Correlations between the Mammographic Features of Triple-Negative and Triple-Positive Breast Cancer

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Abstract: *Purpose*: To comparative analyze the mammographic findings and clinical characteristics of triple negative breast cancer (estrogen receptor [ER] negative, progesterone receptor [PR] negative, and human epidermal growth factor receptor2 [HER2] negative) and triple positive breast cancer (ER positive, PR positive, and HER2 positive).

Materials and Methods: The immunohistochemistry results of 174 cases of TNBC and 97 cases of TPBC were reviewed. All of the patients had undergone mammography. Retrospectively evaluate the visibility, morphology, distribution and size of the lesions (masses and calcifications) and breast density on mammography of TNBC, and to compare with those of TPBC. The age onset and pathologic type were also reviewed.

Results: TNBC more frequently presented as merely a mass (95/150[63.3%]) than TPBC (34/88 [38.6%]) (P<0.01). TNBC were less frequently associated with microcalcifications (33/150[22%]) than were TPBC (39/88 [44.3%]) (P<0.01). Mammographic density and lesion visibility were similar between the two immunophenotypes. The mean age of TNBC (52[32~87]) was older than that of TPBC (48[26~68]) (P=0.002). Infiltrating ductal carcinoma was the main pathologic type of both groups. Basal-like breast cancer accounted for 47.7% (83/174) of TNBC but didn't express in TPBC (0/97).

Conclusion: The mammographic features of TNBC that lesions showed merely a mass with obscured margins, and less associated with microcalcifications might be useful to diagnose triple negative breast cancer.

Keywords: Mammography, Triple negative breast cancer, Microcalcifications, Immunohistochemistry.

INTRODUCTION

Breast cancer, as a kind of malignant tumor with high heterogeneity biology characteristics, has been identified into 5 subtypes by the use of gene expression profiles: luminal A, luminal B/C, human epidermal growth factor receptor 2 (HER2) over express, basal-like (BL) and normal-like. Luminal A and luminal B are ER-positive breast cancers, and HER2-positive and BL subtypes are ER-negative. Luminal C subtype breast cancer has positive expressions of ER, PR and HER2 [1-3]. BL breast cancer (BLBC) is characterized by negative expression of estrogen receptor(ER), progesterone receptor (PR) and HER2, and usually related to BRCA1. Triple negative breast cancer is defined by the use of immunohistochemical assays for ER, PR and HER2. This subtype of breast cancer is characterized by the absence of ER, PR and HER2, and presenting approximately 10%-17% of primary breast cancers [4]. Patients with triple negative breast cancer and basal-like breast cancer usually have shorter life expectancies and poor prognosis, because both subtypes have an aggressive clinical behavior and cannot be treated with endocrine therapy or therapies targeted to HER2 [5-8]. Although BLBC and TNBC share many immunohistochemical and clinical characteristics, they are not the same. TNBC is usually used as surrogate marker for BLBC for convenience in clinical. Early detection of this subtype on mammography could help to make proper plan of treatment and evaluate prognosis, as well as deepen our understanding of the biological behavior of triple negative breast cancer.

The aim of this study was to retrospectively evaluate the mammographic findings of triple negative breast cancer and to compare with those of triple positive breast cancer (TPBC, which is tumor with positive expressions of ER, PR and HER2) in a relatively large population.

1. MATERIALS AND METHODS

1.1. Clinical Data

We retrospectively collected 1102 cases of breast cancer from January 2009 to December 2011 in one hospital. All of the patients had completed mammography at initial diagnosis and pathologically confirmed primary breast cancer after surgical or biopsy. The expression status of ER, PR and HER2 of lesions were detected by immunohistochemical analysis. There were about 174 TNBC patients, 97 TPBC patients and 831 other subtypes of breast

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cancers according to the results of immunohistochemistry. So there were 271 patients totally in our study. All of the patients were female. We reviewed the age, pathologic characteristics and mammographic findings of the patients also.

1.2. Imaging Examination

All of the patients had been undergone mammography by GE-800 breast unit (American) in mediolateral oblique view and craniocaudal view. All the mammograms were reviewed by two breast radiologists without knowledge of clinical and pathological results, and the breast density, visibility and type of the lesion, as well as morphology, margin, size and microcalcifications of the lesions were evaluated according to the Breast Imaging Reporting and Data System lexicon (BI-RADS) published by American College of Radiology [9].

1.3. Histological Evaluation

The expression status of ER, PR and HER2 of patients had been determined by immunohistology which is normal assistant examine in clinical. Nuclear staining in more than 1% of infiltrating tumor cells was defined as ER and PR positive. Strong and complete membranous staining in more than 10% of infiltrating tumor cells was defined as HER2 positive.

1.4. Statistical Analysis

Statistical analysis was carried out by using SPSS 17.0. Breast density, lesion visibility, lesion type as well as the shape and margin of masses and microcalcifications were statistically analyzed by χ^2-*test*; the size of lesions and age onset of patients were statistically analyzed by independent *t-test*, and $P<0.05$ was considered statistically significant.

2. RESULTS

In this study, TNBC represented 15.8% (174/1102) of all breast cancers, and TPBC represented 8.8% (97/1102) of those. The median ages were 53 and 48 years, respectively, for patients in TNBC and TPBC groups (t=3.086, P =0.002) (Table **1**). Breast density of more than 50% was noted in 66.1% (115/174) and

Table 1: Clinical and Histologic Features of TNBC and TPBC

Feature	TNBC(n=174)	TPBC(n=97)	*t*	*P*
Age(years)				
Range	32~87	26~68		
Median	53	48		
Mean	52	48	3.086	0.002
Histologic tumor type			6.596	0.037
DCIS	19[a]	3	5.115	0.024
IDC	136	87		
ILC	1	4		
Medullary	10	0		
Metaplastic carcinoma	2[b]	0		
Mucinous carcinoma	1[c]	2		
Squamous cell carcinoma	2	0		
Invasive apocrine carcinoma	2	0		
Intraductal papillary carcinoma	0	1		
Metastatic carcinoma	1	0		
Basal-like	83	0		
Non basal-like	91	97		

DCIS: ductal carcinoma in situ, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma.
[a]including 3 cases of DCIS, 8 cases of DCIS associated with early invasive, and 1 case of DCIS associated with Paget's Disease,
[b]associated with IDC.
[c]associated with DCIS and Paget's Disease.

Table 2: Mammographic Features of TNBC and TPBC

Features	TNBC (n=174) (%)	TPBC (n=97) (%)	χ^2	*P*
Breast density				
1	33(19.0)	20(20.6)	3.206	0.361
2	26(14.9)	10(10.3)		
3	50(28.7)	22(22.7)		
4	65(37.4)	45(46.4)		
1+2 [a]	59(33.9)	30(30.9)	0.251	0.617
3+4 [a]	115(66.1)	67(69.1)		
Visibility				
Visible	150(88)	88(89)	1.871	0.276
Not visible	24(12)	9(11)		
Abnormality [b]				
Mass only	95(63.3)	34(38.6)	13.628	0.000
Calcifications only	9(6.0)	14(15.9)	6.238	0.013
Mass & calcifications	27(18.0)	25(28.4)	3.519	0.061
Focal asymmetrical density	18(12.0)	12(13.6)	0.135	0.713
Architectural distortion	1(0.7)	3(3.4)	2.524	0.112
Total mass	122(81.3)	59(67.0)	6.216	0.013
Total calcifications	33(22.0)	39(44.3)	13.093	0.000
Mass shape [c]			4.112	0.128
Round or round-like	94(77.0)	38(64.4)		
Lobular	10(8.2)	5(8.5)		
Irregular	18(14.8)	16(27.1)		
Mass margin [c]			6.697	0.082
Circumscribed	14(11.5)	1(8.3)		
Obscured	69(56.6)	35(59.3)		
Microlobulated	23(18.9)	10(16.9)		
Spiculated	16(13.1)	13(22.0)		
Mass size (cm)	2.39±1.16	2.18±7.11	t = 1.392	0.166

[a]1+2：<50% breast density，3+4：>50% breast density, [b]among patients with visible abnormalities only, [c]among patients with masses.

69.1% (67/97) of patients with TNBC and TPBC, respectively (P>0.05). Lesion visibility was noted in 88% (150/174) and 89% (88/97) of patients with TNBC and TPBC, respectively (P>0.05) (Table **2**).

TNBC and TPBC presented as masses in 81.3% and 67.0% of patients (*P*=0.013), and as calcifications in 22.0% and 44.3% of patients, respectively (*P*<0.001). These cancers presented as only masses in 63.3% and 38.6% of patients (*P*<0.001) (Figure **1**), as only calcifications in 6.0% and 15.9% of patients (*P*=0.013), and as masses associated with calcifications in 18.0% and 28.4% of patients, respectively (*P*=0.061) (Figure **2**, **3**). TNBC that appeared as masses were most frequently round or round like in shape, with partial obscured margins, and were less frequently lobular or irregular in shape compared with TPBC. The mean size of masses is 2.39 cm and 2.18 cm in TNBC and TPBC, respectively (P=0.166) (Table **2**) (Figures **4**, **5**).

Histologically, TNBC and TPBC were associated with ductal carcinoma in situ in 10.9% (19/174), and 3.1% (3/97), respectively (*P*=0.024) (Table **1**). The main histological type of TNBC and TPBC were both infiltrating ductal carcinoma, but TNBC were more

frequently presented as basal-like breast cancer (47.7%, 83/174) than that of TPBC (0/97) (Table **1**).

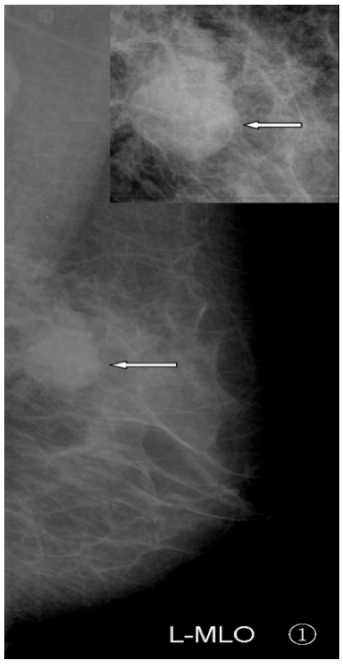

Figure 1: A 50-year-old women presented with a palpable lump in the left breast in the outer upper quadrant. Left lateromedial mammogram demonstrates a 2cm high density mass (arrow) with about 25% indistinct margins in the posterior depth of the superior region, without microcalcifications. Pathology: invasive ductal carcinoma(grade III); immunohistochemistry: ER(-)/ PR(-)/HER2(-).

3. DISCUSSIONS

Human breast tumors have mainly five gene expression profiles. The basal-like breast cancer expressed the characteristics genes of basal epithelial cells, and most of this subtype has negative expression of ER, PR and HER2, the so called “Triple negative breast cancer”. “Triple negative breast cancer” and “basal like breast cancer” were also exchanged in clinical. Although share many similarities, this two subtypes are not the same. In the study of Rakha E.A. *et al.* [10], basal-like breast cancer presented about 56% triple negative breast cancer. In this study, basal-like breast cancer accounted for about 48% TNBC.

This study showed there were some significant differences on mammography between TNBC and TPBC. TNBC mostly presented as a mass with obscured margins on mammography, without associated microcalcifications. The masses of TNBC were usually larger than that of TPBC, though there was no significant difference. All the results above were consistent with the findings of research before [11-13]. Irregular speculated masses and pleomorphic microcalcifications, which are typical features of malignancy, were not usually apparent. On mammography, there was no significant difference in breast density between the two phenotypes of breast cancer.

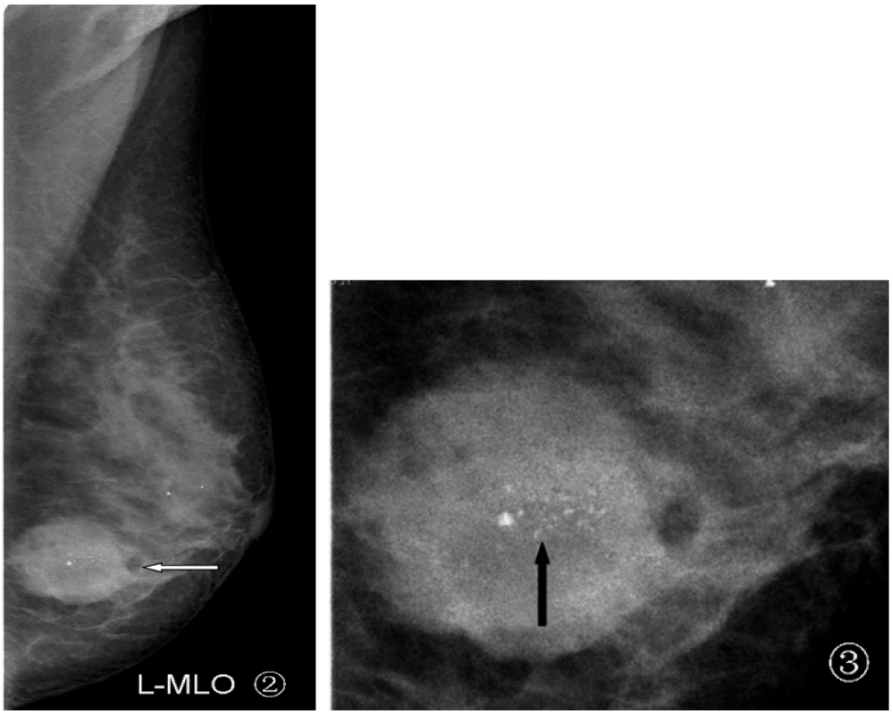

Figure 2,3: A 49-year-old woman presented with a palpable lump in the lower part of left breast. Mammography reveals a lobular high density mass with indistinct margins in the lower region (white arrow). Microcalcifications can be seen inside the mass (black arrow). Pathology: invasive ductal carcinoma(grade III); immunohistochemistry: ER(+)/PR(+)/HER2(+).

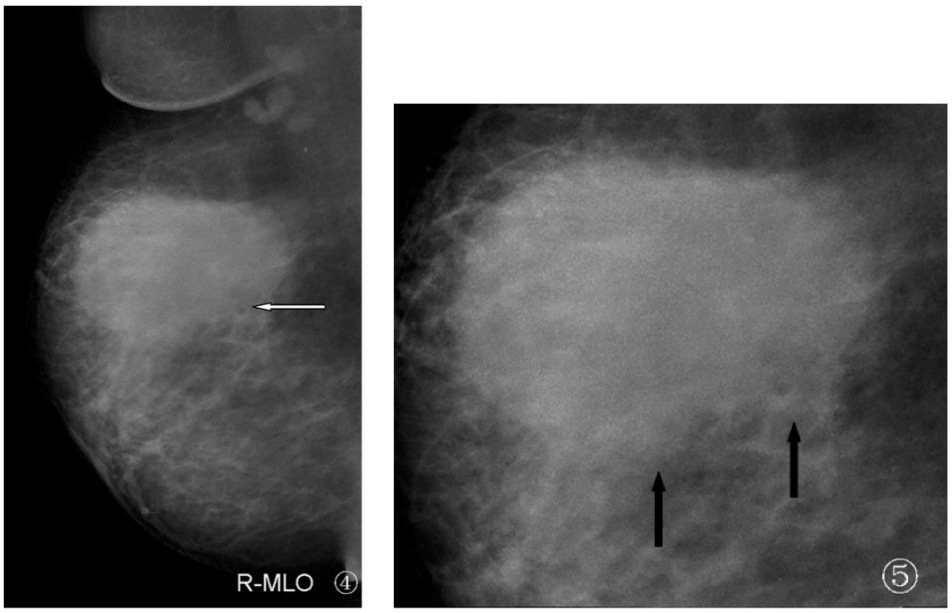

Figure 4,5: A 57-year-old woman presented with a palpable abnormality in the upper part of right breast. Mammography reveals a 7cm high density mass (white arrow) with indistinct margins (black arrow) in the upper region. Pathology: invasive ductal carcinoma(grade III, basal-like); immunohistochemistry: ER(-)/PR(-)/HER2(-).

Yang W.T. *et al.* [11] retrospectively analyzed the mammographic features in 198 young premenopausal women with triple negative breast cancer. Thirty-eight women (19%) had TNBC, 67(34%) had HER2-positive breast cancer and 93(47%) had ER-positive breast cancer. On mammography, TNBC were more likely to be presented as masses, and less frequently associated with microcalcifications. The masses were more frequently presented as round, oval or lobular with obscured margins and less frequently presented irregular in shape or had speculated margins. Dogan *et al.* [12] retrospectively analyzed mammographic, sonographic and magnetic resonance imaging findings in 44 cases of triple negative breast cancer patients. On mammography, about 90% of tumors (39/44) were available. Most of the lesions presented as masses (58%, [25/39]) and focal asymmetries (21%, [9/39]), and less presented as architectural distortions (5%, [2/39]) or groups of calcifications without masses (7%, [3/39]). The masses were more likely to be round or oval in shape (60%, [15/25]), and 32% (8/25) masses had circumscribed margins. Ko *et al.* [13] also came to the similar conclusions in their report, as well as in our study. Therefore, the mammographic findings help to diagnose TNBC.

In the research by Yang W.T. *et al.* [11], TNBC was less likely to present as microcalcifications. They noted that this characteristic were accordance with the low incidence of DCIS in TNBC. The characteristics of mammography and pathology suggested that TNBC has rapid carcinogenesis, leading directly to the development of infiltrating cancers without obvious DCIS or pre-cancerous stage. On the contrary, in our research, TNBC had higher incidence of DCIS than TPBC. Evans *et al.* [14] reviewed DCIS in 126 patients, and noted that there were significantly differences between the characteristics of HER2-positive and HER2-negative breast cancers. When HER2 were absent in express, microcalcifications were less frequently presented on mammography. In our research, the incidence of microcalcifications in TNBC was lower than that of TPBC. This may because HER2 was not express in TNBC lesions.

In our research, we noted that there were significant differences on mammography between TNBC and TPBC. TNBC were most frequently presented as obscured masses without associated with microcalcifications. TPBC group had fewer patients, this may limited to acquire statistical differences. Despite this shortage, we still found that the mammary has certain significance in diagnosing TNBC. But mammography may not be the ideal method. Therefore, we need other imaging methods to assist, for example ultrasound and MRI.

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REFERENCES

[1] Perou CM, Sorlie T, Eisen MB, *et al.* Molecular portraits of human breast tumours. Nature 2000; 406: 747-52. http://dx.doi.org/10.1038/35021093

[2] Sorlie T, Perou CM, Tibshirani R, *et al*. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 2001; 98: 10869-74. http://dx.doi.org/10.1073/pnas.191367098

[3] Brenton JD, Carey LA, Ahmed AA, *et al*. Molecular classification and molecular forecasting of breast cancer: ready for clinical application? J Clin Oncol 2005; 23: 7350-60. http://dx.doi.org/10.1200/JCO.2005.03.3845

[4] Thike AA, Cheok PY, Jara-Lazaro AR, *et al*. Triple-negative breast cancer: clinicopathological characteristics and relationship with basal-like breast cancer. Mod Pathol 2010; 23(1): 123-33. http://dx.doi.org/10.1038/modpathol.2009.145

[5] Bauer KR, Brown M, Cress RD, *et al*. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer 2007; 109(9): 1721-28. http://dx.doi.org/10.1002/cncr.22618

[6] Rakha EA, Reis-Filho JS, Ellis IO. Basal-like breast cancer: a critical review. J Clin Oncol 2008; 26(15): 2568-81. http://dx.doi.org/10.1200/JCO.2007.13.1748

[7] Cheang MC, Voduc D, Bajdik C, *et al*. Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clin Cancer Res 2008; 14(5): 1368-76. http://dx.doi.org/10.1158/1078-0432.CCR-07-1658

[8] Haffty BG, Yang Q, Reiss M, *et al*. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J Clin Oncol 2006; 24(36): 5652-57. http://dx.doi.org/10.1200/JCO.2006.06.5664

[9] American College of Radiology (ACR). Breast imaging reporting and data system (BI-RADS). 4th ed, Reston: American College of Radiology 2003; pp. 1-259.

[10] Rakha EA, El-Sayed ME, Green AR, *et al*. Prognostic markers in triple-negative breast cancer. Cancer 2007; 109(1): 25-32. http://dx.doi.org/10.1002/cncr.22381

[11] Yang WT, Dryden M, Broglio K, *et al*. Mammographic features of triple receptor-negative primary breast cancers in young premenopausal women. Breast Cancer Res Treat 2008; 111(3): 405-10. http://dx.doi.org/10.1007/s10549-007-9810-6

[12] Dogan BE, Gonzalez-Angulo AM, Gilcrease M, *et al*. Multimodality imaging of triple receptor-negative tumors with mammography, ultrasound, and MRI. AJR Am J Roentgenol 2010; 194(4): 1160-66. http://dx.doi.org/10.2214/AJR.09.2355

[13] Ko, Lee BH, Kim HA, *et al*. Triple-negative breast cancer: correlation between imaging and pathological findings. Eur Radiol 2010; 20(5): 1111-17. http://dx.doi.org/10.1007/s00330-009-1656-3

[14] Evans AJ, Pinder SE, Ellis JO, *et al*. Correlations between the mammographic features of ductal carcinoma in situ (DCIS) and C-erB-2 oncogene expression. Clin Radiol 1994; 49(8): 559-562. http://dx.doi.org/10.1016/S0009-9260(05)82937-X

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http://dx.doi.org/10.6000/1927-7229.2013.02.01.4