RESEARCH ARTICLE

Ultrasonographic Features of Triple-Negative Breast Cancer: a Comparison with Other Breast Cancer Subtypes

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Abstract

Background: Triple-negative breast cancer (TNBC) is known to be associated with aggressive biologic features and a poor clinical outcome. Therefore, early detection of TNBC without missed diagnosis is a requirement to improve prognosis. Preoperative ultrasound features of TNBC may potentially assist in early diagnosis as characteristics of disease. Purpose: To retrospectively evaluate the sonographic features of TNBC compared to ER (+) cancers which include HER(-) and HER2 (+), and HER2 (+) cancers which are ER (-). Materials and Methods: From June 2012 through June 2014, sonographic features of 321 surgically confirmed ER (+) cancers (n=214), HER2 (+) cancers (n=66), and TNBC (n=41) were retrospectively reviewed by two ultrasound specialists in consensus. The preoperative ultrasound and clinicopathological features were compared between the three subtypes. In addition, all cases were analyzed using morphologic criteria of the ACR BI-RADS lexicon. Results: Ultrasonographically, TNBC presented as microlobulated nodules without microcalcification (p=0.034). A lower incidence of ductal carcinoma in situ (p<0.001), invasive tumor size that is>2 cm (p=0.011) and BI-RADS category 4 (p<0.001) were significantly associated with TNBC. With regard to morphologic features of 41 TNBC cases, ultrasonographically were most likely to be masses with irregular (70.7%) microlobulated shape (48.8%), be circumscribed (17.1%) or have indistinct margins (17.1%) and parallel orientation (68.9%). Especially TNBC microlobulated mass margins were more more frequent than with ER (+) (2.0%) and HER2 (+) (4.8%) cancers. Conclusions: TNBC have specific characteristic in sonograms. Ultrasonography may be useful to avoid missed diagnosis and false-negative cases of TNBC.

Keywords: Breast cancer - molecular subtypes - TNBC - neoplasms - ultrasonography

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Introduction

Clinically, breast cancers are categorized into one of three major subtypes, using the three standard immunohistochemical markers, to facilitate targeted therapy; these subtypes are ER (+) cancer, HER2 (+) cancer, and triple-negative breast cancer (TNBC) (Dent et al., 2007; Doreen et al., 2011). TNBC is an aggressive cancer characterized by the absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) (Luo et al., 2010). TNBC is known to be associated with aggressive histologic features, a poor clinical outcome, and a shorter survival compared with other breast cancer subtypes (Bauer et al., 2007; Pal et al., 2011; Pradyumna et al., 2014). Contrary to its aggressive nature, TNBC has been described as having benign morphology by conventional imaging modalities (Krizmanich-Conniff et al., 2012; Wojcinski et al., 2012). However, to the best of our knowledge, there are a few studies reporting the imaging features of TNBC, especially compared to non-TNBC. In this study, we retrospectively evaluate the clinicopathological, ultrasonographic features of triple-negative breast cancer in comparison with ER (+) cancer and HER2 (+) cancer.

Materials and Methods

Study population

Our institutional review board approved this study, and the requirement for informed consent was waived. The protocol for this study was performed in accordance with the Helsinki Declaration and approved by the Ethics Committee of Haidian maternal and child health hospital, Beijing, CHINA. From June 2012 through June 2014, a total of 359 patients underwent surgery for breast cancer. In addition, 41 patients were excluded due to the non-availability or poor quality of their preoperative ultrasonographic images. Finally, 319 patients (mean age, 49.1 years; range, 27-73 years) with 321 breast cancers were included in our study.

Imaging analysis

The role of ultrasound is an important complement to both clinical examination and mammography. Ultrasound

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were performed with MyLab20 (Esaote Ultrasound Maastricht, The Netherlands), ultrasound systems using 7.5-12 MHz linear-array transducers, followed by two dedicated breast imaging doctors. lesions were described included findings, mass shape (oval/round, irregular), mass margin (circumscribed, indistinct, angular, microlobulated, spiculated), posterior echoes (enhancement, no change, attenuating), and based on the National Comprehensive Cancer Network Breast Cancer Guidelines China Edition 2011.

Clinicopathologic data

We reviewed the patients' medical records, in order to identify the clinical symptoms. We also use pathological reports to determine the tumor size, histological grade, and presence of axillary lymph node metastasis. The tumors' ER, PR, and HER2 statuses were determined by immunohistochemical analysis. For the immunohistochemical analysis, formalin-fixed, paraffin-embedded tissue sections were immunohistochemically stained. The ER and PR statuses were determined by score. The results were classified as positive when the total score, expressed as the sum of the proportion and immunointensity scores, was 3 or more. The grade of HER2 status defined as positive was 3+, and a 2+ grade was checked by fluorescence in situ hybridization to determine positivity.

Statistical analysis

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

Results

Out of a total of 321 breast cancers, 41 (12.8%) were TNBC, 214 (66.7%) were ER-positive cancer, and 66 (20.6%) were HER2-positive cancer (Table 1). The mean invasive tumor size was 2.3 cm (range, 0.1-6.6 cm) for ER (+) cancers, 2.1 cm (range, 0.1-5.6 cm) for HER2 (+) cancers, and 2.4 cm (range, 0.1-4.2 cm) for TNBC, respectively. The invasive tumor size that is >2 cm was more often in TNBC (56.1%, 23 of 41) compared to ER (+) cancers (45,3%, 97 of 214) and HER2 (+) cancers (45.5%, 30 of 66). Axillary lymph node metastases were significant higher in TNBC 56.1% (23 of 41) than in ER (+) cancers 31.3% (67 of 147), and HER2 (+) cancers 30.3% (20 of 46).

Pathologically invasive ductal carcinoma was the most common histologic type in ER (+) cancer (79.0%, 169 of 214), HER2 (+) cancer (68.2%, 45 of 66), and TNBC (85.4%, 35 of41). Significantly lower incidence of ductal carcinoma in situ (DCIS) was observed in TNBC (7.4%, 3 of 41) compared to ER (+) cancer (11.2%, 24 of 214) and HER2 (+) cancer (31.8%, 21 of 66). There are 3 medullary cancer: TNBC (n=1) and ER (+) cancer (n=2). All adenoid cystic (n =1) carcinomas were TNBC.

By ultrasonography (Table 2), ER (+) cancer, HER2 (+) cancer, and TNBC were detected at levels of 92.5%, 95.5%, and 100% (p=0.013), respectively. The presence of mass or focal asymmetry lacking microcalcifications (80.5% in TNBC *vs* 44.9% in ER (+) cancer *vs* 68.3% in HER2 (+) cancer; p<0.001) was significantly associated with TNBC.

Ultrasonographically, all 302 breast cancer cases which is sonographic abnormality, presented as discrete masses. The mass shape was more commonly irregular in ER (+) cancer, HER2 (+) cancer, and TNBC, separately 80.8%, 160 of 198; 77.3%, 51 of 63; 70.7, 29 of 41 and less commonly oval or round (19.2%, 22.7% and 29.3%) (Table 1). The mass margin was more commonly microlobulated in TNBC (48.8%, 20 of 41) and less commonly circumscribed (17.1%, 7 of 41), indistinct (17.1%, 7 of 41) or angular (14.6%, 6 of 41).On the contrary, ER (+) cancer and HER2 (+) cancer was most commonly with indistinct margin (52.0%, 103 of 198; 58.7% 37 of 63) and less commonly spiculated (26.8%, 53 of 198; 19.0% 12 of 63), circumscribed (18.2%, 36 of 198; 15.9% 10 of 63). The TNBC cases, 68.3% (28 of 41) had posterior acoustic features, of which posterior enhancement was the most common (53.7%, 22 of 41). While there have some difference with ER (+) cancer and HER2 (+) cancer, the most common is no change

Table 1. Clinicopathological According to the Tumor Subtype

Features		TNBC (n=41)	ER (+) (n=214)	HER2 (+) (n =66)	P value
Mean age (years)*		46.5 (32-62)	49.2 (29-73)	50.1 (27-60)	0.223
Palpability	No	6 (14.6)	105 (49.1)	35 (53.0)	0.015
	Yes	35 (85.4)	109 (50.9)	31 (47.0)	
Pathology	Invasive ductal carcinoma	35 (85.4)	169 (79.0)	45 (68.2)	<0.001
	Invasive lobular carcinoma	1 (2.4)	13 (6.1)	0 (0.0)	
	Ductal carcinoma in situ	3 (7.4)	24 (11.2)	21 (21.8)	
	Lobular carcinoma in situ	0 (0.0)	3 (1.4)	0 (0.0)	
	Medullary cancer	1 (2.4)	2 (0.9)	0 (0.0)	
	Adenoid cystic cancer	1 (2.4)	0 (0.0)	0 (0.0)	
	Invasive micropapillary cancer	0 (0.0)	3 (1.4)	0 (0.0)	
Tumor size (cm)	>2	23 (56.1)	97 (45.3)	30 (45.5)	0.011
	≤2	18 (43.9)	117 (54.7)	36 (54.5)	
Axillary lymph node positivity	No	18 (43.9)	147 (68.7)	46 (69.7)	<0.001
	Yes	23 (56.1)	67 (31.3)	20 (30.3)	

Data are the numbers of subjects, with percentages in parentheses, *Numbers in parentheses are age ranges

Table 2. Sonographic Imaging Features according to the Tumor Subtype

Features		TNBC (n=41)	ER (+) (n=214)	HER2 (+) (n=66)	P value
Sonographic abnormality	No	0 (0.0)	16 (7.5)	3 (4.5)	0.013
	Yes	41 (100.0)	198 (92.5)	63 (95.5)	
Shape	Oval/ Round	12 (29.3)	38 (19.2)	15 (22.7)	<0.001
	Irregular	29 (70.7)	160 (80.8)	51 (77.3)	
Mass Margin	Circumscribed	7 (17.1)	36 (18.2)	10 (15.9)	0.204
	Indistinct	7 (17.1)	103 (52.0)	37 (58.7)	
	Angular	6 (14.6)	2 (1.0)	1 (1.6)	
	Microlobulated	20 (48.8)	4 (2.0)	3 (4.8)	
	Spiculated	1 (2.4)	53 (26.8)	12 (19.0)	
Posterior echoes	Enhancement	22 (53.7)	67 (33.8)	12 (19.0)	0.257
	No change	13 (31.7)	102 (51.5)	36 (57.2)	
	Attenuating	6 (14.6)	29 (14.7)	15 (23.8)	
BI-RADS category	Category 3	1 (2.4)	26 (13.1)	19 (30.2)	<0.001
	Category 4	33 (80.5)	110 (55.6)	39 (61.9)	
	Category 5	7 (17.1)	62 (31.3)	5 (7.9)	
Abnormal sonographic finding	Mass only	33 (80.5)	89 (44.9)	43 (68.3)	0.034
	Mass with calcifications	8 (19.5)	109 (55.1)	20 (31.7)	

Data are the numbers of subjects, with percentages in parentheses, *Numbers in parentheses are age ranges

posterior echoes (51.5%, 102 of 198; 57.2%, 36 of 63). The BI-RADS category was based on the ultrasonographic findings. All the ultrasonographic acoustic features cases was before operation. The BI-RADS category for the TNBC cases was most commonly category 4 (80.5%, 33 of 41) and less commonly category 5 (17.1%, 7 of 41). It is similar for the ER (+) cancer, the most commonly category 4 (55.6%, 110 of 198) and less commonly category 5 (31.3%, 62 of 198). For the HER2 (+) cancer, the most commonly also category 4 (61.9%, 39 of 63), there is some different with less commonly category, it is category 3 (30.2%, 19 of 63).

Discussion

Triple receptor-negative cancer (TNBC) is a subtype of breast cancer characterized by negative expression of ER, PR, and HER2 (Irianiwati et al., 2014; Mousumi et al., 2014). In our study, the median age of TNBC is 46.5 years, which is similar with research conducted in China (Li et al., 2013). It has been known to be associated with aggressive histologic features, a poor clinical outcome, and a shorter survival compared with other breast cancer subtypes (Bauer et al., 2007; Pal et al., 2011). Compared with non-TNBC breasts cancers, TNBC cases were of high nuclear grade, and unfavorable histology, such as with anaplastic or metaplastic carcinomas (Rakha et al., 2007).

Our study showed that most TNBC often presented clinically with a palpable mass (85.4%) and all of them can be detected by ultrasonographic examination. Similar with prior reports, invasive tumor size that is >2 cm (56.1%, 23 of 41) were more often in TNBC compared to non-TNBC. Unlike prior studies, axillary lymph node positivity was observed more often in TNCB (56.1%) than in ER (+) cancer (31.3%) and HER2 (+) cancer (30.3%) in our study. We suppose that is associated with when the cancer had been found.

In our results, a significantly higher incidence of micrologulated margin was observed in TNBC compared with ER (+) cancer and HER2 (+) cancer (48.8%, 20 of 41). Similar to other studies (Wojcinski et al., 2012; Mi Young Kim et al., 2013) that TNBC shows circumscribed or lobulated margin more often rather than spiculated or angular margin. Wojcinski et al. described this smooth appearance as a pushing border that is associated with non-infiltrative process by rapid tumor growth. Consequently, we believe that microlobulated margin might be useful to avoiding false-negative cases of TNBC. We also found that TNBC were more likely to be associated with posterior acoustic enhancement (53.3%) than ER (+) cancer (33.8%) and HER2 (+) cancer (19.0%). It is well-known that high grade, highly cellular circumscribed carcinomas tends to have enhanced through-transmission (Kim et al., 2013; Bo et al., 2014).

Our study has several limitations. First, our study is retrospective, and its sample size was small and all patient come from one hospital. Second, we did not analyze the imaging features of TNBC according to the cancer stage, which might influence the imaging features at diagnosis. Third, the results from our study require further confirmation because of the uncertain and complex biological mechanisms in triple-negative oncology. Fourth, we did not include the findings of other imaging modalities such as mammographic and MRI, which may be more sensitive for the diagnosis of TNBC. We did not determine the ultrasound elastography, which may be a proper measure to distinguish the unique phenotype. TNBC were visualized by mammography, ultrasound and MRI in all cases, Dogan et al. confirmed that MRI should not be used only in patients suspected of TNBC with no finding or benign findings in mammography and ultrasound (Dogan BE et al., 2010). Further studies would be required.

In conclusion, combined ultrasonographic features of mass or focal asymmetry without microcalcifications that is hypoechoic mass with microlobulated or circumscribed margin can be suggestive of presence of TNBC. Being familiar with ultrasonographic findings of TNBC would be useful for early detection of TNBC without missing such cancer diagnosis.

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