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FULL PAPER

Mammographic and clinicopathological features of triple-negative breast cancer

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Objective: Triple-negative breast cancer (TNBC) lacks effective treatment and has a poor prognosis. This study assessed mammographic findings and clinicopathological features of TNBC by comparing with non-TNBC in order to improve clinical diagnosis of TNBC.

Methods: A total of 426 patients with pathologically confirmed breast cancer were retrospectively assigned into two groups, TNBC ($n = 54$) and non-TNBC ($n = 372$), and then analysed.

Results: TNBC frequently showed a high histological grade, presented with a mass (79.6%) and was less frequently associated with focal asymmetric density (11.1%), microcalcifications (5.6%) and distortion (3.7%) on mammography. TNBC mammographic masses were most

frequently round/oval (58.1%) or lobular (30.2%) in shape and were less frequently irregular in shape (11.6%). Masses with circumscribed margins were the most frequent (37.2%), with microlobulated (25.6%) and obscured (16.3%) margins being commonly observed, but masses with spiculated margins were rare (9.3%).

Conclusion: TNBC could have distinct mammographic and clinicopathological features compared with non-TNBC, and thus mammography may be useful in the diagnosis of TNBC.

Advances in knowledge: This study demonstrated distinct mammographic and clinicopathological features to help in diagnosis of Chinese patients with TNBC.

Breast cancer is the most common malignancy observed in females. Histologically, breast cancer is a heterogeneous disease with different subtypes and pathology, treatment options and prognosis.¹ Bryan et al² for the first time in 2006 explicitly presented the definition of triple-negative breast cancers (TNBCs) based on the expression of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). Other studies using gene expression profiling were able to classify breast cancer into five subtypes.^{3,4} To date, TNBC is used frequently as a standard procedure to classify breast cancer patients for clinical care. TNBC is similar to the basal-like subtype, which is characterized by negative ER, PR and HER2 expression, and is associated with aggressive histology, poor prognosis and unresponsiveness to the endocrine therapies.^{5,6} Moreover, TNBC has been used as a surrogate marker for the basal-like breast cancer, and approximately 80–90% of TNBCs are basal-like breast cancers.⁷ Younger females have a higher rate of basal or breast cancer susceptibility gene mutation-related

TNBC, whereas older females have a higher proportion of apocrine, normal-like and rare subtypes of TNBC, including neuroendocrine TNBC.⁸ Because only fewer specific targeting therapies and molecular therapies (such as endocrine or target therapy) are available than for other subtypes of breast cancer, the standard treatment for TNBC includes surgery combined with adjuvant chemotherapy and radiotherapy, but clinical outcome is poor.^{7,9} Thus, early detection of this subtype of breast cancer is vital to improve the survival of patients.

Although TNBC has been studied extensively in clinical and pathological literature, there are few reports on the radiological characteristics of this subtype of breast cancer. To date, mammography is known to be a precise diagnostic technique with high sensitivity and specificity in the evaluation of breast lesions, and the current reference standard in breast cancer screening is mammography with the sensitivity to detect early-stage breast cancer. Therefore, this study evaluated the mammographic and clinicopathological

Table 1. Comparison of clinicopathological features of triple-negative breast cancer (TNBC) with non-TNBC

Features	TNBC, <i>n</i> = 54 (%)	Non-TNBC, <i>n</i> = 372 (%)	<i>p</i> -value
Age (years)			
Mean	48.9	49.8	0.6550
Range	32–72	29–88	
Tumor size (cm)			
Mean	2.35	2.38	0.9280
Range	0.6–4.0	0.8–6.6	
Axillary lymph node			
Positive	22 (40.7)	138 (37.1)	0.6050
Negative	32 (59.3)	234 (62.9)	
Pathological type			
IDC	42 (77.8)	290 (78.0)	0.9760
All others	12 (22.2)	82 (22.0)	
Grade of IDC			
I/II	10 (23.8)	220 (75.9)	<0.0001
III	32 (76.2)	70 (24.1)	

IDC, invasive ductal carcinoma.

features of TNBC by comparing these features to those of non-TNBC in order to make a more precise diagnosis.

METHODS AND MATERIALS

Patients

We retrospectively recruited a total of 426 females with invasive breast cancer who were treated in our institution (The Second Affiliated Hospital, Harbin Medical University, Harbin, China) between July 2011 and December 2012. They all accepted mammography before undergoing the surgery. After surgical resection of tumour lesions, all tissue samples were immunohistochemically stained for the expression of ER, PR and HER2, which divided them into two groups, TNBC (*n* = 54) and non-TNBC (*n* = 372) (*i.e.*, having at least one of the three positive biologic markers). The mammographic and clinicopathological data for these patients were retrieved from their medical records using the Electronic Medical Record Search Engine and retrospectively reviewed and analysed according to TNBC and non-TNBC groups. This study was approved by our institutional review board. Informed consent was obtained from each patient included in the study, and ethical approval for this study was given by the Ethics Committee at The Second Affiliated Hospital, Harbin Medical University, Harbin, China. The study has been performed in accordance with the ethical standards.

Diagnostic imaging

Mammography had been performed for each patient using a digital technique Lorad Selenia unit (Hologic, Bedford, MA). Mammograms with mediolateral oblique and craniocaudal views were performed on each patient, and additional views were also performed if necessary. In all cases, mammograms were retrospectively reviewed by three experienced Mammography Quality Standards Act-certified breast radiologists with 5–12 years of breast imaging experience who had no knowledge about the clinical and

pathological findings of the patients. Mammograms were evaluated according to the 4th edition of American College of Radiology Breast Imaging Reporting and Data System.¹⁰ Any discrepancy was re-reviewed by all three breast radiologists together to reach a conclusion. Breast density was rated as fatty, scattered fibroglandular, heterogeneously dense or dense. The mammographic findings were described as masses, masses with calcifications, only calcifications, focal asymmetric densities or architectural distortions; and masses were evaluated for size, shape and margin. Margins of a mass were reviewed for being circumscribed, obscured, microlobulated, indistinct and spiculated.

Histological assessment of tissue specimens

All resected tissue specimens were diagnosed histologically. Haematoxylin–eosin staining was performed in formalin-fixed, paraffin-embedded tissue sections for pathological diagnosis. The following histological parameters were analysed: histological type, histological grade and the presence of hormone receptors (status of ER, PR and HER2 was determined by immunohistochemical analysis as part of routine pathological assessment for clinical management). The status of each receptor was considered to be negative if the expression was <10% and positive if the expression was ≥10%. The HER2 status was graded as 0, 1+, 2+ and 3+. HER2 score of 3+ was defined as positive, and 2+ was checked by fluorescence *in situ* hybridization for its positivity. Breast cancers with negative ER, PR and HER2 staining were grouped as TNBC.

Statistical analysis

All analyses were performed using statistical software (SPSS® v. 19.0; SPSS Inc., Chicago, IL). Patient characteristics were tabulated by immunophenotype or described by their median and range, as appropriate. The χ^2 test or the Student's *t*-test was used for the comparison between the groups. A *p*-value <0.05 was considered statistically significant.

Table 2. Comparison of mammographic features of triple-negative breast cancer (TNBC) with non-TNBC

Feature	TNBC, <i>n</i> = 54 (%)	Non-TNBC, <i>n</i> = 372 (%)	<i>p</i> -value
Mass			
Yes	34 (63.0)	132 (35.5)	<0.0001
No	20 (37.0)	240 (64.5)	
Mass + calcifications			
Yes	9 (16.7)	158 (42.5)	<0.0001
No	45 (83.3)	214 (57.5)	
Calcifications			
Yes	3 (5.6)	32 (8.6)	0.4460
No	51 (94.4)	340 (91.4)	
Focal asymmetric density			
Yes	6 (11.1)	30 (8.1)	0.4520
No	48 (88.9)	342 (91.9)	
Architectural distortion			
Yes	2 (3.7)	20 (5.4)	0.6040
No	52 (96.3)	352 (94.6)	
Total mass			
Yes	43 (79.6)	290 (78.0)	0.7810
No	11 (20.4)	82 (22.0)	
Total calcification			
Yes	14 (25.9)	204 (54.8)	<0.0001
No	40 (74.1)	168 (45.2)	
Breast density			0.8590
Fatty	4 (7.4)	37 (9.9)	
Scattered fibroglandular	17 (31.5)	127 (34.1)	
Heterogeneously dense	27 (50.0)	175 (47.0)	
Dense	6 (11.1)	33 (8.9)	
Mass shape			<0.0001
Round/oval	25 (58.1)	64 (22.1)	
Lobular	13 (30.2)	91 (31.4)	
Irregular	5 (11.6)	135 (46.6)	
Mass margin			<0.0001
Circumscribed	16 (37.2)	10 (3.4)	
Obscured	7 (16.3)	18 (6.2)	
Microlobulated	11 (25.6)	87 (30.0)	
Indistinct	5 (11.6)	80 (27.6)	
Spiculated	4 (9.3)	95 (32.8)	

RESULTS

Clinicopathological data

Clinical and histological features of TNBC and non-TNBC patients are summarized in Table 1. Of the 426 breast cancer patients, 54 were TNBC (12.7%). There were more statistically significant high-grade tumours in the TNBC group than those in the non-TNBC

group [grade 3: 32/42 (76.2%) vs 70/290 (24.1%), respectively] ($p < 0.0001$). However, there was no tumour size-related bias or age-related bias between the TNBC group and the non-TNBC group. There was no difference in the axillary lymph nodal status between the two groups, although there was a trend for more metastases in the TNBC group (40.7% vs 37.1%; $p = 0.605$).

Figure 1. Mammogram imaging of a 52-year-old female with triple-negative breast cancer. (a) Left lateromedial mammogram revealed a 1.9 cm round high-density mass with circumscribed margin in the posterior depth of the superior region. (b) Left craniocaudal mammogram showed a portion of the mass (arrow).

The most common histological type in TNBC was invasive ductal carcinomas (77.8%), but there was no statistically significant difference between the two groups.

Figure 2. Mammogram imaging of a 71-year-old female with triple-negative breast cancer. (a) Right lateromedial mammogram revealed an 8.2-cm oval high-density mass with circumscribed margin in the superior region. An enlarged lymph node (arrow) was noted in the right axillary region. (b) Right craniocaudal mammogram showed another 1.4-cm oval iso-density mass with microlobulated margin.

Figure 3. Mammogram imaging of a 72-year-old female with triple-negative breast cancer. (a) Left lateromedial mammogram revealed a 1.2-cm oval isodensity mass with microlobulated margin in the posterior depth of the superior region. (b) Left craniocaudal mammogram showed a portion of the mass (arrow).

Mammographic features

The mammographic features for TNBC and non-TNBC are summarized in [Table 2](#). TNBCs most commonly had masses without calcifications (34/54, 63.0%) ([Figures 1–3](#)) compared with

Figure 4. Mammogram imaging of a 62-year-old female with non-triple-negative breast cancer. (a) Right craniocaudal mammogram and (b) right lateromedial mammogram revealed a 2.0-cm irregular isodensity mass with spiculated margin, along with segmental pleomorphic calcifications.

Figure 5. Mammogram imaging of a 54-year-old female with non-triple-negative breast cancer. (a) Left lateromedial mammogram and (b) left craniocaudal mammogram revealed a 3.0-cm oval high-density mass with spiculated margin.

non-TNBCs (132/372, 35.5%; $p < 0.0001$). TNBCs had fewer masses with calcifications (9/54, 16.7%), focal asymmetric density (6/54, 11.1%), calcifications alone (3/54, 5.6%) or architectural distortion (2/54, 3.7%). Non-TNBCs most commonly presented as a mass with calcifications (158/372, 42.5%; Figure 4). There was no statistically significant difference for focal asymmetric density, calcifications alone and architectural distortion between the two

groups. Breast density of TNBC was most frequently heterogeneously dense (50.0%) or scattered fibroglandular (31.5%), but there was no statistically significant difference between these two groups.

Shapes and margins of tumour masses were also assessed mammographically. Tumour lesions of TNBC showed more oval or round shapes (Figures 1 and 2) than those of non-TNBC (58.1% vs 22.1%; $p < 0.0001$). Tumour lesions of TNBC were of irregular shape (5/43, 11.6%) and non-TNBC was frequently irregular (Figure 4) in shape (135/290, 46.6%). In the TNBC group, tumour masses with circumscribed margins (Figures 1 and 2) were the most frequent (16/43, 37.2%), whereas microlobulated margins (11/43, 25.6%) (Figure 3) and obscured margins (7/43, 16.3%) were commonly observed, but spiculated margins (4/43, 9.3%) and indistinct margins (5/43, 11.6%) were rare. Both irregular shape and spiculated margins are typical features for the diagnosis of malignancy. By contrast, in the non-TNBC group, tumour masses with spiculated margins (Figures 4 and 5) were the most frequent (95/290, 32.8%), whereas microlobulated margins (87/290, 30.0%) and indistinct margins (80/290, 27.6%) were commonly observed; circumscribed margins (10/290, 3.4%) and obscured margins (18/290, 6.2%) were rare.

DISCUSSION

Many studies have focused on TNBC because of its distinctive pathological and molecular characteristics. TNBC lacks therapeutic options, such as molecular therapy or targeted therapy (endocrine or HER2-directed inhibitors); thus, the prognosis of TNBC is dismal compared with other subtypes of breast cancer. Currently, surgery plus chemotherapy or chemotherapy alone is the only systemic option for improving the prognosis of TNBC. This implies that early detection of this aggressive type of breast cancer is necessary owing to the rapid progress and failed

Table 3. Comparison of mammographic features of triple-negative breast cancer in different studies

Study	Number of cases	Normal mammogram (%)	Mass (%)	Mass and calcification (%)	Calcifications only (%)	Focal asymmetry or density seen on only one view (%)	Architectural distortion (%)
Yang et al ²⁰	38	13.0	85.0	15.0	0	0	0
Wang et al ²¹	33	18.0	48.0	12.0	9.0	12.0	0
Dogan et al ²²	43	9.3	53.5	4.7	7.0	20.9	4.7
Ko et al ²³	87	0	49.0	21.0	7.0	22.0	1.0
Kojima and Tsunoda ²⁴	85	9.4	49.4	12.9	11.8	9.4	7.0
Boisserie-Lacroix et al ²⁵	73	15.9	59.3	10.2	13.6	16.9 ^a	
Krizmanich-Conniff et al ²⁶	207	5 ^b	58.0	29.0	7.0	–	–
Current study	54	0	63.0	16.7	5.6	11.1	3.7

^aArchitectural distortion or focal asymmetry.

^bNumber of cases.

prognosis. In this study, we assessed mammographic imaging and clinicopathological features of TNBC by comparing it with non-TNBC. We found that TNBC frequently showed a high histological grade. On mammography, TNBC usually presented with a mass but was less frequently associated with focal asymmetric density, microcalcification and distortion. TNBC mammographic masses were most frequently round/oval or lobular in shape and less frequently irregular in shape. Tumor masses with circumscribed margins were the most frequent, whereas microlobulated and obscured margins were commonly observed, but spiculated margins were rare. Thus, this study concluded that TNBC mammographic features lack typical signs of malignancy, but did have some distinct features that could be useful in the diagnosis of TNBC.

Clinically, the prevalence of TNBC reported in the literature was inconsistent owing to different races and regions. Patients with TNBC account for approximately 8.1–21.4% of all breast cancers.^{11,12} The prevalence of TNBC in this study was 12.7%, but it is slightly lower than the percentages that have been reported in Japanese and South Korean populations. The incidence of TNBC in Japan has been reported as 14.4% (data from Registration Committee of the Japanese Breast Cancer Society 2004–2009), and the incidence of TNBC in South Korea is 14.7%.¹³ Moreover, in this study, a significant difference of the onset age between TNBC and non-TNBC was not observed, which coincides with the study by Uematsu et al,¹⁴ but it is contrasting from other studies.^{15,16} Generally, TNBC is more commonly found in young patients.⁸ In addition, this study did not show any difference in tumour size and in the axillary lymph nodal status between TNBC and non-TNBC, although there was a trend for more axillary lymph nodal metastases in TNBC. Previous studies^{16,17} show that the patients with TNBC were significantly more likely to have larger tumour sizes and positive axillary lymph nodes than the patients with non-TNBC.

Pathologically, this study showed that the most common histological type of TNBC was invasive ductal carcinoma, although there was no statistically significant difference between the two groups. Consistent with other studies,^{14,18,19} our results showed that the majority of the patients with TNBC were of histological Grade 3.

There have been few studies describing mammography findings of TNBC (Tables 3 and 4). This study showed that approximately 80% of TNBC patients had a visible tumour mass on mammography, and the masses were less frequently associated with microcalcification. This finding is consistent with previous studies^{20–26} that observed TNBC was most commonly presented as a mass (58.2–100%), and the mass was less frequently associated with microcalcifications (4.7–29%). Our data showed that the shape of TNBC lesions was more likely to be round/oval (58.1%), which is consistent with previous studies.^{20–22,25} The broadly rounded shape of the masses can be explained by the rapid growth of these tumours that do not produce stromal reaction in breast cancer.²⁷ However, in contrast with this study and others,^{20–25} Krizmanich-Conniff et al²⁶ reported that TNBC was mainly characterized by irregular masses (49%). Moreover, other studies^{20,21,25,26} showed that the most common margins of

Table 4. Features of masses on mammography of triple-negative breast cancer in different studies

Study	Mass, <i>n</i> (%)	Mass shape (%)				Mass margin (%)			
		Oval/ round	Lobular	Irregular	Circumscribed	Obscured	Microlobulated	Indistinct	Spiculated
Yang et al ²⁰	33 (100.0)	48.0	27.0	24.0	24.0	12.0	0	45.0	18.0
Wang et al ²¹	20 (60.0)	50.0	20.0	30.0	30.0	5.0	5.0	45.0	15.0
Dogan et al ²²	25 (58.2)	60.0	–	–	32.0	–	–	–	–
Kojima and Tsunoda ²⁴	53 (62.3)	–	–	–	20.8	0	39.6	32.0	7.5
Boisserie-Lacroix et al ²⁵	– (69.5)	55.0	10.0	35.0	15.0	2.5	12.5	55.0	15.0
Krizmanich-Conniff et al ²⁶	133 (87.0)	31.0	20.0	49.0	8.0	19.0	5.0	47.0	21.0
Current study	43 (79.6)	58.1	30.2	11.6	37.2	16.3	25.6	11.6	9.3

tumour masses on mammography were indistinct (45–55%); however, in this study, the most common mass margins on mammography were circumscribed (37.2%), and less commonly mass margins were microlobulated (25.6%), which was consistent with the study reported by Dogan et al.²² Our results confirmed the findings of previous studies^{20–26} that showed TNBC was less likely to have spiculated margins. Overall, TNBC presented most frequently as round or oval masses with circumscribed margins. This is important because a smooth mass border is frequently used as a factor for finding a benign lesion. Therefore, TNBC is likely to manifest benign morphological features. Moreover, this study revealed that on mammography TNBC was less frequently associated with calcifications (total calcification: 25.9%, only calcification: 5.6%), which was consistent with other studies^{20–26} (total calcification: 11.7%–36%, only calcification: 0%–13.6%). Yang et al.²⁰ indicated that the relative low levels of calcification in TNBC

were consistent with the low incidence of ductal carcinoma *in situ* in TNBC. Ko et al.²³ noted that the combined mammographic and pathological features of TNBC suggested a more rapid growing pattern of carcinogenesis, leading directly to invasive cancers, with no major *in situ* components or pre-cancerous stage. However, this study did have some limitations. For example, the sample size was relatively small, which may have limited the statistical power. In order to further confirm our conclusion, a larger sample size is needed. In addition, this study only assessed TNBC and non-TNBC. Future studies should be performed to compare TNBC with other immunohistochemical subtypes of breast cancers.

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