RESEARCH ARTICLE

Associations Between Mammography and Ultrasound Imaging Features and Molecular Characteristics of Triple-negative Breast Cancer

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Abstract

Background: The triple-negative breast cancer (TNBC) is an aggressive cancer characterized by the absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). Preoperative mammography and ultrasound features of TNBC may potentially suggest characteristics of the disease and assist in treatment decisions. Materials and Methods: The study covered 153 patients with TNBC from May 2011 to May 2012 who were confirmed by postoperative pathology results in our hospital. We compared the radiological findings among the patients and sought to determine the significant iconographic features. The biomarkers p53 and Ki-67 are regarded as significant factors in TNBC. They were therefore used to divide the TNBC into four groups for assessment of relationships with TNBC imaging features. Results: On mammography, most TNBCs exhibit obscure (44.3%) masses. On ultrasound, the majority of masses (95.4%) were predominantly indistinct (50.7%), irregular (76.0%) or featuring posterior echo enhancement/shadowing. Color Doppler flow imaging (CDFI) emphasized hypervascular (32.9%) masses. Differences in CDFI by ultrasound among the four groups were statistically significant (p=0.009). There were obvious differences in the percentages of spiculated margin (p=0.049) and intensive posterior echo (p=0.006) with spotty flow imaging by ultrasound between the Ki-67 (+) p53 (+) and other groups. Conclusions: A combination of mammography and ultrasound revealed the imaging characteristics of TNBC included an obscure mass with less attenuated posterior echoes and some vascularity. A worse prognosis was associated with spiculated margin and intensive posterior echoes with spotty flow imaging.

Keywords: Triple-negative breast cancer - mammography - ultrasound - p53 - Ki-67

Asian Pac J Cancer Prev, **15 (8)**, 3555-3559

Introduction

Triple-negative breast cancer (TNBC) is an aggressive cancer characterized by the absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) (Carey et al., 2006; Kim et al., 2006). Patients showing triple-negative tumors with mutation of the p53 gene and suppressed BRCA1 function have a relatively high malignancy potential and an adverse prognosis. These patients do not benefit from endocrine therapy or therapies targeted to HER2 (Foulkes et al., 2010). At present, chemotherapy is the mainstay of holistic treatment (Cleator et al., 2007; Reis-Filho and Tutt, 2008; Doreen and Donovan, 2011). In a microarray-based expression profiling studied by Perou et al. (2000), breast cancers were divided into five molecular types: luminal A and luminal B (two estrogen receptors positive), normal breast-like, HER2 positive and basal-like (three estrogen receptor negative). There were more triple-negative and less luminal A tumors in the group with younger patients (Tang et al., 2011). The TNBCs were heterogeneous, with most showing a basal-like phenotype. The predictive biomarkers that respond to chemotherapy for TNBC may differ from those associated with other subgroups of breast cancer. The biomarkers p53 and Ki-67 are regarded as significant factors in TNBC. Breast cancer with high Ki-67 expression responds better to chemotherapy, and p53 dependents chemotherapy sensitivity specific to TNBC. The survival rate nevertheless denotes poor, despite a high response rate to chemotherapy. The overall survival (OS)rate is lower in the p53 (+) group than in the p53 (-) group (Chae et al., 2009). A high Ki-67 expression is associated with poor relapse-free survival (RFS) and OS in TNBC (Keam et al., 2011). TNBC accounts for 11%-20% of all sub-types of breast cancer (Itoh et al., 2006). Therefore, it is essential for us to recognize the features of TNBC, especially the imaging appearance. In this paper, we describe the mammography and ultrasound features of TNBC in Chinese patients, which could potentially preoperatively suggest the disease and assist in the treatment.

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Materials and Methods

We received written informed consents from all the patients. The protocol for this study was performed in accordance with the Helsinki Declaration and approved by the Ethics Committee of The Third Affiliated Hospital of Harbin Medical University, Harbin, CHINA.

Patients

Data from 153 women with TNBC were collected from our hospital between May 2011 and May 2012. All cases were confirmed by postoperative pathology. We identified all patients between the ages of 29 and 81 years (median age was 46 years). Routine examinations of patients by mammography and ultrasound were conducted before operation and any other therapy.

The standard examination for women undergoing either symptomatic mammography or a screening examination consisted of a lateral oblique and a cranio-caudal view of each breast. The GE Senographe 2000D system (GE Medical Systems, Milwaukee, WI, USA) or prototype digital breast tomosynthesis system (Selenia, Hologic, Santa Clara, Calif, USA) was used to examine the patients. In all cases, mammograms were retrospectively reviewed by two breast radiologists for evaluation of the TNBC features of present sign (no abnormalities, masses, focal asymmetries, architectural distortion, calcifications), mass border (circumscribed, microlobulated, obscured, spiculated) and mass with calcifications, according to the National Comprehensive Cancer Network Breast Cancer Guidelines China Edition 2011.

The role of ultrasound is an important complement to both clinical examination and mammography. Ultrasound were performed with the modern HD15 (Philips Ultrasound, Bothell, WA, USA) and Acuson Sequoia 512 (Siemens Medical Solutions, Mountain View, CA, USA) ultrasound systems using 7-12 MHz linear-array transducers, followed by two dedicated breast imaging experts. The imaging included findings (no abnormalities, masses, architectural distortion), mass shape (oval, round, irregular), mass margin (circumscribed, indistinct, angular, microlobulated, spiculated), posterior echoes (enhancement, no change, attenuating), and CDFI (avascular, spotty, hypovascular, hypervascular) based on the National Comprehensive Cancer Network Breast Cancer Guidelines China Edition 2011.

Pathology complete resection were assessed by two experienced pathologists independently. Buffered formalin is applicable for tissue preservation. Hematoxylin and eosin staining was used for pathological diagnosis. ER, PR, and HER2 were assessed by immunohistochemical analysis. ER and PR were evaluated by Allred score. The grade of HER2 status defined as positive was 3+, and a 2+ grade was checked by fluorescence in situ hybridization to determine positivity. The expression of p53 was calculated by the positive nuclear staining fraction of tumor cells, with score 0 regarded as negative and scores 1-3 as positive. Ki-67 was calculated by counting the percentage of stained Ki-67 positive cells among the total number of counted tumor cells. We considered Ki-67 positive when ≥10% and negative when <10% (Keam et al., 2011).

Statistical evaluation was performed using SPSS software (v13.0; IBM Corporation, Armonk, NY, USA). We used chi-square test to assess association between the imaging features of ultrasound and molecular characteristics of TNBC. A p value less than 0.05 was considered statistically significant.

Table 1. The Basic Data of Triple-negative Breast Cancer Patients

Triple-negative breast cancer n=153	
BMI (kg/m^2)	
Lower than 19	9 (5.9%)
19-24	71 (46.4%)
24-29	59 (38.6%)
29-34	12 (7.8%)
More than 34	2 (1.3%)
Menopausal	82 (53.6%)
Oral contraceptive use	24 (15.7%)
Family history of cancer	35 (22.9%)
History of breast cancer	13 (37.1%)
History of other cancers	22 (62.9%)

Table 2. Pathology of Triple-negative Breast Cancer

Pathology type	n=153
IDC	109 (71.2%)
IDC+DCIS	17 (11.1%)
DCIS	3 (2.0%)
Others	24 (15.7%)

*Abbreviations: IDC, invasive ductal carcinoma, DCIS, ductal carcinoma in situ

Results

The basic data of TNBC patients are provided in Table 1. The vast majority of patients had a BMI within 19 to 24 kg/m^2 (71/153, 46.4%) or 24 to 29 kg/m^2 (59/153, 38.6%). Women with TNBC were more likely to be menopausal at a median age of 46 years. Few patients (35/153, 22.9%) had a family history of cancer, especially breast cancer.

Pathological types of TNBC are listed in Table 2. Most masses demonstrated invasive ductal carcinoma (IDC) (109/153, 71.2%), IDC with ductal carcinoma in situ (DCIS) (17/153, 11.1%). Few DCIS (3/153, 2.0%) were observed. Other pathological types (24/153, 15.7%) were rare, with its nuclear grades more likely to be histologically intermediate or high-grade tumors.

Table 3 summarizes the mammography and ultrasound features of triple-negative carcinoma. Mammography findings were as follows: the images were more likely to exhibit as masses (122/153, 79.7%). One case (0.7%) showed no signs of abnormality, focal asymmetries were noted in 16.9% (26/153) of the cases, architectural distortion was revealed in one case (0.7%), and calcifications, regarded as a specific manifestation of DCIS, were noted in 3 patients (2.0%). Most TNBCs exhibited obscured (54/122, 44.3%) or spiculated (41/122, 33.6%) masses, whereas others showed circumscribed (22/122, 18.0%) or microlobulated (5/122, 4.1%) margins. Calcifications emerged in 56.9% of diagnoses; calcifications accounted for only 29.5% of the masses. Ultrasound findings were as follows: the number of patients showing no abnormalities by ultrasound was negligible (1/153, 0.7%). The majority of the patients showed masses (146/153, 95.4%) that

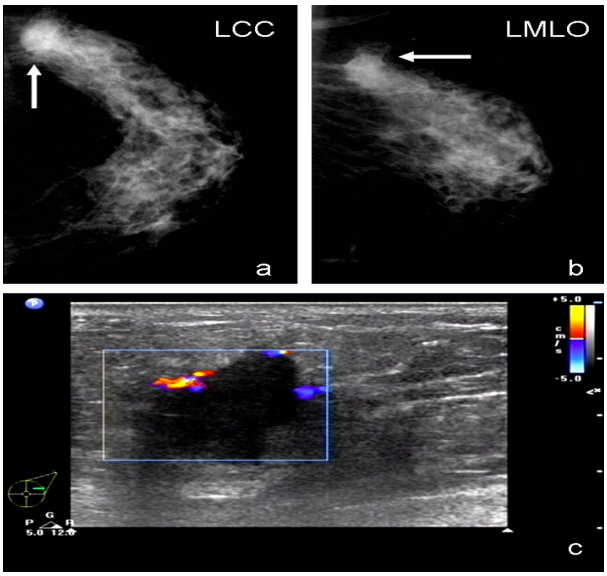

Figure 1. a) and b) Mammography Revealed a High Density Mass with Spiculated Border in the Outer Upper Quadrant of the Left Breast (arrows). c) In Ultrasound, the Mass Showed a Low Echoic Area with Irregular Shape and Spiculated Margin, Plunging Arteries, and Attenuating Posterior Echoes

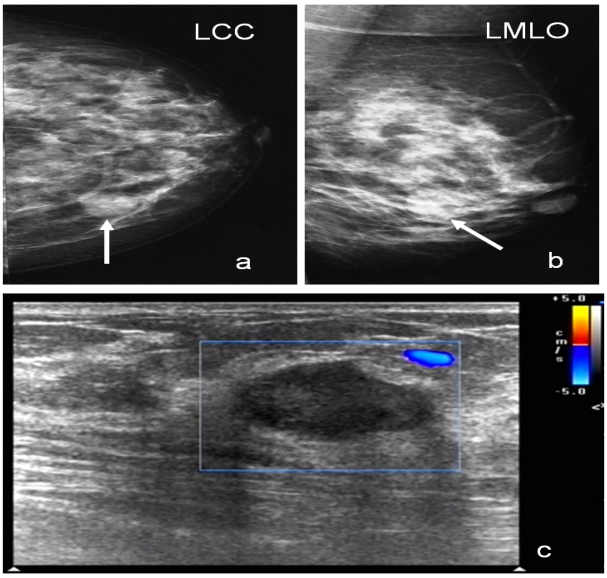

Figure 2. a) and b) Mammography displayed an isodensity TNBC Mass with Circumscribed Margin in the Inner Upper Quadrant of the left Breast(arrows). c) In Ultrasound, the Mass had a Low Echoic Area with Regular Shape and Circumscribed Margin, Avascular Flow Imaging and no Change Posterior Echoes

Table 3. Mammography and Ultrasound Features of Triple-negative Breast Cancer

Mammography		Ultrasound	
Present sign	(n=153)	Findings	(n=153)
No abnormalities	1 (0.7%)	No abnormalities	1 (0.7%)
Masses	122 (79.7%)	Masses	146 (95.4%)
Focal asymmetries	26 (16.9%)	Architectural distortion	6 (3.9%)
Architectural distortion	1 (0.7%)	Mass shape	(n=146)
Calcifications only	3 (2.0%)	Oval	31 (21.2%)
Mass border	(n=122)	Round	4 (2.7%)
Circumscribed	22 (18.0%)	Irregular	111 (76.0%)
Microlobulated	5 (4.1%)	Mass margin	(n=146)
Obscured	54 (44.3%)	Circumscribed	27 (18.5%)
Spiculated	41 (33.6%)	Indistinct	74 (50.7%)
Calcifications	87 (56.9%)	Angular	10 (6.8%)
Mass with calcifications	36 (29.5%)	Microlobulated	14 (9.6%)
		Spiculated	21 (14.4%)
		Posterior echoes	(n=152)
		Enhancement	39 (25.7%)
		No change	80 (52.6%)
		Attenuating	33 (21.7%)
		CDFI	(n=152)
		Avascular	14 (9.2%)
		Spotty	45 (29.6%)
		Hypovascular	43 (28.3%)
		Hypervascular	50 (32.9%)

were predominantly indistinct (74/146, 50.7%), irregular (111/146, 76.0%) and with posterior echoes enhancement (39/152, 25.7%). CDFI emphasized the hypervascular (50/152, 32.9%) masses which were significantly different from the avascular (14/152, 9.2%) ones.

Figure 1 and 2 show two representative cases. In first case, mammography revealed a high density mass with spiculated border in the outer upper quadrant of the left breast. In ultrasound, the mass had a low echoic area with irregular shape and spiculated margin, plunging arteries, and attenuating posterior echoes. The pathological result confirmed invasive ductal carcinoma with a nuclear grade 2. Immunohistochemical findings were ER negative,

Table 4. Ultrasound Characteristics of Masses According to p53 and Ki-67 Status

	Ki-67(-) p53(-) n=27	Ki-67(-) p53(+) n=23	Ki-67(+) p53 (-) n=41	Ki-67(+) p53(+) n=55	*p* value
Mass shape					
Oval	7(25.9%)	5(21.7%)	9(22.0%)	10(18.2%)	0.41
Round	2(7.4%)	0(0%)	2(4.9%)	0(0%)	
Irregular	18(66.7%)	18(78.3%)	30(73.2%)	45(81.8%)	
Mass margin					
Circumscribed	7(25.9%)	3(13.0%)	7(17.1%)	10(18.2%)	0.144
Indistinct	10(37.0%)	12(52.2%)	23(56.1%)	29(52.7%)	
Angular	2(7.4%)	3(13.0%)	3(7.3%)	2(3.6%)	
Microlobulated	4(14.8%)	0(0%)	7(17.1%)	3(5.5%)	
Spiculated	4(14.8%)	5(21.7%)	1(2.4%)	11(20.0%)	
CDFI					
Avascular	5(18.5%)	2(8.7%)	2(4.9%)	5(9.1%)	0.009*
Spotty	8(29.6%)	4(17.4%)	9(22.0%)	22(40.0%)	
Hypovascular	4(14.8%)	12(52.2%)	18(43.9%)	8(14.5%)	
Hypervascular	10(37.0%)	5(21.7%)	12(29.3%)	20(36.4%)	
Posterior echoes					
Enhancement	3(11.1%)	4(17.4%)	9(22.0%)	19(34.5%)	0.070
No change	13(48.1%)	14(60.9%)	22(53.7%)	29(52.7%)	
Attenuating	11(40.7%)	5(21.7%)	10(24.4%)	7(12.7%)	

*means *p* value less than 0.05

PR negative and HER2 negative. The Ki-67 index was approximately 30%, and p53 expression was positive. In figure 2, mammography displayed an isodensity TNBC mass with circumscribed margin in the inner upper quadrant of the left breast. In ultrasound, the mass had a low echoic area with regular shape and circumscribed margin, avascular flow imaging and no change posterior echoes. The Ki-67 index was 8%, p53 expression was negative.

The p53 and Ki-67 status were adopted to divide the masses with ultrasound into four groups. The results are shown in Table 4. There were 146 cases that present as masses. Difference of mass shapes or mass margin among four groups did not reach the statistical significance, as compared with posterior echoes. In comparison, CDFI served a diverse (p=0.009). Ki-67 (-) p53 (-) group usually revealed avascular flow imaging, Ki-67 (-) p53 (+) often

showed hypovascular flow imaging, while Ki-67 (+) p53 (+) presented as spotty flow imaging.

When we compared the Ki-67 (+) p53 (+) with other three groups respectively, spotty flow imaging was significant higher in Ki-67 (+) p53 (+)masses than Ki-67 (-) p53 (+) ones, but hypovascular masses was lower in Ki-67 (+) p53 (+) masses (p=0.006). Masses that were Ki-67 (+) p53 (+) tended to depict spotty flow imaging during ultrasound, whereas Ki-67 (+) p53 (-) masses depicter hypovascular inversely (p=0.013). There were obvious differences in the percentages of masses margin by ultrasound between Ki-67 (+) p53 (+) and Ki-67 (+) p53 (-) groups (p=0.049). Ki-67 (+) p53 (+) masses usually revealed spiculated. Ki-67 (+) p53 (+) and Ki-67 (-) p53 (-) groups of posterior echoes distribution had significant differences (p=0.006). Enhancement ratio of Ki-67 (+) p53 (+) group was higher than Ki-67 (-) p53 (-) group whereas attenuating proportion was lower than Ki-67 (-) p53 (-) ones.

Discussion

With the patients in our study, the breasts were almost heterogeneously dense. Ma et al. (2009) reported there was no difference in the association between breast cancer risk and breast density for ER+/PR+/HER2- versus TNBC. Phipps et al. (2012) further reviewed breast density as an important risk factor for all the breast cancer subtypes. Therefore, the density was not a specific indicator of any of the subtypes of breast tumor. Phipps et al. (2012) also indicated that BMI is positively associated with risk of TNBC. Consistent with this finding, our results showed that 47.7% of our patients had BMIs out of the normal range.

In our research, the median age of TNBC was 46 years, which was similar with studies conducted in China or African American, and lower than Turkish or Caucasian patients. The reason might be due to the diversity of race, menopausal status or weight in different regions. (Sachdev et al., 2010; Li et al., 2013; Somali et al., 2013)

Similar to other studies (Crook et al., 1997; Noguchi et al., 1999; Claus et al., 2005; Yang et al., 2008), DCIS was rare among our TNBCs lacking mammographic calcifications. As we all know, calcifications were regarded as the specific pictures of DCIS. TN DCIS develops rapidly in a brief period of time, making it difficult to be detected at a precancerous state. Yang et al. (2008) suggested that biological differences exist among breast cancer subtypes and that TNBCs may have a distinct etiology. The results proved that TNBC was an aggressive cancer with a rapid progression to invasive cancer. According to other studies with TNBC, the mammography images displayed masses with indistinct border or spiculated shapes, lacking any distinctive features. As such, mammography may be of limited value for those who develop TNBC.

Ultrasound sometimes presents a mass with an oval profile and enhancement of posterior echoes that may be benign. Posterior echo enhancement may also indicate an internal fluid element, such as in tumor necrosis, which is a feature regularly reported on pathological appraisal in TNBC (Lerma et al., 2007).

In our study, ultrasound can pick up the patient who appeared as normal in mammography. Although mammography is a gold standard for breast cancer screening , mammography combined with ultrasound may become one of the useful tools to lower the rate of missed diagnosis. Both systems tend to complement rather than substitute for each other.

TNBC has a high response to neoadjuvant chemotherapy (NAC) but poor survival rate. A few studies have reported the usefulness of p53 and Ki-67 as predictive or prognostic values among patients with TNBC and treated with NAC. In breast cancer cases, p53 expression was positively correlated with Ki-67 (Bottini A et al., 2001), TN tumors had higher expressions of Ki-67 and p53 compared with non-TN ones. There is no report about the relationship between these two factors and TNBC imaging features. Keam et al. (2011) reported that a high Ki-67 expression was significantly associated with poor RFS and OS in TNBC, regardless of the pathologic complete response (PCR). This finding is similar for p53 in TNBC (Chae et al., 2009), which when positive or overexpressed, resulted in non-ideal or poor RFS and OS. Our data showed that Ki-67 (+) p53 (+) masses in ultrasound tended to reveal posterior echo enhancements, but Ki-67 (-) p53 (-) masses drew attenuating posterior echoes. One reason to explain the worse prognosis in p53 (+) TNBC is that it has more necrosis, thereby presenting a poorer response to chemotherapy than p53 (-) TNBC. Ki-67 (+) p53 (+) group was more presented as spotty and spiculated masses. Spiculated margin may be related to the way of the expansive growth of tumor, and the lack of tumor angiogenesis is responsible for the spotty flow imaging. Correspondingly, dismal prognosis masses more presented as spiculated shapes and intensive posterior echoes, which were spotty CDFI.

Our original intention was to describe and compare the practical imaging features of the aggressive TNBC, which has been reported to be concealed by conventional imaging techniques, as well as to emphasize a suitable measure for diagnosis. As such, a control group of patients with hormone positive and HER2 positive breast cancer was not included. In this study, we only researched the correlations of imaging features to prognostic molecular markers, but not to survival rates. We did not determine the ultrasound elastography, which may be a proper measure to distinguish the unique phenotype. Further studies would be required. Dogan et al. (2010) investigated the features of TNBC by mammography, ultrasound and magnetic resonance imaging (MRI). TNBC were visualized by MRI in all cases, and in 91% and 93% of cases by mammography and ultrasound respectively which the percentages of conceal cases were higher than our study. One proper reason was our DCIS cases -a developing TNBC- are fewer than theirs. The report also analyzed the specific diagnosis of TNBC by MRI. However, as MRI is not a part of regular clinical examination. It should not be used only in patients suspected of TNBC with no finding or benign findings in mammography and ultrasound. The results from our study require further confirmation because of the uncertain and complex biological mechanisms in triple-negative oncology. MRI is also a very precise

modality of follow up response in chemotherapy candidates, especially in such sector of patients that will need to do a routine follow up every 3 months in the first year and every 6 months in the second year. If there is no socioeconomic obstacle, MRI is highly recommended in the routine examination for such patients in order to set a base imaging features for therapy response.

In conclusion, mammography and ultrasound combination revealed that the imaging characteristics of TNBC included an indistinct mass with less attenuated posterior echoes and some vascularity. Grave prognosis more presented masses as spiculated margin and intensive posterior echoes with spotty flow imaging.

Acknowledgements

This work is supported by the Science and Technology Research Project of Heilongjiang Province Department of Education, China (Grant No. 12521247). We thank Lei Zhang from The Third Affiliated Hospital of Harbin Medical University for his help in the statistical analysis.

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