

## Sonographic Features of Triple-Negative Breast Cancer in an Asian Population

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### ABSTRACT

**Introduction:** Triple-negative breast cancer (TNBC) is well known for its unique clinical and pathological characteristics. Our study compared the sonographic features of TNBC with those of non-TNBC according to the sonographic classification system of the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS).

**Methods:** This was a retrospective study involving sonographic images from 50 patients with TNBC and 52 patients with non-TNBC diagnosed from 2016 to 2020, which were reviewed by two reviewers simultaneously according to the fifth edition of BI-RADS and a result was reached by consensus.

**Results:** TNBCs were significantly associated with higher tumour grade ( $p < 0.001$ ), higher tumour stage ( $p = 0.006$ ) and larger tumour size ( $p < 0.001$ ). Compared with non-TNBCs, TNBCs had a significantly higher incidence of the following features: oval or round shape ( $p = 0.006$ ), microlobulated margin ( $p = 0.006$ ), parallel orientation ( $p = 0.001$ ), posterior acoustic enhancement ( $p = 0.007$ ), and less architectural distortion ( $p < 0.001$ ).

**Conclusions:** TNBCs have their own distinct sonographic features compared with non-TNBCs. Clinicians should be alert to these features since they mimic a benign lesion but show aggressive clinical behaviours.

**Key Words:** Breast neoplasms; Triple negative breast cancer

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## 中文摘要

### 亞洲人群中三陰性乳腺癌的超聲特徵

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**引言：**三陰性乳腺癌（TNBC）有其獨特的臨床和病理特徵。我們的研究根據美國放射學會乳腺成像報告和數據系統比較TNBC與非TNBC的超聲特徵。

**方法：**這項回顧性研究納入2016年至2020年診斷的50例TNBC患者和52例非TNBC患者的超聲圖像，並由兩名醫生根據第5版乳腺成像報告和數據系統同時分析並達成共識。

**結果：**TNBC與更高腫瘤分級（ $p < 0.001$ ）、更高腫瘤分期（ $p = 0.006$ ）和腫瘤更大（ $p < 0.001$ ）顯著相關。與非TNBC相比，TNBC具有以下特徵的發生率顯著更高：橢圓形或圓形（ $p = 0.006$ ）、微分葉狀邊緣（ $p = 0.006$ ）、平行面向（ $p = 0.001$ ）、聲學後部增強（ $p = 0.007$ ）和更少的架構變形（ $p < 0.001$ ）。

**結論：**與非TNBC相比，TNBC有其獨特的超聲特徵。這些特徵類似良性病變但卻表現出侵襲性的生物學行為，因此臨床醫生應對這些超聲特徵保持警惕。

## INTRODUCTION

Triple-negative breast cancer (TNBC) is well known for its unique clinical, radiological and pathological characteristics. It refers to the distinct subtype of breast cancer where the three main breast cancer biomarkers, i.e., oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2), are absent.<sup>1</sup>

TNBC constitutes 10% to 20% of all newly diagnosed breast cancers. Affected patients tend to be younger at diagnosis than those with non-TNBC according to several population-based cohorts. The incidence of TNBC is also higher in African Americans.<sup>2,3</sup>

It is important to distinguish TNBC from other breast cancers because of its distinct clinical features, including aggressive tumour behaviour, higher potential for distant metastases, increased risk of distant recurrence, and consequent poorer prognosis.<sup>4</sup> On the contrary, TNBCs tend to share benign imaging features despite their aggressiveness. Their management options differ to those for other subtypes of breast cancer because of its lack of response to hormonal and targeted therapies but increased chemosensitivity.<sup>5-7</sup> Therefore, early detection of these lesions is essential.

Breast ultrasonography is the most common imaging for women with clinical or mammographically suspicious

breast lesions. It is particularly heavily relied on in young women and in Asians with dense breasts. Evaluation of breast lesions is standardised according to the sonographic classification system of the Breast Imaging Reporting and Data System (BI-RADS) of the American College of Radiology (ACR) that provides predefined terminology to describe dominant features of breast lesions.<sup>8</sup>

The main purpose of our study was to identify distinguishing sonographic features of TNBC compared with non-TNBC, as ultrasound is the main investigation applied in our local population with dense breasts. Various studies have described the unique radiological features of TNBC compared with non-TNBC<sup>9-18</sup> but with variable results. We performed this retrospective study to evaluate the sonographic features of TNBC according to BI-RADS's ultrasound classification and compare them with those of non-TNBC in an ethnically Asian population. We sought to determine whether the previously reported features of TNBC are applicable in our locality.

## METHODS

This is a single-centre retrospective study. Patients who attended the Department of Radiology, North District Hospital, New Territories, Hong Kong from 2016 to 2020 were reviewed.

## Patients

Patients were referred to the Department of Radiology of North District Hospital for imaging of specific breast-related complaints such as palpable breast mass, breast pain or suspicious mammographic findings. Sonographic examinations are performed as part of our routine practice and service of our breast imaging centre. All sonographically visible lesions with subsequent biopsy performed were documented in a centralised database within our department. We regularly performed follow-up and documented pathological results of all biopsied lesions. Non-TNBC was defined as a tumour with at least one of the three biomarkers (oestrogen receptor, progesterone receptor or HER2 receptor) positive. The most recent pathologically confirmed TNBC lesions (n = 50) and non-TNBC lesions (n = 52) were used for the study, dating back from July 2020. The included TNBC lesions had their diagnostic sonographic examination performed between January 2016 and May 2020, and non-TNBC lesions between April 2020 and July 2020. Lesions with incomplete information about receptor status were excluded.

## Sonography Examination

The sonographic examinations were performed by radiologists with at least 5 years' experience in breast imaging. All ultrasound examinations were performed with a GE Logiq E9 equipped with an ML6-15D linear transducer (6-15 MHz). All patients underwent bilateral whole breast and axillae sonography.

All lesions were evaluated by conventional ultrasound. All images were captured in two planes, along the longest axis of the lesion and orthogonal to it. Three dimensions of the lesion were measured along the longest axis, perpendicular to the first measurement, and from the view orthogonal to the first image. After ultrasound examination, all lesions with suspicious imaging features were subjected to ultrasound-guided biopsy, either in the same session or within the next 2 weeks. At least three cores of tissue were obtained from each lesion during the biopsy.

## Pathological Examinations

All pathological and immunohistochemical examinations were performed at the breast centre under North District Hospital.

Oestrogen receptor, progesterone receptor, and HER2 levels were determined by immunohistochemistry

according to a standardised institutional protocol. Additional fluorescence in situ hybridisation was performed to detect possible gene amplification and HER2 positivity with score  $\geq 2$ . Scores of 1 or 0 were defined as HER2 negative. Lesions with negative results for all tests were classified as TNBC. Histological grade was reported only in excisional surgical specimens.

## Image Analysis

Two reviewers with 3 years' and 4 years' experience in breast imaging reviewed images simultaneously on a picture archiving and communication system. Evaluation was based on the sonographic classification system of ACR BI-RADS Atlas Fifth Edition<sup>8</sup> and by consensus. The two reviewers were blinded to the pathology results.

## Statistical Analysis

Statistical analysis was performed using SPSS (Windows version 26.0; IBM Corp, Armonk [NY], United States). The Student's *t* test was used for continuous data and comparison of means. Sonographic features of TNBC and non-TNBC were compared by Pearson's Chi squared tests for categorical data. A statistical significance level of  $p < 0.05$  was used for all tests.

## RESULTS

### Demographic and Histopathological Findings

The results of demographic and histopathological findings are summarised in Table 1. The mean age of the subjects in the TNBC group and non-TNBC group was similar.

The mean tumour size represented by the largest dimension estimated by sonography was significantly larger in the TNBC group compared with the non-TNBC group (4.1 cm vs. 2.4 cm;  $p < 0.001$ ).

Regarding the tumour, node, and metastasis staging, the TNBC group had a significantly higher tumour (T) stage ( $p = 0.006$ ) and a tendency to higher nodal (N) stage ( $p = 0.07$ ) at diagnosis. There was no significant difference between the two groups in presence of distant metastases (M) [ $p = 0.717$ ]. Regarding the differentiation of the tumours, results were available for 36 TNBC (72%) and 30 (58%) non-TNBC lesions. TNBCs were more likely to be poorly differentiated (Grade 3) than non-TNBCs (42% vs. 13.5%;  $p < 0.001$ ). There was no significant difference between the two groups for histological subtype of breast cancer.

**Table 1.** Demographic and histopathological data for triple-negative and non-triple-negative breast cancer groups.\*

Characteristics		TNBC (n = 50)	Non-TNBC (n = 52)	p Value
Age, y		61.3 ± 13.9	63.8 ± 14.3	0.752
Estimated tumour size on sonography in maximal dimension, cm		4.1 ± 3.01	2.4 ± 1.86	<0.001
Tumour stage (T)	1	11 (22%)	19 (36.5%)	0.006
	2	17 (34%)	23 (44.2%)	
	3	12 (24%)	1 (1.9%)	
	4	10 (20%)	9 (17.3%)	
Nodal stage (N)	0	21 (42%)	29 (55.8%)	0.07
	1	18 (36%)	11 (21.2%)	
	2	6 (12%)	11 (21.2%)	
	3	5 (10%)	1 (1.9%)	
Metastases (M)	0	42 (84%)	45 (86.5%)	0.717
	1	8 (16%)	7 (13.5%)	
Grade <sup>†</sup>	1	1 (2%)	11 (21.2%)	<0.001
	2	14 (28%)	12 (23.1%)	
	3	21 (42%)	7 (13.5%)	
Tumour type	Invasive ductal	48 (96%)	45 (86.5%)	
	Invasive lobular	1 (2%)	5 (9.6%)	
	Other mixed	1 (2%)	2 (3.8%)	

Abbreviation: TNBC = triple-negative breast cancer.

\* Data are shown as mean ± standard deviation or No. (%), unless otherwise specified.

† Results of tumour grading are only available in 36 (72%) TNBC and 30 (58%) non-TNBC patients.

## Sonographic Features

The results of sonographic features of TNBC and non-TNBC groups are summarised in Table 2.

### Shape and Orientation

TNBCs were more likely than non-TNBCs to be oval (20% vs. 3.8%) or round (6% vs. 0%; Figure 1) [ $p = 0.006$ ], and of parallel orientation (92% vs. 63.5%;  $p = 0.001$ ).

### Margins

Lesions were classified as either circumscribed or non-circumscribed in margin. Circumscribed margin was defined as the presence of an abrupt line surrounding the entire lesion from the background parenchyma. If the lesion was non-circumscribed, its margin was further classified as indistinct, angular, microlobulated or spiculated.<sup>8</sup> There was a significantly higher incidence of microlobulated margins (40% vs. 9.6%) [Figures 2 to 4], and significantly lower incidence of indistinct (26% vs. 42.3%) and angular margins (26% vs. 42.3%) in TNBC group compared with non-TNBC group ( $p = 0.006$ ).

### Echo Pattern and Posterior Acoustic Features

TNBCs were more likely than non-TNBCs to be complex cystic and solid (16% vs. 1.9%;  $p = 0.042$ ) [Figure 5]

and heterogeneous (88% vs. 61.5%;  $p = 0.005$ ) in appearance. They were also more likely to have posterior acoustic enhancement (76% vs. 50%;  $p = 0.007$ ) and less posterior acoustic shadowing (6% vs. 25%;  $p = 0.008$ ).

### Architectural Distortion, Duct Changes and Skin Changes

Architectural distortion was less common in TNBC group (6% vs. 57.7%,  $p < 0.001$ ), but more ductal changes (22% vs. 5.8%,  $p = 0.017$ ) were observed. There was no significant difference in the presence of skin changes between the two groups.

### Vascularity, Calcification, and Elasticity Assessment

TNBCs tended to be more vascular than non-TNBCs, of which most showed internal vascularities (76% vs. 53.8%;  $p = 0.04$ ). There was a tendency for less calcification in TNBCs but the result was not significant (34% vs. 46.2%;  $p = 0.211$ ). Also, data for elastography were only available for four TNBC lesions and two non-TNBC lesions. All were stiff.

## DISCUSSION

The results of our study revealed that the patient's age at diagnosis for TNBC and non-TNBC was similar,

**Table 2.** Sonographic features of triple-negative and non-triple-negative breast cancer based on the sonographic classification system of American College of Radiology's BI-RADS® Atlas Fifth Edition.\*

Subgroup	TNBC (n = 50)	Non-TNBC (n = 52)	p Value
Shape			
Oval	10 (20%)	2 (3.8%)	0.006
Round	3 (6%)	0	
Irregular	37 (74%)	50 (96.2%)	
Orientation			
Parallel	46 (92%)	33 (63.5%)	0.001
Non-parallel	4 (8%)	19 (36.5%)	
Margin			
Circumscribed	1 (2%)	0	0.006
Indistinct	13 (26%)	22 (42.3%)	
Angular	13 (26%)	22 (42.3%)	
Microlobulated	20 (40%)	5 (9.6%)	
Spiculated	3 (6%)	3 (5.8%)	
Echo pattern			
Anechoic	0	0	0.042
Hyperechoic	0	0	
Complex cystic and solid	8 (16%)	1 (1.9%)	
Hypoechoic	42 (84%)	51 (98.1%)	
Isoechoic	0	0	
Heterogeneity			
Heterogeneous	44 (88%)	32 (61.5%)	0.005
Homogeneous	6 (12%)	20 (38.5%)	
Posterior features			
No posterior features	9 (18%)	13 (25%)	0.007
Enhancement	38 (76%)	26 (50%)	
Shadowing	3 (6%)	13 (25%)	0.008
Combined pattern	0	0	
Calcifications			
In a mass	17 (34%)	24 (46.2%)	0.211
Outside of a mass	0	0	
Architectural distortion	3 (6%)	30 (57.7%)	<0.001
Duct changes	11 (22%)	3 (5.8%)	0.017
Skin changes			
Skin thickening	30 (60%)	39 (75%)	0.137
Skin retraction	6 (12%)	16 (30.8%)	
Vascularity			
Absent	12 (24%)	24 (46.2%)	0.04
Internal vascularity	38 (76%)	28 (53.8%)	
Vessels in rim	0	1 (1.9%)	
Elasticity assessment			
Soft	0	0	
Intermediate	0	0	
Hard	4 (8%)	2 (3.8%)	

Abbreviation: TNBC = triple-negative breast cancer.

\* Data are shown as No. (%), unless otherwise specified.

although not statistically significant ( $p = 0.752$ ). This is contrary to previous studies in which TNBC patients were usually younger at diagnosis.<sup>10-13,17-19</sup> The difference could be due to the different ethnicity of subjects, i.e., only Asians were included in our study. The tumour (T) stage and histological grade were both higher in TNBC group with a tendency towards higher nodal (N) stage,

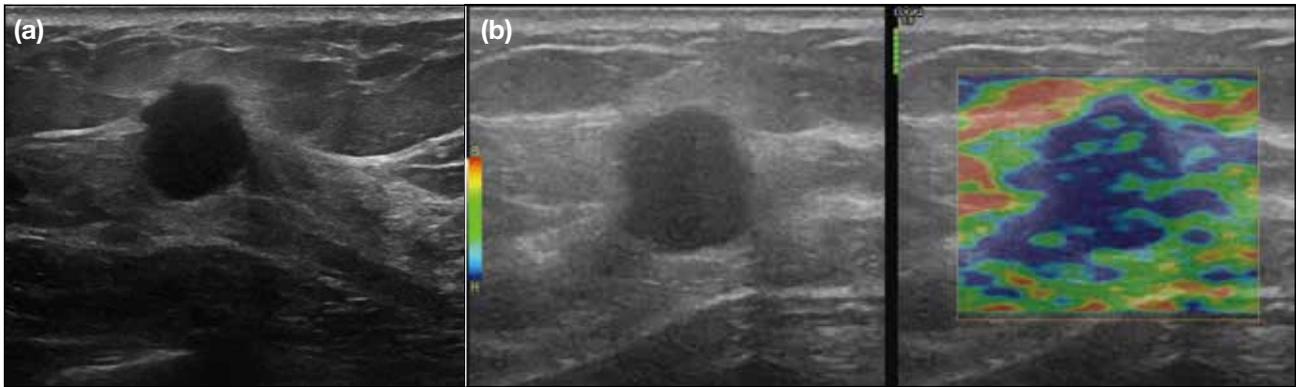
suggesting more aggressive disease at diagnosis. Early detection of this aggressive subtype of breast cancer therefore has an important prognostic implication. Accurate sonographic detection and subsequent guided biopsy are vital to early tumour identification.

Previous meta-analyses<sup>19</sup> have shown that TNBC lacks the typical malignant sonographic features of breast cancer, including features of irregular shape, non-circumscribed margin, non-parallel orientation, posterior acoustic shadowing, and microcalcification (Figures 6 to 8).

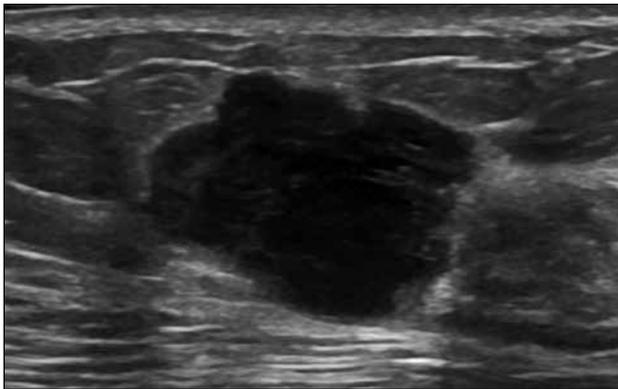
In our study, TNBCs were significantly more likely to be parallel in orientation, associated with posterior acoustic enhancement and with a lack of architectural distortion compared with non-TNBC breast cancers. Although similar to non-TNBCs in that both subtypes of cancers are most commonly irregular in shape, the prevalence of oval or round shape was still higher in TNBC group than non-TNBC group (Table 2 and Figure 1). This is in concordance with previous studies.<sup>9-13,15-17,20</sup> The above sonographic features are usually regarded as benign features in ACR BI-RADS, in contrast to the aggressive nature of this subtype of tumour. The relatively benign sonographic appearance of TNBC can probably be explained by their rapid cellular proliferation and therefore reduced likelihood of sufficient time to induce stromal reactions,<sup>20</sup> with a consequent typical growth pattern of a 'pushing border' in the absence of infiltration.

Fortunately, there are distinctive features that allow TNBC to be differentiated from benign lesions such as fibroadenoma. In our study, the incidence of a circumscribed appearance in TNBC was lower than that reported elsewhere.<sup>20</sup> The sonographic features of margin were diverse and included microlobulated, indistinct, angular and spiculated, of which the incidence of microlobulated margins was highest (Figures 2 to 4). This is in accordance with some previous studies<sup>10,11,15</sup> although others also reported ill-defined margin as the most commonly occurring margin.<sup>20</sup> The microlobulated margin is a useful sonographic feature to distinguish TNBC from benign lesions, and this appearance is again explained by the pushing margin phenomenon.

TNBC has a significantly more heterogeneous echo pattern than non-TNBC. This could be partially explained by the larger size of TNBC lesions in our cohort, where lesion matrix could be more easily evaluated than in smaller-sized non-TNBC lesions that usually appear



**Figure 1.** (a) Triple-negative breast cancer (invasive ductal carcinomas) in a 55-year-old woman. The tumour is round with a microlobulated margin and posterior acoustic enhancement. Note the absence of architectural distortion and calcification. (b) Elastography of the same lesion demonstrates the stiffness of the lesion in relation to background breast parenchyma.

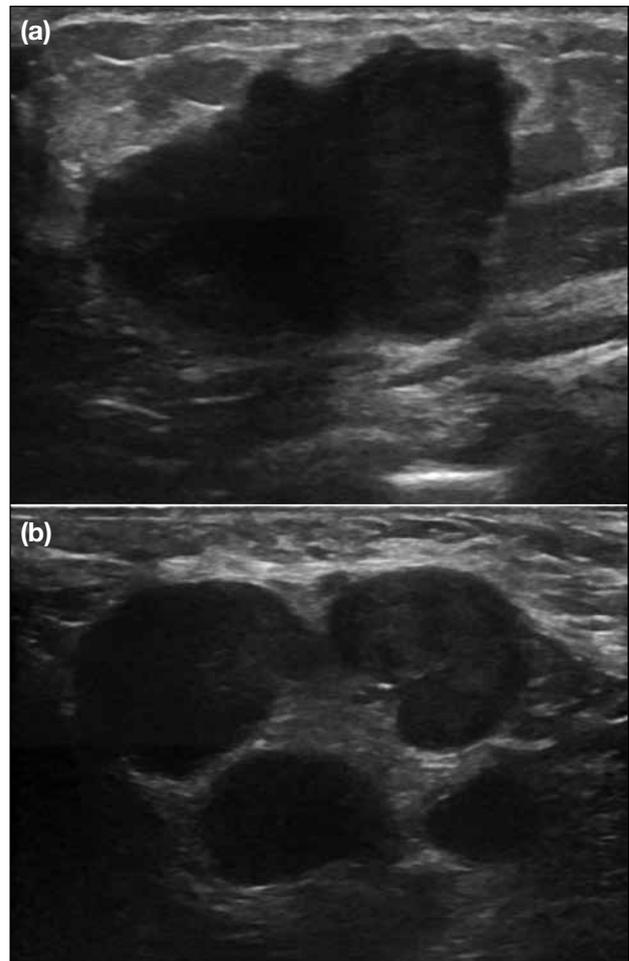


**Figure 2.** Triple-negative breast cancer in a 53-year-old woman. It is oval with microlobulated margin and heterogeneous echogenicity. Anechoic cystic areas with posterior acoustic enhancement are noted.

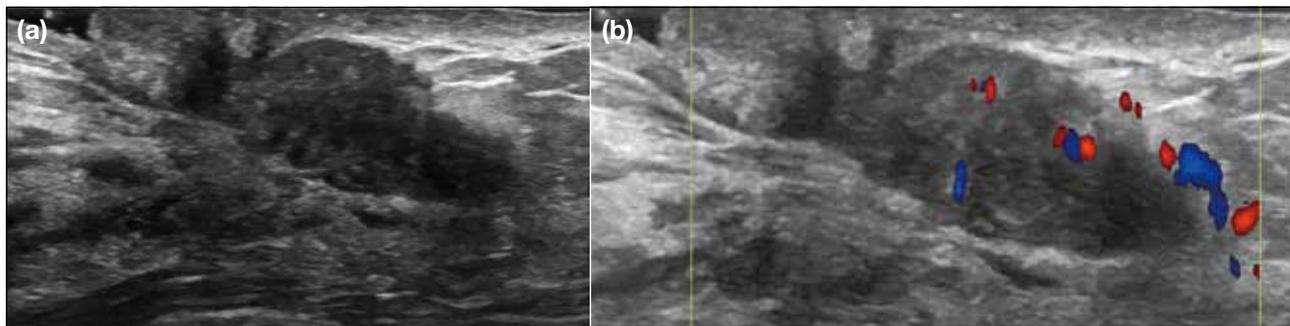
homogeneous in echogenicity at their early stage. For the same reason, a significantly higher incidence of intralesional vascularity on Doppler ultrasound could be identified in the larger-sized TNBC lesions than the non-TNBC lesions.

There were also significantly more TNBC lesions that were complex cystic and solid in echo pattern (Figure 5). This could be due to a higher tumour grade with more necrosis and thus fluid in the lesion. The same phenomenon also accounts for the increased incidence of posterior acoustic enhancement in TNBC.<sup>21</sup>

Similar to other studies, although the incidence of calcification was lower in TNBC group than non-TNBC group in this cohort, it was not a rare feature in either and the difference was not statistically significant (Table 2 and Figure 8).<sup>11,13,16</sup> The pathological basis of



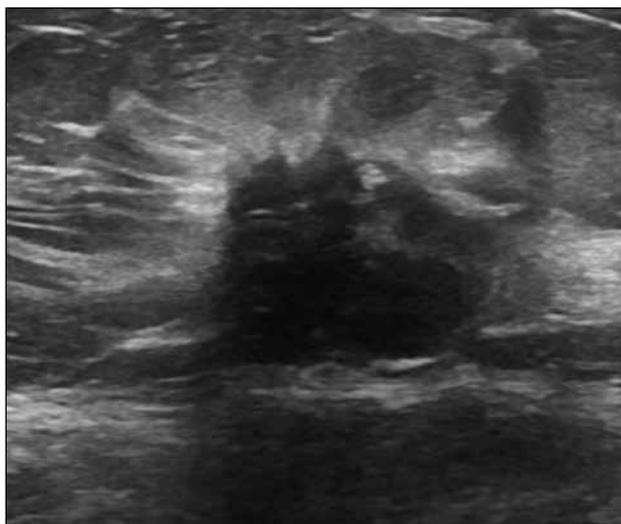
**Figure 3.** (a) Biopsy-proven triple-negative breast cancer in a 64-year-old woman. Microlobulated lesion with posterior acoustic enhancement was noted. (b) Cluster of enlarged ipsilateral axilla nodes with loss of hilar architecture suggestive of nodal metastases in the same patient.



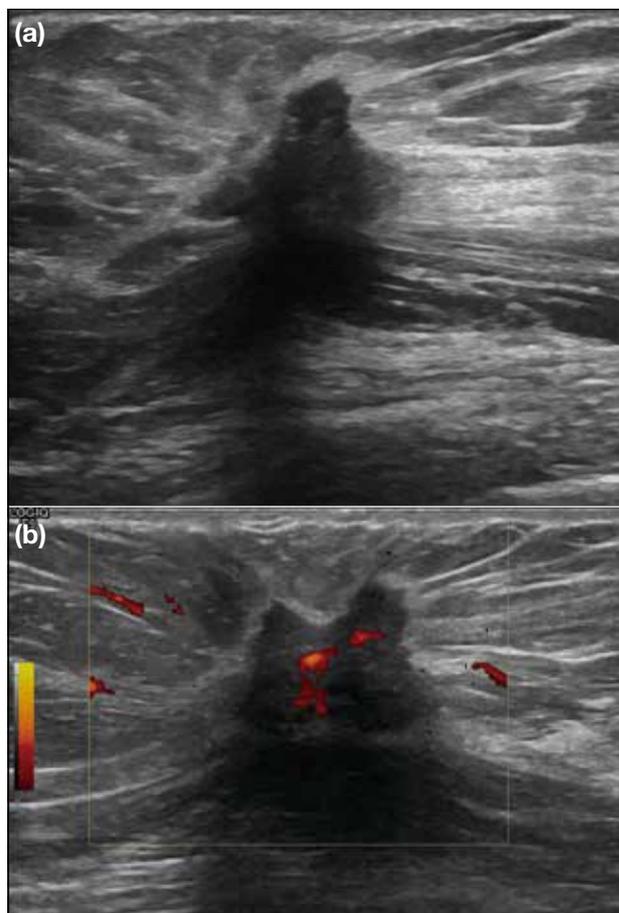
**Figure 4.** (a) Biopsy-proven triple-negative breast cancer in a 59-year-old woman. Subareolar parallel lesion with a microlobulated margin was noted. (b) Doppler study of the same lesion showing moderate intralesional and peripheral vascularity.



**Figure 5.** Complex cystic mass in a 77-year-old woman with biopsy-confirmed triple-negative breast cancer. Note the thick wall of this cystic lesion and fluid content with internal echoes.



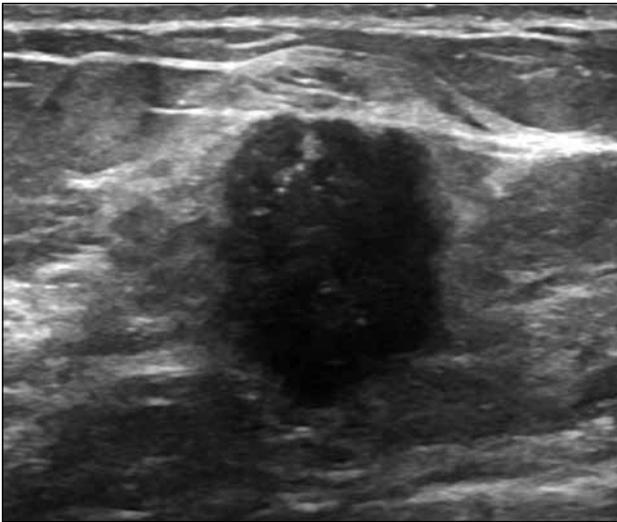
**Figure 6.** Oestrogen receptor positive invasive lobular carcinoma in a 63-year-old woman. The margins are spiculated and associated with architectural distortion.



**Figure 7.** (a) Oestrogen and progesterone receptor positive invasive ductal carcinoma in a 70-year-old woman. The lesion is non-parallel with angular margins and associated with architectural distortion. Posterior acoustic shadowing is demonstrated. (b) Doppler study of the same lesion showing moderate intralesional vascularity, angular margin, and posterior acoustic shadowing.

microcalcification is partial necrosis and local ischaemia. Nonetheless sonography is not the most optimal tool to evaluate the presence and morphology of calcifications.

These features are better seen on complementary mammography. Calcification is not a useful feature to distinguish between TNBC and non-TNBC.



**Figure 8.** Oestrogen receptor positive invasive ductal carcinoma in a 68-year-old woman. The lesion is non-parallel with internal calcification. The margins are indistinct.

We observed a higher incidence of duct distension in TNBC lesions. This feature has not been reported or evaluated in previous studies. In our cohort, the size of TNBC lesions associated with duct distension was not significantly different to those without duct distension (mean diameter 3.26 cm and 4.31 cm for TNBC and non-TNBC groups, respectively). Further studies will evaluate the relationship between TNBC and duct changes.

### Limitations of Our Study

Our study was limited by the relatively small sample size. It was a retrospective study and therefore some parameters were not measured or documented during examination (e.g., elastography), limiting full evaluation and comprehensive comparison. The ultrasound images were evaluated by consensus reading by two reviewers and therefore inter-observer agreement was not assessed. Further prospective studies with larger sample size and evaluation by individual observers may aid in arriving at more consistent and significant results.

### CONCLUSIONS

TNBC has its own distinct sonographic features, enabling it to be distinguished from its non-TNBC counterparts. Most of our findings from our local population echoed those of previous studies. By identifying the distinguishing sonographic features of

TNBC, radiologists can be alerted to the need for early biopsy when these features are encountered and reach a definitive diagnosis.

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