Association Between Imaging Characteristics and Different Molecular Subtypes of Breast Cancer

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Rationale and Objective: Breast cancer can be divided into four major molecular subtypes based on the expression of hormone receptor (estrogen receptor and progesterone receptor), human epidermal growth factor receptor 2, HER2 status, and molecular proliferation rate (Ki67). In this study, we sought to investigate the association between breast cancer subtype and radiological findings in the Chinese population.

Materials and Methods: Medical records of 300 consecutive invasive breast cancer patients were reviewed from the database: the Breast Imaging Reporting and Data System. The imaging characteristics of the lesions were evaluated. The molecular subtypes of breast cancer were classified into four types: luminal A, luminal B, HER2 overexpressed (HER2), and basal-like breast cancer (BLBC). Univariate and multivariate logistic regression analyses were performed to assess the association between the subtype (dependent variable) and mammography or 15 magnetic resonance imaging (MRI) indicators (independent variables).

Results: Luminal A and B subtypes were commonly associated with "clustered calcification distribution," "nipple invasion," or "skin invasion" ($P < 0.05$). The BLBC subtype was more commonly associated with "rim enhancement" and persistent inflow type enhancement in delayed phase ($P < 0.05$). HER2 overexpressed cancers showed association with persistent enhancement in the delayed phase on MRI and "clustered calcification distribution" on mammography ($P < 0.05$).

Conclusion: Certain radiological features are strongly associated with the molecular subtype and hormone receptor status of breast tumor, which are potentially useful tools in the diagnosis and subtyping of breast cancer.

Key Words: Subtype; MRI; multivariate logistic regression analysis.

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INTRODUCTION

Breast cancer is one of the most common cancers and one of the leading causes of death among women worldwide (1). It is a heterogeneous disease with several distinct molecular subtypes based on receptor status, including expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2–neu (HER2). Immunochemistry staining of the proliferation marker Ki67 and epidermal growth factor receptor (EGFR) also aid in the molecular subtyping of breast cancer. There are four major molecular subtypes: luminal A (ER+ or PR+ and HER2−), luminal B (ER+ or PR+ and HER2+), HER2 (ER− and PR− and HER2+), and basal-like breast cancer (BLBC) (ER−, PR−, and HER2−), which has a significant overlap with triple-negative breast cancer (2–4). Determination of molecular subtype may aid in treatment planning and monitoring the efficacy of therapy (5).

The different tumor biology of the molecular subtypes of breast cancer exhibits different morphologic patterns and microscopic pathology appearances (6). Different pathologic subtypes may cause different imaging features (7–10). We sought to investigate the association between imaging characteristics (ultrasound mammography and magnetic resonance imaging [MRI]) and the pathologic subtype of tumors.

A recent pilot study investigated the relationship of MR image phenotypes and the underlying global gene expression patterns (11), and presented a new approach to understand the underlying molecular biology of breast cancer. Additionally, MRI findings such as tumor size, morphology, shape, and enhancement characteristics have been shown to be useful in differentiating breast cancer subtypes (8,12,13). However, the diagnoses are usually established with indicators that are dependent on the operators and not comprehensive or

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quantitative. Very few studies have been carried out in the Chinese population. In this study, we aimed to investigate the association of breast cancer subtypes and radiological findings in Chinese patients.

MATERIALS AND METHODS

Patients

A retrospective review of medical records of 300 consecutive patients with invasive breast cancer in Shenzhen People's Hospital, from 2003 to 2013, was performed. All patients had undergone MRI, and histopathological examination of biopsy or surgical specimens was done within a month of MRI examination. The mean age (±standard deviation) of the patients was 46 ± 10 years (age range, 21–77 years). The baseline characteristics, clinical presentation, and mammography and MRI data were compiled. All patients provided written informed consent for the operation and inclusion of personal data in a scientific database, and this retrospective study was approved by the institutional ethics committee of Shenzhen People's Hospital.

The expression of the ER, PR, HER2, and Ki67 antigen was determined on immunohistochemical analysis to define molecular subtypes: (1) luminal A: ER+ and/or PR+, HER2−, CK5/6± , and Ki67 <14%; (2) luminal B: ER+ and/or PR+, CK5/6± , HER2+, or Ki67 ≥14%; (3) HER2 overexpressed: ER−, PR−, HER2+, and CK5/6±; and (4) BLBC: ER−, PR−, HER2− (triple negative), CK5/6+, and/or EGFR+.

Mammography

Digital mammography was performed with Siemens Mammomat Inspiration (Siemens Healthineers, Erlangen, Bavaria, Germany) using mediolateral oblique and craniocaudal views of both breasts with the following equipment and parameters: VA10: 20–40, 40–70 mAs; −45–180 angle; magnetic force: 60–90 N; thickness: 40–70 mm; anode/filter: W/Rh; glandular dose: 0.0 mGy.

Magnetic Resonance Imaging

MRI was performed using a Siemens Avanto 1.5T MR system made in Germany, with a dedicated breast coil. The patients were placed in prone position. All patients underwent routine transverse T1/T2WI scan and sagittal fat suppression T1/T2WI scan. Diffusion-weighted imaging was performed using single-shot echo-planar imaging technique (parameters: time of repeat (TR): 6–400 ms; time of echo (TE): 97 ms; matrix: 192 × 192; slice thickness: 4 mm; interlayer spacing: 1 mm; field of view: 350 mm; b values: 50, 500, 1000). Fat suppression short time inversion recovery (STIR) sequence was used and the following were the parameters: TR: 5000 ms; TE: 58 ms; field of view: 320 cm; matrix: 384 × 384; slice thickness: 4 mm; interlayer spacing: 0.8 mm; TR/TE: 6400/97 ms; excitation frequency: 8. Dynamic contrast-enhanced scan was performed with 3D-FLASH fat suppression sequence, and the following were the parameters for the axial scan: TR: 5.2 ms; TE: 2.4 ms; deflection angle: 80°C; matrix: 384 × 384; slice thickness: 1 mm; excitation frequency: 8; 3D scan time: 61 seconds. Sagittal bilateral breast images on 3D-FLASH fat suppression sequence were obtained using the following parameters: TR: 26.0 ms; TE: 6.4 ms; matrix: 512 × 512; thickness: 1.0 mm, no interval. Gadolinium diethylene triaminepenta acetate (Gd-DTPA) (0.1 mmol/kg) was injected intravenously using a high-pressure syringe at a flow rate of 3 mL/s, followed by normal saline flush (20 mL, 2.5 mL/s).

Quantitative Indicators

Based on the Breast Imaging Reporting and Data System and the guidelines from the National Comprehensive Cancer Network, 25 important variables were selected as indicators (named from X1 to X25), as shown in Table 1. Each indicator was assigned an integer value. Each image was independently scored by five blinded radiologists and the mean values were obtained.

For quantization of the MR and x-ray findings, we proposed a scoring system. Considering the inter-observer variability in the interpretation, we introduced a score system in which 15 MRI indicators were reviewed and scored by five radiologists independently and the mean of the five scores was used (Table 2). The resulting scores were not only "yes" or "no" (1 or 0), but also a value between 0 and 1. For example, during MRI evaluation, if three radiologists interpreted the lesion as "almost entirely fat," and two interpreted it as "scattered fibroglandular tissue," then the breast tissue would be scored 0.6 ("almost entirely fat") and 0.4 ("scattered fibroglandular tissue"), respectively.

Statistical Analysis

First, data were checked for inconsistency and the invalid index data were deleted. Next, prior to multivariate analysis for pathologic molecular subtypes (four types), each indicator variable was converted to classification or index level data.

All selected indicators were estimated by *t* test, analysis of variance, non-parametric test, chi-square test, and Pearson and Spearman correlation analyses.

The pathologic molecular subtype (BLBC as the control variable) was set as the dependent variable. Each index selected after index clustering analysis was set as independent variable. Multivariate logistic regression analysis was performed to screen significant indicators.

All analyses were performed using SPSS 19.0 (IBM, International Business Machines Corp. New York, U.S.); $P < 0.05$ was considered indicative of a statistically significant difference. Logistic regression analyses were used to determine the association between tumor molecular subtype and radiological features. Between-group differences with respect to distribution of demographic, radiological, and pathologic characteristics by molecular subtype were evaluated using Pearson's chi-square test.

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