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Eun Sook Ko
Byung Hee Lee
Hyun-A Kim
Woo-Chul Noh
Min Suk Kim
Sang-Ah Lee

Triple-negative breast cancer: correlation between imaging and pathological findings

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E. S. Ko (✉) · B. H. Lee
Department of Radiology,
Korea Cancer Centre Hospital,
215-4 Gongneung-Dong, Nowon-Gu,
Seoul, 139-706, Korea
e-mail: esko@kcch.re.kr
Tel.: +82-2-9701275
Fax: +82-2-9702433

H.-A. Kim · W.-C. Noh
Department of Surgery,
Korea Cancer Centre Hospital,
Seoul, Korea

M. S. Kim
Department of Pathology,
Korea Cancer Centre Hospital,
Seoul, Korea

S.-A. Lee
Department of Preventive Medicine,
Kangwon National University,
Hyuja2-dong Chucheon-si,
Kangwon-do, 110-799, Korea

Abstract *Objective:* This study was designed to investigate the mammography and ultrasound findings of triple-negative breast cancer and to compare the results with characteristics of ER-positive/PR-negative/HER2-negative breast cancer and ER-negative/PR-negative/HER2-positive breast cancer. *Methods:* From January 2007 to October 2008, mammography and ultrasound findings of 245 patients with pathologically confirmed triple-negative (n=87), ER-positive/PR-negative/HER2-negative (n=93) or ER-negative/PR-negative/HER2-positive breast cancers (n=65) were retrospectively reviewed. We also reviewed pathological reports for information on the histological type, histological grade and the status of the biological markers. *Results:* Triple-negative breast cancers showed a high histological grade. On mammography, triple-negative breast cancers usually presented with a mass (43/87, 49%) or with focal asymmetry (19/87, 22%), and were less associated with calcifications. On ultrasound, the cancers were less frequently seen as non-mass lesions (12/87, 14%), more likely to have circumscribed margins (43/75, 57%), were markedly hypoechoic (36/75, 57%) and less likely to show posterior shadowing (4/75, 5%). Among the three types of breast cancers, ER-negative/PR-negative/HER2-positive breast cancers most commonly had associated calcifications (52/65, 79%) on mammography and were depicted as non-mass lesions (21/65, 32%) on ultrasound. *Conclusion:* Our results suggest that the imaging findings might be useful in diagnosing triple-negative breast cancer.

Keywords Mammography · Ultrasound · Triple-negative breast cancer · Breast neoplasm · Breast carcinoma · Sonography

Introduction

Determination of oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) positivity of invasive breast cancers is useful as a prognostic and predictive factor and has become standard practice in the management of breast cancer as ER and HER2 positivity predict response to endocrine therapy or targeted therapy with monoclonal antibodies directed against HER2 [1]. Recently, the use of microarray profiling of invasive breast cancer has identified five distinct subtypes of morphologically similar breast cancers: luminal A, luminal B, normal breast-like, HER2 overexpressing and basal-like [2–4]. The basal-like subtype, characterised by negativity for ER, progesterone receptor (PR) and HER2, is associated with aggressive histological features, poor prognosis, unresponsiveness to usual endocrine therapies, shorter survival and *BRCA1*-related breast cancer [1, 2, 5, 6].

Although basal-like breast cancer is not identical to triple-negative (negativity for ER, PR and HER2) breast cancer, triple-negativity is used as a surrogate marker for basal-like breast cancer for convenience as these three stains are already used routinely in the clinical work-up of breast cancer [4, 6, 7]. If it is possible to predict the

presence of triple-negative breast cancer based on mammography or ultrasound features, this information will be beneficial for both pretreatment planning and prognosis, and will add to the understanding of the biological behaviour of this disease entity.

There have been a few studies on the relationship between tumour subtype and imaging findings. However, these studies have usually analysed only one receptor or two receptors (not all three receptors). Even had they, they contained a relatively small number of patients. The purpose of our study was to evaluate retrospectively the mammography and ultrasound findings of triple-negative breast cancer and to compare the findings with those of ER-positive/PR-negative/HER2-negative and ER-negative/PR-negative/HER2-positive breast cancers in a large population.

Materials and methods

Patients

One investigator (E.S.K.) searched the pathological database of our institution and identified 87 patients with triple-negative breast cancer between January 2007 and October 2008. All patients were women between the ages of 26 and 86 years (mean age 49 years). As control patient groups, 93 consecutive patients (age range 31–77 years, mean 54 years) with ER-positive/PR-negative/HER2-negative breast cancer and 65 patients (age range 31–86 years, mean age 52 years) with ER-negative/PR-negative/HER2-positive breast cancer identified in the same period were recruited for the study. We retrospectively reviewed and recorded clinical, histological, mammography and ultrasound findings of the three patient groups.

Mammography

Mammograms were available for all 245 patients. Mammography in two standard imaging planes (mediolateral oblique and craniocaudal) was performed with the use of a Selenia system (Lorad, Bedford, CT, USA). Mammograms were retrospectively reviewed by two breast radiologists for focal asymmetry, masses, masses with calcifications, calcifications and architectural distortion, according to the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) lexicon [8].

Ultrasound

Three radiologists performed whole-breast ultrasound in all 245 patients. Ultrasound was performed using 5–12-MHz transducers with an HDI 5000 or IU-22 (Philips Medical Systems, Best, the Netherlands) ultrasound unit. Two breast radiologists with 5 and 20 years of clinical experience (E.S.K. and B.H.L. respectively) retrospectively and independently reviewed the ultrasound images. A consensus interpretation was reached in cases of disagreement. The ultrasound findings were classified as mass or non-mass lesions. In this study, a non-mass lesion was defined as a lesion with minimal or no mass effect, or a lesion that showed focal heterogeneity distinct from the adjacent normal breast parenchyma, which may represent dilated ducts (Fig. 1). Conversely, a mass was defined as a space-occupying lesion that was observed in two different projections. In patients with masses visible on ultrasound, the ultrasound findings of lesions according to the BI-RADS lexicon were recorded [8]. Noted features included shape (oval, round or irregular), margin (circumscribed or not circumscribed), lesion boundary (abrupt interface or

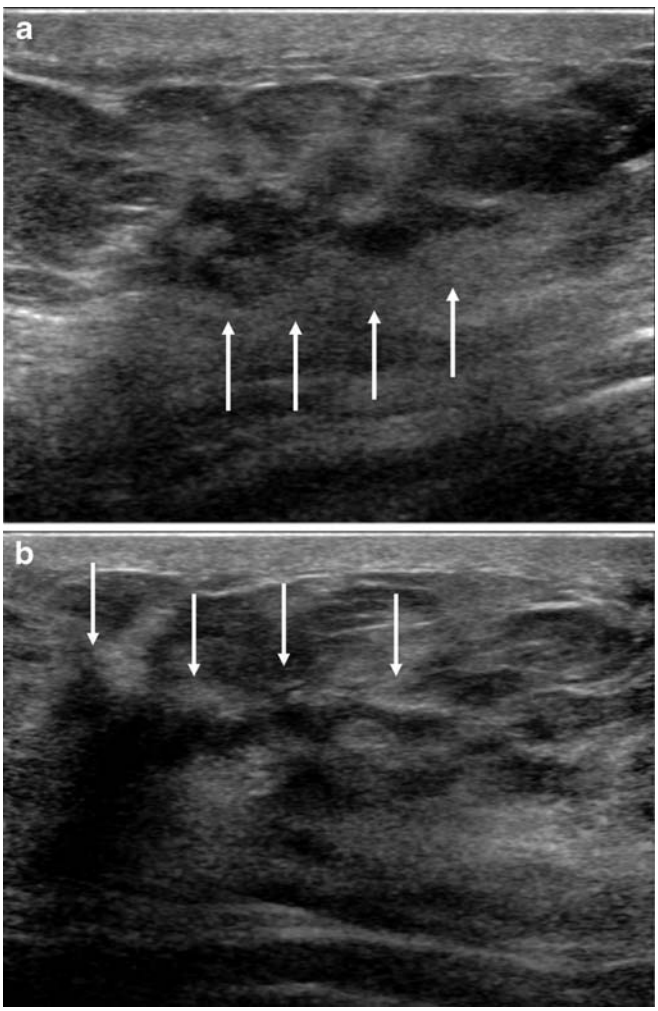

Fig. 1a, b A 37-year-old woman with a palpable lump in the right breast. **a** and **b** Orthogonal ultrasound images show an irregularly shaped, heterogeneously echoic area (*arrows*) in the right breast. Surgery confirmed the presence of a triple-negative invasive ductal carcinoma

echogenic halo), echo pattern (isoechoic, hypoechoic, markedly hypoechoic, complex or hyperechoic), posterior acoustic features (none, enhancement or shadowing) and orientation (parallel to the skin or not parallel to the skin). In terms of echo pattern, we added "markedly hypoechoic" for further classification. It was used when the echogenicity of the mass was so low that it might be misinterpreted as a cyst.

Histopathological analysis

Histopathological findings from excisional biopsies, breast-conserving surgery or mastectomy specimens were used as the reference standard. The following histological parameters were analysed: histological grade, histological type, the presence of hormone receptors and HER2 oncogene expression.

Formalin-fixed, paraffin-embedded tissue sections were immunohistochemically stained with appropriate antibodies for ER (Neomarker, Fremont, CA, USA), PR (Dako, Carpinteria, CA, USA) and HER2 (Zymed, San Francisco, CA, USA). The cutoff point for ER- and PR-positive expression was 10%. HER2 status was graded as 0, 1+, 2+ and 3+, and 3+ was deemed to be positive.

Statistical analysis

To compare the mammography and ultrasound findings among triple-negative, ER-positive/PR-negative/HER2-negative and ER-negative/PR-negative/HER2-positive breast cancers, the chi-squared test was used. All analyses were performed with the use of statistical software (SPSS, version 10.0; SPSS, Chicago, IL, USA), with $P<0.05$ to indicate a significant difference.

Results

Table 1 shows the clinicopathological data. Women with triple-negative breast cancer were likely to have histologically intermediate or high grade tumours. This trend was the same for patients with ER-negative/PR-negative/HER2-positive breast cancers, compared with patients with ER-positive/PR-negative/HER2-negative breast cancers. Metaplastic carcinomas were more frequently associated with triple-negative cancers. Mucinous carcinoma and invasive lobular carcinoma were associated with ER-positive/PR-negative/HER2-negative breast cancer.

Mammography findings according to the immunophenotype are shown in Table 2. Most triple-negative breast cancers were seen as focal asymmetry or as a mass and were less likely to have associated calcification compared with ER-positive/PR-negative/HER2-negative and ER-negative/PR-negative/HER2-positive breast cancers, with statistical significance. In particular, ER-negative/PR-negative/HER2-positive breast cancers were more likely to be associated with calcifications. There was no statistically significant frequency difference for a negative mammogram or architectural distortion among the lesions in the three patient groups.

On ultrasound, 75 out of 87 (86%) triple-negative breast cancer patients presented with masses and 12 (14%) patients exhibited non-mass lesions (Table 3). ER-positive/PR-negative/HER2-negative breast cancers showed a similar pattern. However, for ER-negative/PR-negative/HER2-positive breast cancers, 21 out of 65 (32%) cancers were seen with non-mass lesions; this finding was statistically significant ($P=0.0099$). Table 4 shows the ultrasound findings of cancers that presented as mass lesions according to the immunophenotype. Triple-negative breast cancers were usually irregular (87%) in shape, as were the other two types of cancers. Notably, the triple-negative breast

Table 1 Characteristics of breast cancer patients according to the tumour phenotype

	Triple-negative cancer ($n=87$)	ER(+)/PR(-)/HER2(-) ($n=93$)	ER(-)/PR(-)/HER2(+) ($n=65$)
Age	49 (26–86)	54 (31–77)	52 (31–86)
Tumour size (cm)	2.51	2.18	2.14
Histologic tumour grade			
Low	2 (2%)	22 (24%)	2 (3%)
Intermediate	31 (36%)	40 (43%)	26 (40%)
High	54 (62%)	31 (33%)	37 (57%)
Histologic tumour type			
Invasive ductal carcinoma	80 (92%)	82 (88%)	64 (98%)
Invasive lobular carcinoma	2 (2%)	5 (5%)	0 (0%)
Papillary carcinoma	1 (1%)	1 (1%)	1 (2%)
Tubular carcinoma	0 (0%)	0 (0%)	0 (0%)
Metaplastic carcinoma	4 (5%)	1 (1%)	0 (0%)
Mucinous carcinoma	0 (0%)	4 (4%)	0 (0%)

Table 2 Comparison of mammography findings for breast cancer patients according to the tumour phenotype

Mammography findings	Triple-negative cancer (n=87)	ER(+)/PR(-)/HER2(-) (n=93)	ER(-)/PR(-)/HER2(+) (n=65)	P value
Normal	0 (0%)	4 (4%)	2 (3%)	0.1692
Focal asymmetries	19 (22%)	7 (8%)	4 (6%)	0.0030
Masses	43 (49%)	42 (45%)	7 (11%)	<0.0001
Masses with calcifications	18 (21%)	26 (28%)	29 (45%)	0.0055
Calcification only	6 (7%)	12 (13%)	23 (35%)	<0.0001
Architectural distortion	1 (1%)	2 (2%)	0 (0%)	0.4797

cancers more frequently had an oval shape (16%). However, there was no significant difference in the shape of lesions among the three patient groups (P=0.2539), although we did find a significant association between lesion margin on breast ultrasound and immunophenotype (P<0.0001). Triple-negative breast cancers significantly had circumscribed (57%) as opposed to non-circumscribed margins. For lesion boundary, ER-positive/PR-negative/HER2-negative breast cancers more frequently had echogenic halos than lesions of the other two groups, with statistical significance (P= 0.0007). The echogenicity of triple-negative breast cancers was usually complex echoic (11%), hypoechoic (41%) or markedly hypoechoic (48%), and most typically markedly hypoechoic (P<0.0001) (Fig. 2). Posterior shadowing was not common in triple-negative breast cancers compared with the other two types of lesions (P=0.0189).

Discussion

Recently, gene expression profiling has allowed the classification of breast cancers into five subtypes based on distinctive gene expression patterns [3]. Among the subtypes, basal-like-subtype tumours express genes that are characteristic of basal epithelial cells; the tumours are predominantly negative for ER, PR and HER2, and the tumours are often referred to as 'triple-negative breast cancers'. Clinicians often use the terms 'triple-negative breast cancer' and 'basal-like breast cancer' interchangeably. Although the two tumour subtypes share numerous clinical and pathological features, they are not identical.

Table 3 Comparison of ultrasound findings for breast cancer patients according to the tumour phenotype

	Triple-negative cancer (n=87)	ER(+)/PR(-)/HER2(-) (n=93)	ER(-)/PR(-)/HER2(+) (n=65)	P value
Mass	75 (86%)	78 (84%)	44 (68%)	0.0099
Non-mass lesion	12 (14%)	15 (16%)	21 (32%)	

Basal-like breast cancer is a more modern term that can be characterised by certain gene expression clusters that are commonly expressed in the basal layer of the breast epithelium and are involved in cellular proliferation, suppression of apoptosis, cell migration and cell invasion. These tumours form 56–85% of triple-negative breast cancers [9, 10].

Anthracycline- and taxane-based regimens have traditionally been used in breast cancer patients, including triple-negative breast cancer patients, with evidence of antitumour activity and improvement in clinical outcome. There is evidence that triple-negative breast cancers are sensitive to chemotherapy and exhibit a greater likelihood of complete response to neoadjuvant therapy. The cancers, however, are associated with a poor overall prognosis. Triple-negative breast cancers may respond better to chemotherapy because of a high proliferation index, indicated by high expression of Ki-67. However, patients who fail to achieve complete response tend to relapse earlier and subsequently have poor outcomes [11]. These paradoxical outcomes may reflect a lack of available endocrine or targeted therapy options to improve prognosis further.

Similar to other studies [5, 12, 13], in our study almost all triple-negative breast cancers were intermediate or high grade (98%). In addition, we found that metaplastic carcinoma was more frequently associated with triple-negative breast cancer, which is in agreement with a previous report [4] that demonstrated that these types of carcinomas show a basal-like subtype. However, this finding is of unknown significance because of the limited number of patients.

Our study results showed that several mammography or ultrasound findings are suggestive of triple-negative breast cancer. Triple-negative breast cancers were usually seen as a mass (49%) or focal asymmetry (21%) on mammography. The lesions less frequently had associated microcalcifications, with statistical significance. On ultrasound, triple-negative breast cancers were more likely to be seen as mass lesions with circumscribed margins, were markedly hypoechoic and were less likely to show posterior shadowing; some of the lesions might be misinterpreted as benign, similar to other subtypes of high grade tumours and familial breast cancers [14]. Thus, even though masses looked benign

Table 4 Comparison of ultrasound findings of lesions that presented as masses for breast cancer patients according to the tumour phenotype

Ultrasound findings	Triple-negative cancer (n=75)	ER(+)/PR(-)/HER2(-) (n=78)	ER(-)/PR(-)/HER2(+) (n=44)	P value
Shape				0.2539
Oval	12 (16%)	6 (8%)	3 (7%)	
Round	1 (1%)	1 (1%)	2 (4%)	
Irregular	62 (83%)	71 (91%)	39 (89%)	
Margin				<0.0001
Circumscribed	43 (57%)	15 (19%)	10 (23%)	
Indistinct	9 (12%)	7 (9%)	6 (14%)	
Angular	12 (16%)	28 (36%)	14 (32%)	
Microlobulated	7 (9%)	18 (23%)	12 (27%)	
Spiculated	4 (5%)	10 (13%)	2 (5%)	
Lesion boundary				0.0007
Abrupt interface	63 (84%)	50 (64%)	40 (91%)	
Echogenic halo	12 (16%)	28 (36%)	4 (9%)	
Echo pattern				<0.0001
Complex	8 (11%)	1 (!%)	2 (5%)	
Hypoechoic	31 (41%)	60 (77%)	30 (68%)	
Markedly hypoechoic	36 (48%)	11 (14%)	12 (27%)	
Isoechoic	0 (0%)	6 (8%)	0 (0%)	
Posterior feature				0.0189
No feature	34 (45%)	40 (51%)	16 (36%)	
Enhancement	37 (49%)	23 (29%)	22 (50%)	
Shadowing	4 (5%)	15 (19%)	6 (14%)	
Orientation				0.0017
Parallel	53 (71%)	56 (72%)	34 (77%)	
Not parallel	22 (29%)	22 (28%)	10 (23%)	

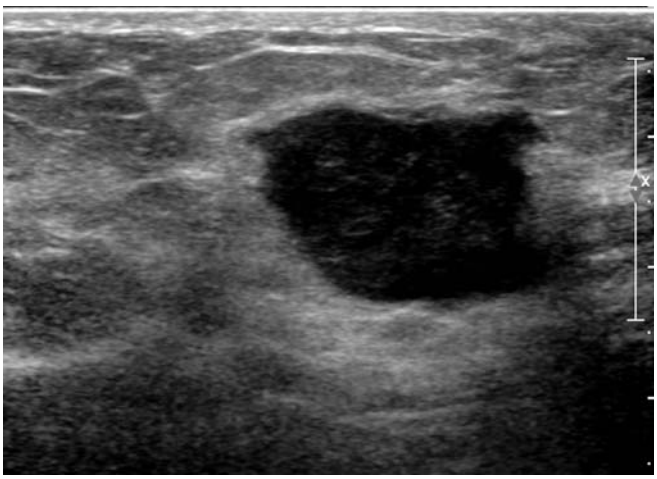

Fig. 2 A 63-year-old woman with triple-negative invasive ductal carcinoma. Ultrasound image shows an irregularly shaped, markedly hypoechoic mass with a circumscribed margin in the right breast

on mammography or ultrasound, tissue sampling cannot be replaced.

Although both ER-positive/PR-negative/HER2-negative breast cancer and ER-negative/PR-negative/HER2-positive breast cancer were more likely to have associated micro-calcifications, this trend was more remarkable for ER-negative/PR-negative/HER2-positive cancers (41 versus 78%). Moreover, the cancers were frequently seen as non-mass lesions known as one of the ultrasound presentations of ductal carcinoma in situ (DCIS) [15–17], with statistical significance (P=0.0099). We speculate that this trend might have been because ER-negative/PR-negative/HER2-positive breast cancers were more often accompanied by DCIS, as was also similarly described in a previous report by Yang et al. [18]. However, a difference between the two studies exists. According to the study by Yang and colleagues, triple-negative breast cancers, HER2-positive breast cancers and ER-positive breast cancers presented as calcifications in 15, 67 and 61% of patients, respectively. Histologically, these

cancers were associated with DCIS in 18, 57 and 48% of patients respectively. Except for triple-negative breast cancers, the two other cancer subtypes showed similar profiles, compared with our results. We believe that this difference resulted from the fact that patients that showed both ER and HER2 positivity were included in the study by Yang et al. Therefore, we suspect that expression of HER2 may have had more of an influence on the radiological presentation of breast cancer.

Similar to our study, Wang et al. [19] compared the mammography and ultrasound findings of ER-negative/HER2-negative cancers with findings of ER-negative/HER2-positive cancers and concluded that ER-negative/HER2-positive breast cancers were likely to have spiculated margins and to be associated with calcifications. They found that lesion margin and presence of calcifications on images as well as the cancer stage at the time of diagnosis were significantly associated with HER2 status in patients with ER-negative breast cancer.

Yang et al. [18] insisted that the mammography finding of triple-negative breast cancer in their study, i.e. lack of mammographic calcifications, is concordant with a low incidence of associated DCIS in triple-negative breast cancers, which reflects biological differences that exist among breast cancer phenotypes and indicates that triple-negative breast cancer is a distinct clinical entity. According to these investigators, the combined mammographic and pathological features of triple-negative breast cancer suggest a more rapid pattern of carcinogenesis that leads directly to invasive cancer, with no major in situ component or precancerous stage.

Our study has the following limitations. First, we did not analyse the incidence of associated DCIS. Although our results agree with a previous study in which ER-negative/PR-negative/HER2-positive breast cancers were more frequently associated with microcalcification, our assumption that ER-negative/PR-negative/HER2-positive breast cancers frequently present with DCIS in contrast to triple-negative breast cancers may not be precise. Second, the number of patients with ER-positive/PR-negative/HER2-negative breast cancer and ER-negative/PR-negative/HER2-positive breast cancer was relatively small. Our assumption that the HER2 status has a greater influence on the radiological presentation compared with the influence of other receptors might be less persuasive. Third, we did not correlate with cancer stage at diagnosis, which might influence imaging features. In spite of these limitations, we showed that the tumour phenotype could be associated with particular imaging findings, which we speculate will have the potential to assist in the prediction of responsiveness to various therapies.

Conclusion

Combined mammography or ultrasound imaging findings of a non-calcified mass that is seen as a markedly hypoechoic mass with a circumscribed margin can be used to predict the presence of triple-negative breast cancer. Although a triple-negative breast cancer can mimic a lesion with a benign morphology, the mammography or ultrasound imaging recognition of triple-negative breast cancer can assist in both pretreatment planning and prognosis as well as adding to a greater understanding of the biological behaviour of the disease entity.

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