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ORIGINAL PAPER

Mammographic and ultrasonographic features of triple-negative breast cancer compared with non-triple-negative breast cancer

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Abstract

Objective To evaluate and compare the mammographic and ultrasonographic features of TNBC with non-TNBC.

Methods A retrospective review of 193 invasive breast cancer patients (TNBC = 32 and non-TNBC = 161) was collected from January 2014 to June 2019. The imaging features were reviewed according to the 5th edition of the American College of Radiology Breast Imaging Reporting and Data System lexicon. We used the student *t*-test, Mann–Whitney *U* test, and Fisher's exact test for statistical analyses.

Results Mass without calcifications was the most mammographic feature of TNBC (22 of 32, 68.8%) and more commonly found in TNBC than in non-TNBC ($p = 0.007$). The irregular shape (19 of 28, 67.9%) and indistinct margin (10 of 28, 35.7%) were the most common findings in the TNBC group. However, TNBC lesions appeared as round or oval shape and micro-lobulated margin more frequently than non–TNBC lesions ($p < 0.001$). Additionally, the tumor size and histological grade of TNBC were significantly higher than non-TNBC ($p < 0.001$).

Conclusion TNBC has distinct imaging features compared to non-TNBC. The imaging features on mammography combined with ultrasonography can be used to detect and differentiate this subtype from other breast cancers.

Keywords Breast cancer · Triple-negative · Mammography · Ultrasonography · Imaging features

Introduction

Breast cancer comprises different histopathological and biological features; each exhibits distinct behaviors, and treatment responses result in various therapeutic approaches [1, 2]. Determination of the immunohistochemistry (IHC) markers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) is essential for therapeutic decision making and prognosis of breast cancer because ER and PR status are considered together as decisive positive predictive factors for targeted hormone therapy response. In contrast, HER2 positivity is used for selecting targeted therapy with monoclonal antibodies against HER2 [1–3].

Triple-negative breast cancer (TNBC) is a distinctive subtype of breast cancer that does not express ER, PR, and HER2. This subtype constitutes 15–20% of all breast cancers and has the worst prognosis among all subtypes because of its aggressive tumor biology, mutation of the TP53 gene, and a high degree of correlation with suppressed BRCA1 function [3–5]. Due to the absence of effective targeted therapy, chemotherapy is currently the main systemic treatment option in TNBC [6–8]. However, some studies have identified specific receptors as targets for new therapeutic strategies to improve the survival rate of patients [9, 10].

Therefore, the ability to predict the presence of TNBC based on mammography combine with ultrasonography, which is an available reference standard diagnostic modality for breast cancer evaluation [11, 12], would lead to rapid pretreatment planning and improve clinical outcomes. Several previous studies reported on the aggressive clinical characteristics and significant imaging features of TNBC [13–19], however, most of the studies either evaluated only one imaging modality or did not compare both

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mammographic and ultrasonographic features of TNBC with those of all non-TNBC.

The aim of this retrospective study thus to identify the imaging features of TNBC using information obtained from mammography and ultrasound according to the 5th edition of the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) lexicon and compare the imaging features of TNBC with those of non-TNBC.

Materials and methods

Study population

We conducted a retrospective review of 254 Thai women diagnosed with invasive breast cancer at Thammasat University Hospital from January 2014 to June 2019. All lesions were confirmed by histopathological samples obtained either surgery or biopsy and available images on Picture Archiving and Communication System (PACS) of Thammasat University Hospital.

Of the initial 254 patients with invasive breast cancer, 61 were excluded from our study for the following reasons: patients had a history of breast cancer and received neoadjuvant chemotherapy ($n=13$), no complete both mammographic and ultrasonographic imaging at our institution ($n=11$), and no molecular data for all three biologic markers: ER, PR, and HER2 ($n=37$). Finally, a total of 193 patients were included in our study. TNBC has found 32 cases, and non-TNBC has seen 161 cases. For 161 cases of non-TNBC, 35 cases were luminal A tumors, 111 cases were luminal B tumors, and 15 cases were HER2-enriched tumors.

Ethical approval

The study was approved by the human ethics committee of Thammasat University Hospital.

Mammography technique

Two standard imaging views (craniocaudal and mediolateral oblique views) were performed, with additional views if necessary, using digital technique Lorad Selenia (Hologic) for all patients in our institution.

Ultrasonography technique

The sonographic examinations were performed by radiologists after mammographic evaluation in all cases at our institution, using a Samsung RS80A equipped with an L3-12A linear transducer (3–12 MHz, 5.0 cm), or a Philips IU22 equipped with an L12-5 linear transducer (5–12 MHz, 5.0 cm). The breast imaging protocol in our institution includes measurement and documentation of tumor size at least two planes (the longest diameter of the tumor and the perpendicular plane to the longest diameter) and using Doppler ultrasound for all lesions. In addition, strain elastography was performed in some cases.

Data collection

The patient's clinical information was retrieved from electronic medical records, including age at diagnosis, clinical presentation (palpable mass, breast pain, nipple discharge, or screening), and histologic tumor grade at diagnosis (using Scarff-Bloom-Richardson grading system). Imaging features on mammography and ultrasonography were retrieved retrospectively from PACS and reviewed before analysis. All data were collected in the case record form.

Imaging interpretation

Two radiologists independently reviewed the images with 10 and 11 years of experience in breast imaging. Both reviewers were blinded to the clinical information and the histopathologic result. In cases with discrepant results, a final consensus was reached after discussion.

For image interpretation, we used the morphologic criteria described for mammography and ultrasonography according to the 5th edition of the ACR BI-RADS lexicon. The following mammographic features were identified: (a) breast density which was classified as almost entirely fat, scattered areas of fibroglandular density, heterogeneously dense, or extremely dense; (b) the presence of a lesion, which was classified as a mass without calcifications, mass with calcifications, suspicious calcifications only, others (focal asymmetry and architectural distortion), or negative; (c) mass shape which was classified as round, oval, or irregular; and (d) mass margin which was classified as circumscribed, obscured, microlobulated, indistinct, or spiculated.

The following ultrasonographic features of lesions were identified: (a) mass shape, which was classified as round, oval, or irregular; (b) mass margin, which was classified as circumscribed, angular, microlobulated, indistinct, spiculated, or combined margin (i.e., having both angular and microlobulated margins); (c) orientation of lesions when referencing to the skin surface which was classified as parallel, or not parallel; (d) echogenicity which was classified as anechoic, hyperechoic, complex cystic and solid, hypoechoic, isoechoic, or heterogeneous; (e) posterior acoustic features which were classified as no posterior acoustic features, enhancement, shadowing, or combined pattern; (f) vascularity which was classified as absent, internal vascularity, or

vessels in the rim; (g) size (the longest diameter) which was re-measured by reviewers; and (h) elastography (using strain ratio) which was available in 18 patients in TNBC group and 96 patients in the non-TNBC group.

Histopathological analysis

Histologic tumor grade was retrieved from the patient's pathology reports and classified as grade 1, 2, or 3 using the Scarff-Bloom-Richardson grading system. Immunohistochemical staining for all three biologic markers (ER, PR, and HER2) was performed by standard methods. HER2 negativity was defined as 0 or 1 positive at immunohistochemical straining or two positives at immunohistochemical straining without amplification by fluorescence in situ hybridization. Conversely, a score of 3 positive at immunohistochemical straining or amplification by fluorescence in situ hybridization was defined as HER2 positivity.

Statistical analysis

The descriptive statistics were reported with means and SDs for normally distributed continuous data, or medians and ranges for non-normally distributed continuous data, and counts and percentages for categorical data. To compare the clinicopathological characteristics and the imaging features between TNBC and non-TNBC, we used the Student t-test for the normally distributed continuous data or Mann–Whitney *U* test for the non-normally distributed continuous data and Fisher's exact test for the categorical data. All statistical analyses were performed with STATA software (version 14.0; Stata Corp, College Station, TX), with $p < 0.05$ considered to indicate a significant difference.

Results

Clinicopathological characteristics

Data of clinicopathological characteristics of patients with TNBC and non- TNBC were listed in Table 1. The mean ages of patients had no statistically significant differences between the groups ($p = 0.745$). The mean ages of the patients with TNBC were 56.7 years (range 33–88 years), and the mean ages of the patients with non-TNBC were 57.4 years (range 35–82 years).

There were no statistically significant differences between the groups regarding the clinical presentation ($p = 1.000$). Most patients presented with palpable mass: 29 of 32 (90.6%) for TNBC and 140 of 161 (87.0%) for non-TNBC. For comparison of histologic tumor grade between the groups, the TNBC tumors were a higher grade than the non-TNBC tumors (high-grade tumor (grade 3): 23 of 32 [71.9%] vs. 30 of 161 [18.6%], respectively; $p < 0.001$).

Table 1 Clinicopathological characteristics

Characteristics	TNBC ($n = 32$)	Non-TNBC ($n = 161$)	p value
Age (years)			
Mean (SD)	56.7 (12.26)	57.4 (10.79)	0.745
Range	33–88	35–82	
Clinical presentation, *n* (%)			
Palpable mass	29 (90.6)	140 (87.0)	1.000
Breast pain	0 (0.0)	3 (1.9)	
Screening	3 (9.4)	18 (11.2)	
Histologic tumor grade, *n* (%)			
Grade 1	0 (0.0)	42 (26.1)	<0.001
Grade 2	9 (28.1)	89 (55.3)	
Grade 3	23 (71.9)	30 (18.6)	

Mammographic features

A comparison of mammographic features of TNBC and non-TNBC was summarized in Table 2. There were no statisticall y significant differences in patients' breast density between the groups ($p = 0.672$). However, the heterogeneously dense breast was the most breast density of both groups. Mass without calcifications was the most imaging feature of TNBC (22 of 32, 68.8%) and followed by mass with calcifications (6 of 32, 18.8%). Moreover, mass without calcifications was more commonly found in TNBC than in non-TNBC, significantly (22 of 32 [68.8%] vs. 68 of 161 [42.2%], respectively; $p = 0.007$) (Figs. 1A and 2A). For all 6 cases of mass with calcifications in TNBC, four patients showed a mass with internal pleomorphic microcalcifications (Fig. 3), 1 case showed a mass with internal coarse calcifications, and 1 case showed mass associated with segmental pleomorphic microcalcifications in the same quadrant. Non–TNBC lesions were more equally divided between masses with calcifications (77 of 161, 47.8%) and masses without calcifications (68 of 161, 42.2%). The remaining categories (suspicious calcifications only, others, and negative) were relatively rare in both groups (Fig. 4). For mass shape, TNBC lesions were round or oval more frequently than non–TNBC mass lesions ($p < 0.001$) (Fig. 2A). However, the mass shape in both groups was most commonly irregular (19 of 28 [67.9%] for TNBC, and 135 of 145 [83.9%] for non-TNBC) (Figs. 2A, 3, 5A, and 6A). On review of the mass margin on mammography, TNBC masses had microlobulated, obscured, or circumscribed margin more frequently than non–TNBC masses ($p < 0.001$) (Figs. 1A and 5A). However, the most common margin of TNBC mass lesions was indistinct (10 of 28, 35.7%) (Fig. 2A). In contrast, the most common mass margin of non-TNBC lesions

Table 2 Mammographic features

Mammographic features	TNBC ($n=32$)	Non-TNBC ($n=161$)	p value
Breast density, n (%)			0.672
Almost entirely fat	2 (6.3)	5 (3.1)	
Scattered areas	8 (25.0)	33 (20.5)	
Heterogeneously dense	15 (46.9)	82 (50.9)	
Extremely dense	7 (21.9)	41 (25.5)	
The presence of lesion, n (%)			0.007
Mass without calcifications	22 (68.8)	68 (42.2)	
Mass with calcifications	6 (18.8)	77 (47.8)	
Suspicious calcifications only	0 (0.0)	3 (1.9)	
Others[a]	2 (6.3)	11 (6.8)	
Negative	2 (6.3)	2 (1.2)	
Mass shape[b], n (%)			< 0.001
Round	4 (14.3)	1 (0.6)	
Oval	5 (17.9)	9 (5.6)	
Irregular	19 (67.9)	135 (83.9)	
Mass margin[b], n (%)			< 0.001
Circumscribed	2 (7.1)	1 (0.6)	
Obscured	5 (17.9)	4 (2.8)	
Microlobulated	6 (21.4)	7 (4.8)	
Indistinct	10 (35.7)	61 (42.1)	
Spiculated	5 (17.9)	72 (49.7)	

[a]Others included focal asymmetry and architectural distortion

[b]For mass-like lesions only (TNBC: n = 28; Non-TNBC: n = 145)

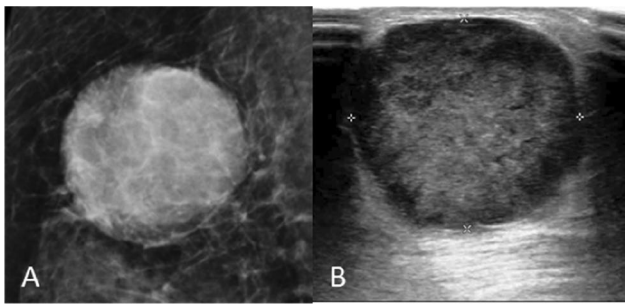

Fig. 1 A 70-year-old female with TNBC presents with a right breast mass. **A** Mammogram shows a round mass with circumscribed margin, and no calcifications. **B** Ultrasound image shows a round heterogeneous mass with circumscribed margin and posterior acoustic enhancement

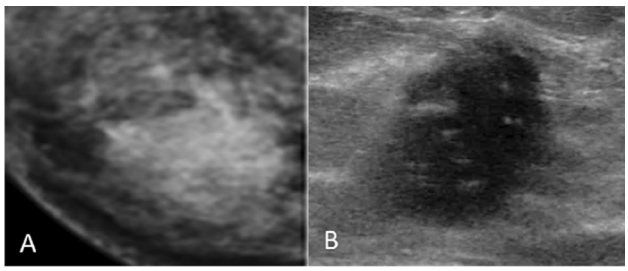

Fig. 2 A 59-year-old female with TNBC presents with a right breast mass. **A** Mammogram shows an irregular mass with indistinct margin, and no calcifications. **B** Ultrasound image shows an irregular hypoechoic mass with indistinct margin and non-parallel to skin

was spiculated margin, which was found significantly more than TNBC lesions (72 of 145 [49.7%] for non-TNBC vs. 5 of 28 [17.9%] for TNBC, $p < 0.001$) (Figs. 6A).

Ultrasonographic features

A comparison of ultrasonographic features of TNBC and non-TNBC was summarized in Table 3. The mass shape on ultrasound images was consistent with the results of mammographic features. Round and oval shapes were more often in TNBC than in non–TNBC ($p = 0.001$) (Fig. 1B). And the mass shape of both groups was most commonly irregular (Figs. 2B, 5B, and 6B). For mass margin, TNBC had microlobulated, circumscribed, or angular margin more frequently than non–TNBC ($p < 0.001$) (Figs. 1B and 5B). In contrast, the mass margin of non–TNBC lesions were more commonly spiculated and was found in non-TNBC more than in TNBC (75 of 161 [46.6%] vs. 6 of 32 [18.8%], respectively) (Fig. 6B). The most posterior acoustic feature of TNBC was enhancing that was more often than non-TNBC (11 of 32 [34.4%] vs. 8 of 161 [5.0%], respectively; $p < 0.001$) (Figs. 1B and

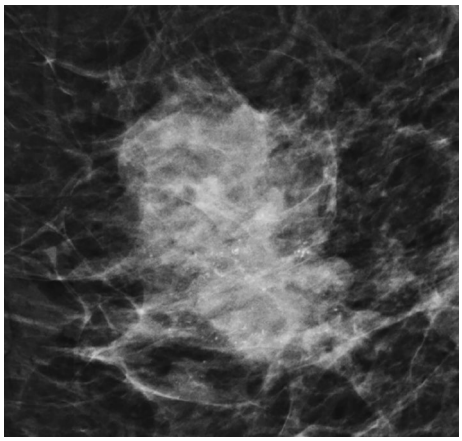

Fig. 3 A 61-year-old female with TNBC presents with a right breast mass. Mammogram shows an irregular mass with internal pleomorphic microcalcifications

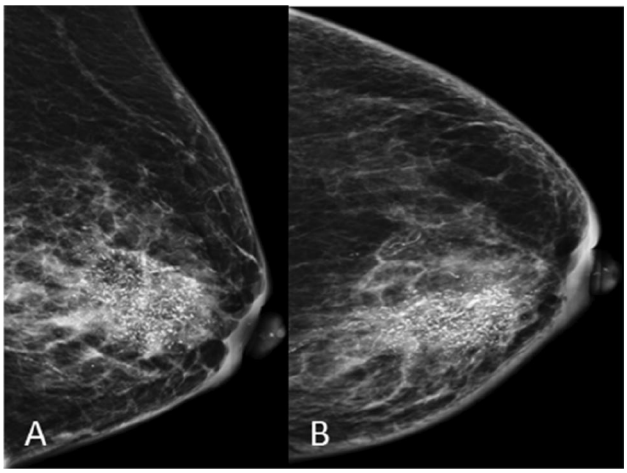

Fig. 4 An 88-year-old female with TNBC presents with a left breast mass. **A** Mediolateral oblique and **B** craniocaudal mammograms of the left breast show focal asymmetry in the mid-inner region associated with segmental distribution of fine linear branching and coarse heterogeneous calcifications

5B). Moreover, TNBC showed posterior acoustic shadowing significantly less frequently than non–TNBC (7 of 32 [21.9%] vs 80 of 161 [49.7%], respectively; $p < 0.001$) (Fig. 6C). The mean tumor size was significantly larger in the TNBC compare to the non–TNBC (33 mm, [range 14–53] vs. 22 mm [range 5–49], respectively; $p < 0.001$).

There were no statistically significant differences between the groups in terms of orientation of lesions ($p = 0.154$), echogenicity ($p = 0.187$), vascularity ($p = 0.800$), and strain ratio of elastography ($p = 0.532$).

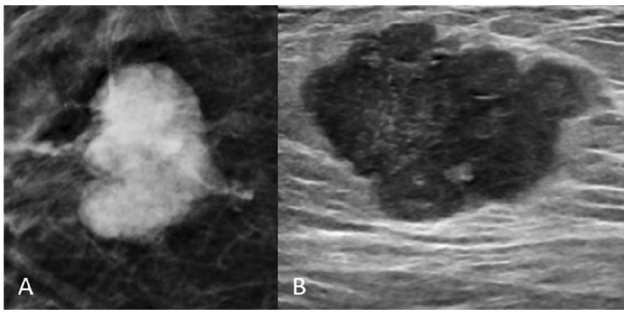

Fig. 5 A 65-year-old female with TNBC presents with a right breast mass. **A** Mammogram shows an irregular mass with microlobulated margin, and no calcifications. **B** Ultrasound image shows an irregular hypoechoic mass with microlobulated margin and posterior acoustic enhancement

Discussion

Although TNBC is a relatively small proportion of breast cancer, this subtype has a high malignancy potential and the worst prognosis. Therefore, the ability to differentiate this subtype from the other subtypes of breast cancer based on imaging features is clinically valuable. According to the previous studies [13–19], TNBC was high-grade breast cancer. In our research, TNBC tumors were significantly higher grade than non-TNBC tumors ($p < 0.001$): most TNBC tumors showed high histological grade (grade 3, 71.9%), and the remaining TNBC tumors showed intermediate histological grade (grade 2, 28.1%). Regarding the clinical presentation of patients with TNBC, our results support the studies of Krizmanich-Conniff et al. [16] and Boisserie-Lacroix et al. [17], which reported that patients with TNBC were more likely to be detected clinically than screening mammography. In our study, the mean age of patients with TNBC was 56.7 ± 12.26 years which no statistically significant differences in comparison with non-TNBC (57.4 ± 10.79 years; $p = 0.745$), while the studies of Wojcinski et al. [15] and Krizmanich-Conniff et al. [16] found that TNBC tended to be occurred in younger women compared with non-TNBC. This inconsistent result may be explained by a small population and the late presentation of patients with TNBC in our study, causing a lack of statistical power.

On mammography, the results of our study confirmed findings from most of the previous studies [14, 17–20] that mass without calcifications was the most imaging feature of TNBC and was more commonly found in TNBC than in non-TNBC ($p = 0.007$). Yang et al. [13] and Ko et al. [19] suggested that TNBC tumors had a more rapid pattern of carcinogenesis that leads directly to invasive cancer, with no major in situ component or precancerous stage. Additionally, our study showed the negative result on mammography was more frequently observed in TNBC (6.3%) than in non-TNBC (1.2%) that is probably due to rapid growth

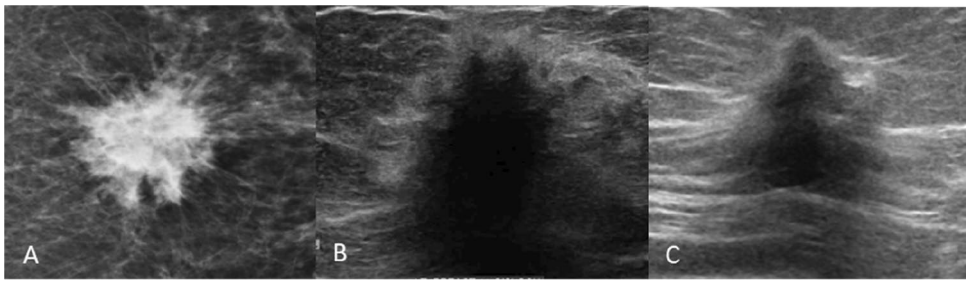

Fig. 6 A 64-year-old female with non-TNBC (luminal B tumor) presents with a left breast mass. **A** Mammogram shows an irregular mass with spiculated margin, and no calcifications. **B** and **C** Ultrasound images show an irregular and marked hypoechoic mass with spiculated margin, posterior acoustic shadowing and non-parallel to skin

of TNBC cause of lack of desmoplastic reaction to create architectural distortion.

TNBC mass lesions were most commonly irregular shape and indistinct margin in our study. These results are consistent with the study of Krizmanich-Conniff et al. [16]. TNBC lesions also had higher number of round or oval shape than non-TNBC. They had microlobulated margin significantly more frequently than non–TNBC lesions ($p \leq 0.001$), which correspond to the study of Boisserie-Lacroix et al. [17]. These results can be explained pathologically by the growth pattern of TNBC, which is described as a "pushing border" in the absence or little of desmoplastic stromal response and infiltrative process [20, 21].

On ultrasonography, our study revealed the presence of posterior acoustic enhancement and the absence of posterior acoustic shadowing in TNBC were significantly more often than in non-TNBC ($p < 0.001$). These results corresponded to the study of Wojcinski et al. [15]. Posterior acoustic enhancement is typically encountered in benign lesions such as fibroadenoma, simple or complicated cyst, or abscess; however, it may also indicate tumor necrosis which is frequently reported on the pathological assessment of TNBC [22]. For tumor size, our study confirmed the studies of Wojcinski et al. [15] and Krizmanich-Conniff et al. [16] that TNBC lesions were significantly larger than non-TNBC lesions ($p < 0.001$).

Our study showed no statistically significant differences between TNBC and non-TNBC in terms of breast density, orientation, and strain ratio of echogenicity. The results were similar to the previous studies [13, 15, 16]. The vascularity in our study had no significant differences between the groups; however, only a few earlier studies with a small number of cases reported discrepant results [14, 17]. For the strain ratio of elastography, there were no statistically significant differences between the groups in our study; however, we had relatively small data for interpretation.

Limitations

There are some limitations to this study. First, this study was performed retrospectively at a single institution with a relatively small population size. Second, some cases were excluded from this study due to imaging was performed from other institutions, and elastography data were not available in all cases.

Thus, although we can show significant differences for some imaging features of TNBC and non-TNBC, we suggest that multicenter clinical trials or a larger population size will be needed to validate the statistically significant differences.

Conclusion

TNBC has distinct imaging features of both mammography and ultrasonography compared to non-TNBC. So these imaging results can be used for early detection and differentiate TNBC subtype from other subtypes of breast cancer. The ability to predict the presence of TNBC based on imaging features should lead to rapid pretreatment planning and improve clinical outcomes.

Table 3 Ultrasonographic features

Ultrasonographic features	TNBC ($n=32$)	Non-TNBC ($n=161$)	p value
Mass shape, n (%)			0.001
Round	4 (12.5)	2 (1.2)	
Oval	5 (15.6)	9 (5.6)	
Irregular	23 (71.9)	150 (93.2)	
Mass margin, n (%)			< 0.001
Circumscribed	3 (9.4)	0 (0.0)	
Angular	2 (6.3)	3 (1.9)	
Microlobulated	9 (28.1)	20 (12.4)	
Indistinct	11 (34.4)	57 (35.4)	
Spiculated	6 (18.8)	75 (46.6)	
Combined[a]	1 (3.1)	6 (3.7)	
Orientation, *n* (%)			0.154
Parallel	7 (21.9)	19 (11.8)	
Not parallel	25 (78.1)	142 (88.2)	
Echogenicity, *n* (%)			0.187
Anechoic	0 (0.0)	0 (0.0)	
Hyperechoic	0 (0.0)	0 (0.0)	
Complex cystic and solid	3 (9.4)	3 (1.9)	
Hypoechoic	22 (68.8)	120 (74.5)	
Isoechoic	0 (0.0)	3 (1.9)	
Heterogeneous	7 (21.9)	35 (21.7)	
Posterior acoustic features, *n* (%)			< 0.001
No features	6 (18.8)	25 (15.5)	
Enhancement	11 (34.4)	8 (5.0)	
Shadowing	7 (21.9)	80 (49.7)	
Combined pattern	8 (25.0)	48 (29.8)	
Vascularity, *n* (%)			0.800
Absent	3 (9.4)	24 (14.9)	
Internal vascularity	23 (71.9)	108 (67.1)	
Vessels in rim	6 (18.8)	29 (18.0)	
Size (mm)			< 0.001
Mean (SD)	33 (11.56)	22 (10.22)	
Range	14–53	5–49	
Strain ratio of elastography[b],			0.532
Median	2.36	2.48	
Range	0.83–6.82	0.97–9.58	

[a]Combined margin was described as having both angular and microlobulated margins

[b]For available data (TNBC: $n=18$; Non-TNBC: $n=96$)

Author contributions LW made contributions in literatures search, study design, data interpretation, draft writing, critical revision and final approval of the final version for submitted. PN made contributions in literatures search, data collection, data analysis and interpretation and KA made contributions in draft writing, critical revision and also faculty collaborations.

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Availability of data and material The data that support the findings of this study are available from Thammasat University Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Faculty of Medicine, Thammasat University and the Thammasat University Hospital.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval and consent to participate The study was approved by the human ethics committee of Thammasat University (MTU-EC-RA-0-245/62) and waived the requirement for inform consent due to the retrospective nature of the study.

Consent for publication Not applicable. This study didn't contain any individual personal's data.

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