Quantitative MRI Phenotyping of Breast Cancer across Molecular Classification Subtypes

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Abstract. The goal of our study was to investigate the potential usefulness of quantitative MRI analysis (i.e., phenotyping) in characterizing and data mining the molecular subtypes of breast cancer in order to better understand the difference among HER2, ER, and PR expression, triple negative, and other molecular classifications. Analyses were performed on 168 biopsy-proven breast cancer MRI studies acquired between November 2008 and August 2011, on which molecular classification was known. MRI-based phenotyping analysis included: 3D lesion segmentation based on a fuzzy c-means clustering algorithm, computerized feature extraction, leave-one-out linear stepwise feature selection, and discriminant score estimation using Linear Discriminant Analysis (LDA). The classification performance between the molecular subtypes of breast cancer was evaluated using ROC analysis with area under the ROC curve (AUC) as the figure of merit. AUC values obtained for 26 HER2+ vs. 142 HER2-, 118 ER+ vs. 50 ER-, 93 PR+ vs. 75 PR-, 40 Triple Negative (ER-, PR-, and HER2-) vs. 128 all others are 0.65, 0.70, 0.57, and 0.68, respectively for the combined datasets that included images from both 1.5T and 3T scanners. Contributions to the classifiers come from the shape, texture, and kinetics of the lesion, triple negative cases exhibiting increased margin variability, distinct kinetics, and increased surface area. Analyzing the datasets within magnet strength substantially improved performances, e.g., the AUC for triple negative vs. all other cancer subtypes increased from 0.69 (SE=0.05) to 0.88 (SE=0.05). The results from this study indicate that quantitative MRI analysis shows promise as a means for high-throughput image-based phenotyping in the discrimination of breast cancer subtypes.

Keywords: Computer-aided diagnosis, Breast MRI, image-based phenotype, molecular classifications.

1 Introduction

Breast cancer is the most frequently diagnosed cancer and is the second leading cause of death in women [1]. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) of the breast has been increasingly used in clinical practice for screening and diagnostic imaging as well as post-treatment evaluation [2, 3]. MRI in addition to mammography was recommended for screening of women at high-risk of developing breast cancer by the American Cancer Society in 2007 [4].

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Breast cancer can be classified based on the receptor status (ER, PR, and HER2) traditionally identified by immunohistochemistry. HER2+ breast cancers tend to be more aggressive and have a poorer prognosis than HER2/neu-negative cancers. However, it is not clear whether HER2/neu status is an independent risk factor. ER+ and PR+ cases have lower risks of mortality compared to women with ER- and/or PR- disease. Triple negative cases (HER2-, ER-, PR-) overall do not respond well to treatment, and thus account for a large portion of breast cancer deaths [5].

The goal of our study was to investigate the potential usefulness of quantitative MRI analysis (i.e., phenotyping) in characterizing and data mining the molecular subtypes of breast cancer in order to better understand the difference among HER2, ER, and PR expression, triple negative, and other molecular classifications. Identification of the molecular subtypes of breast tumors is expected to allow for improved prognostic assessment and more effective cancer treatment plans.

2 Materials and Methods

2.1 Database

Breast DCE-MR images used in this study were obtained retrospectively under an IRB-approved protocol at the University of Chicago Medical Center. Table 1 lists the acquisition parameters.

Table 1. Summary of DCE-MR imaging protocols. TR=repetition time, TE=echo time.

	1.5 Tesla DCE-MRI	**3 Tesla DEC-MRI**
Magnet	1.5 T Philips Achieva	3T Philips Achieva
Number of Coil Channels	16	16
Acquisition Plane	Axial	Axial
Pulse Sequence	3D Gradient Echo (THRIVE)	3D Gradient Echo (THRIVE)
TR/TE (ms)	5.5 / 2.7	5.0 / 2.5
Flip Angle (degrees)	12	10 or 12
Voxel Size (mm^3)	0.74 x 0.74 x 1	0.60 x 0.60 x 0.80
Temporal Resolution	60	70
Number of Post-Contrast	6	5
Fat Suppression (Y or N)	Y	Y
Parallel Imaging (Y or N)	Y	Y

Analyses were performed on 168 biopsy-proven breast cancer MRI studies acquired between November 2008 and August 2011, on which molecular classification was known as listed in Table 2. All cases are invasive ductal carcinoma.

Table 2. Molecularclassifications and distribution of the dataset

	Molecular Classifications and Distribution of the 168 cases	
HER2	HER2-	HER2+
	142	26
ER	ER-	ER+
	50	118
PR	PR-	PR+
	75	93
Triple Negative	Triple Negative	All Others
	40	128

2.2 MRI-Based Phenotyping Analysis

MRI-based phenotyping analysis included several steps: (1) 3D lesion segmentation based on a fuzzy c-means clustering algorithm [6], (2) computerized feature extraction [7-9], leave-one-out linear stepwise feature selection, and discriminant score estimation using Linear Discriminant Analysis (LDA) in a leave-one-out evaluation.

2.3 Performance Evaluation

The classification performance between the molecular subtypes of breast cancer was evaluated using receiver operating characteristic (ROC) analysis [10-12] with area under the ROC curve (AUC) as the figure of merit. The AUC values were calculated to assess the discrimination performance of the individual lesion features/phenotypes as well as the merged lesion signatures in the tasks of distinguishing between HER2+ and HER2-, ER+ and ER-, PR+ and PR-, and triple negative and all others.

3 Results

The performance of individual lesion characteristics/phenotypes in terms of AUC value in the task of distinguishing molecular subtypes is shown in Figure 1.

AUC values obtained for 26 HER2+ vs. 142 HER2-, 118 ER+ vs. 50 ER-, 93 PR+ vs. 75 PR-, 40 Triple Negative (ER-, PR-, and HER2-) vs. 128 all others are 0.65, 0.70, 0.57, and 0.68, respectively for the combined datasets that included images from both 1.5T and 3T MR scanners. Contributions to the classifiers come from the shape, texture, and kinetics of the lesion, triple negative cases exhibiting increased margin variability, distinct kinetics, and increased surface area. One example of image-based phenotype arrays showing the color map of individual features and the output from LDA output on ER status is shown in Figure 2.

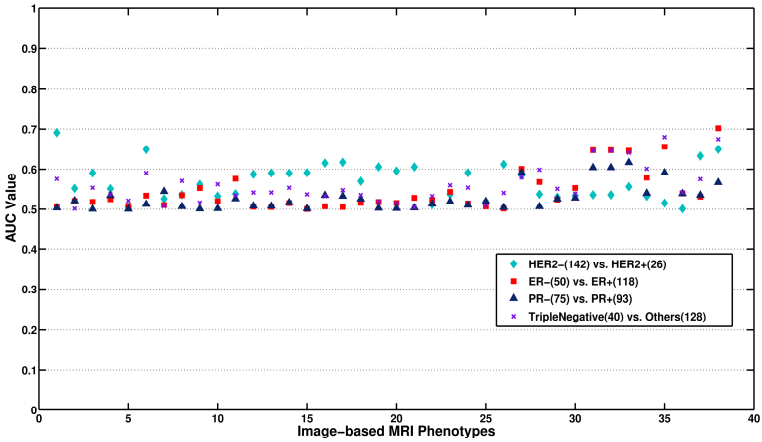

Fig. 1. Lesion features were automatically extracted from dynamic contrast-enhanced breast MRI images (obtained with both 1.5T and 3T scanners) and analyzed on their own as well as merged into lesion signatures for the assessment of molecular classification. Individual lesion features were only weak classifiers, as evidenced by the modest areas under the ROC curve (AUC value). When artificial intelligence was used, however, to merge the features into lesion signatures, performance substantially improved.

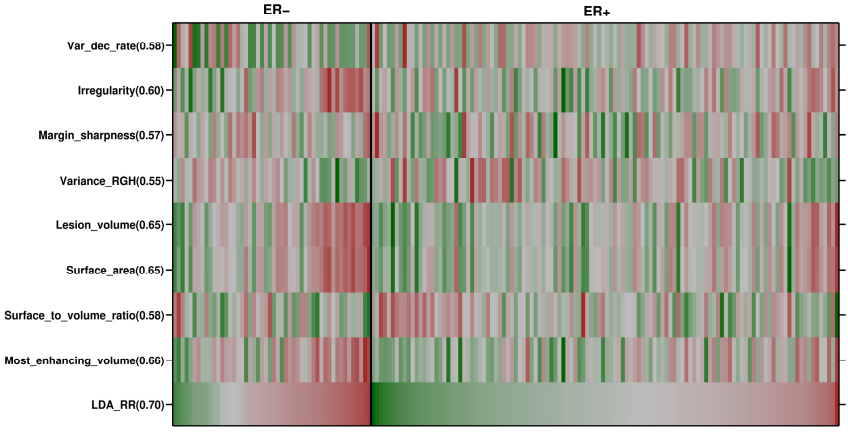

Fig. 2. Image-based phenotype arrays showing the color map of individual features of ER- and ER+ subjects. The individual subjects are ordered based on the output values from the LDA classifier. Values in parentheses corresponded to AUC using image-based phenotypes as decision variables in the task of distinguishing between ER- and ER+ subjects. For each image-based phenotype, red corresponds to high value and green corresponds to low value [13].

Analyzing the datasets within magnet strength substantially improved performances, e.g., the AUC for triple negative vs. all other cancer subtypes increased from 0.69 (SE=0.05) to 0.88 (SE=0.05) as shown in Table 3. This difference in terms of two AUC values is statistically significant with a *p*-value of 0.0017 (95% Confidence Interval of ΔAUC [-0.3593, -0.0832]). This performance difference within magnet strength needs to be further investigated with a larger dataset.

Table 3. Classification performance in the task of distinguishing triple negative cases from other molecular subtypes within magnet strength

	1.5T	**3T**
Cases	**117**	**51**
Triple Negative Cases	29	11
Others	88	40
Features	**AUC**	**AUC**
Size	0.63	0.70
Kinetics	0.61	0.71
Shape	0.56	0.70
Texture	0.56	0.80
Classifier (LDA)	**AUC (SE)**	**AUC (SE)**
	0.69(0.05)	0.88 (0.05)

4 Conclusion

The results from this study indicate that quantitative MRI analysis shows promise as a means for high-throughput image-based phenotyping in the discrimination of breast cancer molecular subtypes.

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