: LQ, XQ, WZ and WH. Writing, review, and revision of the manuscript: LQ, XQ, WZ, WH, LJW and GYJ. Study supervision: GYJ and WH. All authors have read and approved the manuscript.

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Tables

Table 1

Clinical and morphology characteristics between pCR and non-pCR group

Characteristics	pCR(n = 54)	Non-pCR(n = 73)	p value
Age,mean(SD),Y	52.80 + 9.24	50.62 ± 11.19	0.309
Menonpausal status			0.278
premenopausal	15(27.78%)	26(35.61%)	
postmenopausal	39(72.22%)	47(64.39%)	
Enhancement pattern			0.299
Mass	36(66.67%)	53(72.60%)	
non-mass	18(33.33%)	20(27.40%)	
Multifocal or multicenter			0.242
present	42(77.78%)	53(72.60%)	
absent	12(22.22%)	20(27.40%)	
Pre-NAC T stage			0.468
T2	40(74.07%)	53(72.60%)	
T3	14(25.93%)	20(27.40%)	
Pre-NAC N stage			0.211
N0	16(29.63%)	23(31.50%)	
N1	29(53.70%)	38(52.05%)	
N2	5(9.26%)	2(2.74%)	
N3	4(7.41%)	10(13.71%)	
Type of surgery			0.439
Conservation	10(18.52%)	9(12.33%)	
Radical surgery	44(81.48%)	64(87.67%)	

NAC, neoadjuvant chemotherapy PCR, pathological complete response SD, standard deviation

Table 2
The accuracy, sensitivity, specificity and AUC of machine learning
classification based on optimal six features from CE₁

Classifier Model	accuracy	sensitivity	specificity	AUC
Fine Tree	59.1%	48%	67%	0.61
Medium Tree	59.1%	48%	67%	0.62
Coarse tree	60.6%	31%	82%	0.61
Linear Discriminant	68.5%	52%	81%	0.69
Quadratic Discriminant	66.1%	43%	84%	0.66
Logistic Regression	68.5%	52%	81%	0.69
Linear SVM	65.4%	41%	84%	0.69
Quadratic SVM	59.1%	33%	78%	0.57
Cubic SVM	49.6%	48%	51%	0.49
Fine Gaussian SVM	59.8%	44%	71%	0.64
Medium Gaussian SVM	62.2%	35%	82%	0.70
Coarse Gaussian SVM	66.1%	29%	95%	0.68
Fine KNN	60.6%	54%	66%	0.60
Medium KNN	59.8%	44%	71%	0.67
Coarse KNN	57.5%	0%	100%	0.64
Cosine KNN	63.8%	59%	67%	0.62
Cubic KNN	59.8%	44%	71%	0.67
Weighted KNN	60.6%	52%	67%	0.64
Boosted Trees	61.4%	54%	67%	0.67
Bagged Trees	59.1%	52%	64%	0.65
Subspace Discriminant	68.5%	52%	81%	0.69
Subspace KNN	60.6%	54%	66%	0.60
RUS Boosted trees	63.0%	52%	71%	0.75

KNN, k nearest neighbor SVM, support vector machine RUS, random undersampling ROC, receiver operating characteristic

Table 3
The accuracy, sensitivity, specificity and AUC of machine learning
classification based on optimal six features from CE_m

Classifier Model	accuracy	sensitivity	specificity	AUC
Fine Tree	69.3%	61%	75%	0.74
Medium Tree	69.3%	61%	75%	0.74
Coarse tree	77.2%	72%	81%	0.75
Linear Discriminant	79.5%	74%	84%	0.84
Quadratic Discriminant	78.7%	72%	84%	0.84
Logistic Regression	79.5%	74%	84%	0.84
Linear SVM	79.5%	74%	84%	0.84
Quadratic SVM	70.1%	61%	77%	0.74
Cubic SVM	40.9%	20%	56%	0.30
Fine Gaussian SVM	74.8%	69%	79%	0.77
Medium Gaussian SVM	78.7%	70%	85%	0.79
Coarse Gaussian SVM	78.7%	72%	84%	0.85
Fine KNN	67.7%	61%	73%	0.67
Medium KNN	74.0%	59%	85%	0.81
Coarse KNN	57.5%	0%	100%	0.78
Cosine KNN	78.7%	78%	79%	0.76
Cubic KNN	74.0%	59%	85%	0.81
Weighted KNN	66.9%	57%	74%	0.68
Boosted Trees	67.7%	61%	73%	0.76
Bagged Trees	67.7%	61%	73%	0.76
Subspace Discriminant	79.5%	74%	84%	0.84
Subspace KNN	67.7%	61%	73%	0.67
RUS Boosted trees	68.5%	65%	71%	0.75

KNN, k nearest neighbor SVM, support vector machine RUS, random undersampling ROC, receiver operating characteristic

Figures

Figure 1

Flow chart of patient recruitment in this study

Figure 2

ROC of liner SVM predicting pCR and non-pCR

Figure 3

ROC of Logistic Regression predicting pCR and non-pCR

Figure 4

Rad-score box plot for pCR classification based on the CE_1 and CE_m

Supplementary Files

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- [SupplementaryMaterial.docx](#)