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Role of ultrasound in predicting the molecular subtypes of invasive breast ductal carcinoma

Lamiaa M. R. Khalaf^{1*} and Rania A. Herdan²

Abstract

Background: Breast cancer is a heterogeneous disease that was explained recently by the presence of multiple molecular subtypes. These subtypes are the luminal A (LA), luminal B (LB), human epidermal growth factor receptor 2 (HER2), and triple-negative (TN). In this study, we aim to investigate whether ultrasound imaging features can play a role in predicting the molecular subtypes of invasive ductal breast cancer (IDC) and to assess whether the nodal metastasis is an independent predictor for each subtype.

Results: The predictive sonographic signs for each subtype are as follows: echogenic halo, posterior shadowing, angular or spiculated margin, and unifocal mass for LA subtype; irregular shape for LB subtype; unifocal mass, abrupt interface of the tumor boundary, and posterior enhancement or no posterior change for HER2 subtype; and circumscribed or lobulated margin, oval or rounded shape, posterior enhancement or no posterior change, abrupt interface of the tumor boundary, and parallel orientation of the mass for TN. By multivariate logistic regression, presence of nodal metastasis is the strongest independent predictor for HER2 subtype, and its absence is the strongest independent predictor for LA subtype.

Conclusions: Certain sonographic signs are predictors for each molecular subtype of IDC. Nodal metastasis is an independent predictor for HER2 subtype when present and for LA subtype when absent.

Keywords: Breast, Invasive, Carcinoma, Ultrasound, Molecular subtype

Background

Breast cancer is the most common malignancy in women worldwide [1]. It has been described as a heterogeneous disease that was explained recently by the presence of multiple molecular subtypes [2]. These subtypes are the luminal A (LA), luminal B (LB), human epidermal growth factor receptor 2 (HER2), and triple-negative (TN). They were identified according to the presence of estrogen (ER) or progesterone (PR) receptors and whether or not the HER2 is expressed [3]. Identifying these subtypes has aid significantly in treatment selection and prediction of disease course and progression.

Many studies have demonstrated that patients with HER2 and TN tumors have poorer prognosis compared with patients with LA and LB tumors and that those with LA tumors have a better prognosis than those with LB tumors [3]. Although core needle biopsy is the gold standard for pathological assessment, it is invasive and might cause physical and psychological discomfort in patients and may not be an option in certain circumstances. Ultrasound is a simple and noninvasive method for diagnosis of breast cancer, but little is known about its ability to differentiate the molecular subtypes of the breast cancer. Trying to determine specific sonographic features of each subtype that reflect the tumor aggressiveness may allow better organization of the degree of primary care for the patient and probably share in planning for the treatment [4]. Many authors have looked

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into the mammographic and sonographic features of triple-negative breast cancer because it is the most aggressive subtype [5], and a few studies have focused on ultrasound features of the other subtypes [6, 7] and the relation of the distribution of these subtypes to the lymph node affection [8].

As immunohistochemistry is not available in all institutes, trial to find specific sonographic criteria for each molecular subtype could propose a diagnostic algorithm for each subtype. The purpose of our study is to investigate whether ultrasound can play a valuable role in predicting the molecular subtypes of invasive ductal breast cancer. We also evaluate the possibility of using nodal involvement as an independent predictor of each subtype.

Methods

Patient's selections

This study was approved by our institutional review board, and informed consent was obtained from all patients. This study was carried out from December 2016 to June 2017. Throughout this period, we retrospectively reviewed the pathological database of our institution and identified 160 patients with invasive ductal carcinoma who has complete ultrasound, histopathological, and immunohistochemistry reports.

Ultrasound analysis

The breast ultrasound was performed using 7–14 MHz linear array transducer by a trained sonographer with more than 10 years' experience. The reviewed ultrasound (US) findings were according to the American College of Radiology Breast Imaging Reporting and Data System (ACR BIRADS) lexicon [9]. The following ultrasound features were analyzed: tumor shapes (rounded or oval versus irregular), the tumor margins (circumscribed or lobulated versus angular or spiculated), the posterior acoustic features (posterior enhancement or no posterior change versus posterior shadowing), lesions boundary (abrupt termination versus echogenic halo), echo pattern (hypochoic or heterogeneous versus isochoic), and orientation (parallel to the skin versus non parallel). Nodal metastasis was diagnosed as malignant when we found the following features: rounded shape, hypochoic texture, eccentric or loss of hilum, and non hilar blood flow.

Histological analysis and immunohistochemistry

The pathological reports of the surgical specimens were reviewed. Histological grade was classified as 1, 2, or 3 according to the Elston and Ellis grading system [10]. In our study, grades 1 and 2 were considered low grade, whereas grade 3 was considered high grade. The hormone receptor (HR) status, ER, PR, HER2, and Ki-67

were determined through surgical specimen. ER and PR statuses were defined as positive when more than 1% of the tumor cells showed positive nuclear staining for either ER or PR, respectively. HER2 status was graded as 0, 1+, 2+, and 3+. It was considered negative when the grade was 0 or 1+, positive when it was 3+, or borderline when it was 2+. Fluorescence in situ hybridization (FISH) was performed on all HER2(2+) tumors to make a final determination on status. In our study, the Ki-67 index was scored as high when 14% or more of the tumor cells were immunohistostained and low when less than 14% of the tumor cells were immunohistostained in accordance with the St. Gallen International Expert Consensus guidelines. Molecular subtypes were categorized according to the St. Gallen Consensus 2011 [11] (Table 1).

Statistical analysis

All analyses were performed with the use of statistical software (SPSS version 19). The clinico-pathologic data and sonographic features were tabulated for all patients. We correlated the clinico-pathologic data and ultrasound features of the breast mass with the molecular subtypes using chi square test. We considered the TN patients as the reference group. Any sonographic feature with a significant statistical difference was analyzed using univariate and multivariate logistic regression analyses to identify the significant predictive sonographic signs (SS) and the independent predictors of each molecular subtype. The odds ratio (OR) and 95% confidence interval (CI) were calculated for each significant factor. The statistical difference was considered significant when the *P* value was < 0.05.

Results

The mean age of our enrolled 160 patients was 52 ± 12.73 years (range, 23–86 years). The mean tumor size was 3.1 ± 1.61 cm (ranges, 1–9 cm). LA was the most common subtype which represented 51.2% of our patients ($n = 82$) (Table 2). LA and LB subtypes represented most of the low grade tumors (69% LA and 20% LB), while most of the high grade tumors were TN (44%) and HER2 (36%) subtypes.

Table 1 Simplified St. Gallen categories of the molecular subtypes

LA subtype	ER and/or PR positive, HER2 negative, and Ki-67 index < 14%
LB (HER2-) subtype	ER and/or PR positive, HER2 negative, and Ki-67 > 14%
LB (HER2+) subtype	ER and/or PR positive and HER-2 positive and Ki-67 > 14%
HER2 subtype	ER, PR negative, and HER 2 positive
TN subtype	ER, PR, and HER 2 negative

Table 2 Clinico-pathologic data and sonographic features of female patients with invasive ductal carcinoma

	No. (n = 160)	Percentage %
Age (years)		
Mean ± SD	52.69 ± 12.73	
Range	23.0–86.0	
Size of lesion (cm)		
Mean ± SD	3.10 ± 1.61	
Range	1.0–9.0	
Echogenicity		
Isoechoic	30	18.8
Heterogeneous	20	12.5
Hypoechoic	110	68.8
Shape		
Oval	22	13.8
Rounded	54	33.8
Irregular	84	52.5
Margin		
Angular	14	8.8
Spiculated	77	48.1
Circumscribed	18	11.3
Lobulated	51	31.9
Orientation		
Parallel	30	18.8
Non parallel	130	81.3
Boundary		
Abrupt interface	73	45.6
Echogenic halo	87	54.4
Calcification		
Present	62	38.8
Absent	98	61.3
Posterior feature		
Posterior shadowing	68	42.5
Posterior enhancement	46	28.7
No posterior change	46	28.7
Lymph node status		
Nodal metastasis	71	44.4
No nodal metastasis	89	55.6
Multiplicity		
Unifocal	122	76.3
Multicentric or multifocal	38	23.8
Grade of IDC		
Grade I	15	9.4
Grade II	95	59.4
Grade III	50	31.3
Type		

Table 2 Clinico-pathologic data and sonographic features of female patients with invasive ductal carcinoma (*Continued*)

	No. (n = 160)	Percentage %
Luminal A	82	51.2
Luminal B	26	16.3
Human epidermal growth factor receptor 2	26	16.3
Triple negative	26	16.3

SD standard deviation

From Table 3, there was no statistical significant difference among the four molecular subtypes regarding the patient age, tumor size, or the tumor echogenicity. Angular or spiculated margin, echogenic halo, and posterior shadowing occurred more frequently in LA subtype than in LB subtype (74.4%, 61.5%/76.8%, 53.8% and 63.4%, 38.5%, respectively). Non parallel orientation was more likely to be seen in LB subtype than in LA subtype (92.3% and 85.4%, respectively) (Figs. 1 and 2). Irregular shape was seen more frequently in LB followed by HER2 (76.8% and 61.5%, respectively). Nodal metastasis was highly characteristic for both LB and HER2 subtypes (84.6% and 76%, respectively) (Figs. 1 and 3), while it was rarely associated with LA (28%) and TN (23.1 %) subtypes (Figs. 2 and 4). Circumscribed or lobulated margin, posterior enhancement or no posterior changes, and abrupt interface of the tumor boundary from the surrounding breast parenchyma were highly characteristic for TN and HER2 (92.3%, 84.6%/92.3%, 53.8% and 84.6%, 76.9%, respectively). Calcification more commonly appeared in HER2 subtype (61.5%). It was noteworthy that TN subtype was more likely to have oval or rounded shape (92.3%) and parallel orientation (38.5%) than the LB, HER2, and LA subtypes.

By univariate logistic regression analysis (Table 4), the predictive sonographic signs of the LA subtype were echogenic halo (OR = 7.46), posterior shadowing (OR = 6.72), angular or spiculated margin (OR = 4.65), absence of nodal metastasis (OR = 4.10), and presence of unifocal mass (OR = 4.03). The predictive SS of LB subtype were nodal metastasis (OR = 9.54) and irregularity of the tumor shape (OR = 3.65). The predictive SS of HER2 were nodal metastasis (OR = 5.43), presence of unifocal mass (OR = 5.35), abrupt interface of the tumor boundary (OR = 5.09), posterior enhancement or no posterior change (OR = 5.03), and presence of calcification (OR = 3.06). The predictive SS of TN were circumscribed or lobulated margin (OR = 23.73), oval or rounded shape of the tumor (OR = 18.92), posterior enhancement or no posterior change (OR = 11.65), abrupt interface of the tumor boundary (OR = 8.95), parallel orientation of the mass (OR = 3.56), and absence of nodal metastasis (OR = 3.14).

Table 3 Distribution of demographic, radiologic, and pathologic findings according to molecular classification

	TN (n = 26)		Luminal A (n = 82)		Luminal B (n = 26)		HER2 (n = 26)		P value ¹	P value ²	P value ³
	No.	%	No.	%	No.	%	No.	%			
Age (years)											
Mean ± SD	53.39 ± 9.58		53.49 ± 13.35		52.31 ± 11.34		49.85 ± 14.86		0.778	0.713	0.114
Range	36.0–70.0		23.0–75.0		34.0–70.0		28.0–86.0				
Size of lesion (cm)											
Mean ± SD	2.95 ± 1.68		3.18 ± 1.83		3.08 ± 1.51		3.02 ± 0.73		0.733	0.970	0.182
Range	1.0–8.0		1.3–9.0		1.5–6.0		1.8–4.0				
Echogenicity											
Isoechoic	6	23.1	14	17.1	4	15.4	6	23.1	0.564	0.482	1.000
Hypoechoic/heterogeneous	20	76.9	68	82.9	22	84.6	20	76.9			
Shape											
Oval or rounded	24	92.3	36	43.9	6	23.1	10	38.5	0.000*	0.000*	0.000*
Irregular	2	7.7	46	56.1	20	76.9	16	61.5			
Margin											
Angular or spiculated	2	7.7	61	74.4	16	61.5	12	46.2	0.000*	0.000*	0.002*
Circumscribed or lobulated	24	92.3	21	25.6	10	38.5	14	53.8			
Calcification											
Present	6	23.1	28	34.1	12	46.2	16	61.5	0.290	0.080	0.005*
Absent	20	76.9	54	65.9	14	53.8	10	38.5			
Orientation											
Parallel	10	38.5	12	14.6	2	7.7	6	23.1	0.009*	0.008*	0.229
Non parallel	16	61.5	70	85.4	24	92.3	20	76.9			
Boundary											
Abrupt interface	22	84.6	19	23.2	12	46.2	20	76.9	0.000*	0.004*	0.482
Echogenic halo	4	15.4	63	76.8	14	53.8	6	23.1			
Posterior feature											
Posterior shadowing	2	7.7	52	63.4	10	38.5	4	15.4			
Posterior enhancement or no posterior change	24	92.3	30	36.6	16	61.5	22	84.6	0.000*	0.008*	0.084
LN status											
Nodal metastasis	6	23.1	23	28.0	22	84.6	20	76.9	0.618	0.000*	0.000*
No nodal metastasis	20	76.9	59	72.0	4	15.4	6	23.1			
Multiplicity											
Unifocal	22	84.6	72	87.8	16	61.5	12	46.2	0.739	0.061	0.004*
Multifocal or multicentric	4	15.4	10	12.2	10	38.5	14	53.8			
Grade of IDC											
Low grade	4	15.4	76	92.7	22	84.6	8	30.8	0.000*	0.000*	0.188
High grade	22	84.6	6	7.3	4	15.4	18	69.2			

*Result with statistically significant difference $P < 0.05$

¹P value calculated the difference between TN and luminal A

²P value calculated the difference between TN and luminal B

³P value calculated the difference between TN and HER2

Using multivariate logistic regression (Table 4), we found that absence of nodal metastasis was the strongest independent predictor for LA subtype (OR = 5.40), but it is among the important predictors for the TN subtype

(OR = 2.09). The presence of nodal metastasis was the strongest independent predictor for HER2 subtype (OR = 4.17), but it is among the important predictors for LB subtype (OR = 2.54).

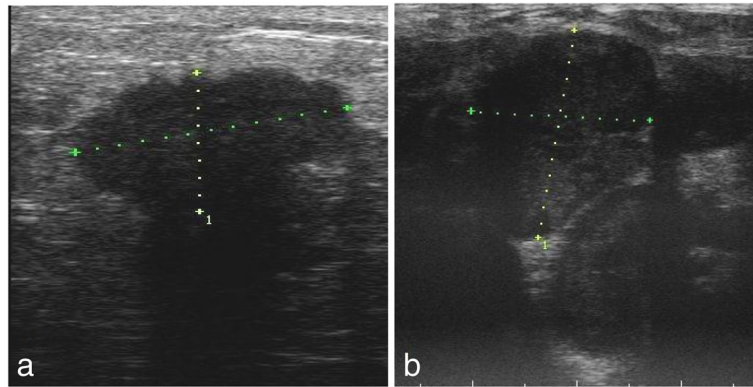


Fig. 1 **a** Ultrasound of the right breast and **b** right axilla in 40 years old women shows **a** a unifocal mass with irregular shape, spiculated margin, echogenic halo with non-parallel orientation, and posterior shadowing; it measures 15 × 9 mm. **b** Multiple malignant featuring right axillary lymph nodes. The mass proved pathologically to be low grade invasive ductal carcinoma with malignant infiltration of the LN and luminal B subtype

Discussion

The development of molecular biology of the breast cancer allowed the management to be personalized according to the molecular subtype. So identification of the breast cancer subtypes by ultrasonographic features could be of pivotal interest to the radiologist as it has a direct effect on the decision of the clinicians. As the axillary lymph node metastasis remains the most important prognostic factor in breast cancer and it has a considerable impact on the outcome of the patient and on the course of the disease, detection of the relationship of nodal metastasis to the molecular subtypes of the breast cancer is of great value [12].

Our data demonstrated that the main predictive SS of the LA subtype are spiculated or angular margin, post-acoustic shadowing, echogenic halo, absence of nodal metastasis, and unifocal mass. Similar data were described by Zhang et al. [13]. Two other studies done by Kim et al. and Ko et al. [14, 15] proved that echogenic

halo and post-acoustic shadowing are more commonly seen in ER-positive/PR-negative/HER2-negative breast cancers that represent the LA subtype in our study. Similar to our results, Wiechmann et al. [16] reported that the LA subtype is less likely to be associated with multicentric or multifocal breast cancer and nodal metastasis than HER2 and LB subtypes, so when a breast mass encounters these sonographic features, the radiologist would be reminded that it has a minor chance to be LA subtype.

Jiang et al. [17] demonstrated that the absence of echogenic halo was a characteristic sign of the LB subtype using 2D ultrasound, and Yang et al. [18] reported that the absence of retraction phenomena and presence of calcification are predictive factor of LB subtype using 3D ultrasound; both results are inconsistent with our results that found the predictive SS of the LB subtype are the presence of nodal metastasis (OR = 9.54) and irregular tumor shape (OR = 3.65). Such discrepancy may be

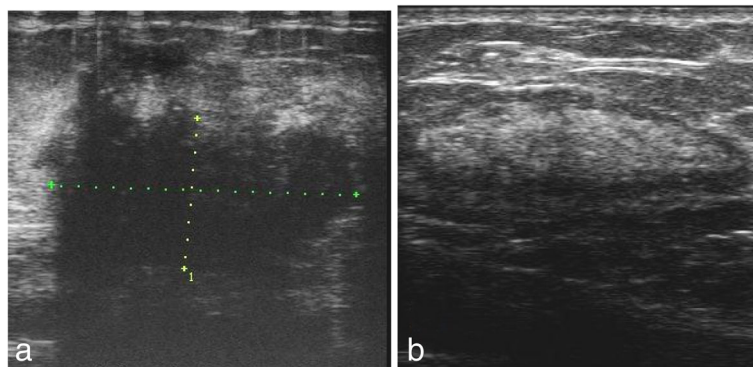


Fig. 2 **a** Ultrasound of the right breast and **b** right axilla in 55 years old women shows **a** a unifocal mass with irregular shape, spiculated margin, echogenic halo, parallel orientation, and posterior shadowing; it measures 10 × 20 mm. **b** Benign featuring right axillary lymph nodes. The mass proved pathologically to be low grade invasive ductal carcinoma with no nodal infiltration and luminal A subtype

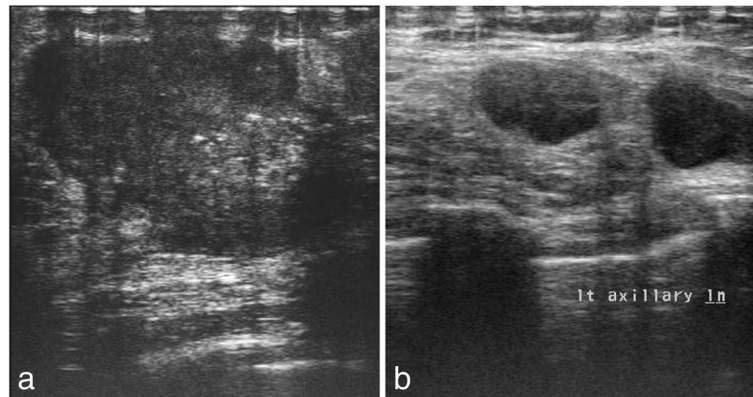


Fig. 3 **a** Ultrasound of the left breast and **b** left axilla in 50years old women shows **a** breast mass with irregular shape, lobulated margin, calcification, and abrupt interface of the tumor boundary with no posterior change. **b** Multiple malignant featuring left axillary lymph nodes. The masses proved to be high grade invasive ductal carcinoma with ductal carcinoma in situ component and malignant infiltration of the lymph nodes and HER2 subtype pathologically

due to difference in the sample size of LB subtype between their study and ours. Similar to our results, Goldhirsch et al. [19] demonstrated that patients with LB subtype are more likely to associate with nodal metastasis.

As noted in our study that LA subtype followed by LB subtype shows the highest rate of low grade tumors (69% and 20%, respectively) and sonographically tend to have angular or spiculated margin, echogenic halo, and posterior shadowing. This was also described by Irshad et al. [20]. The mechanism of their formation could be attributed to the great desmoplastic reaction which strongly related to the low grade tumor [21]. As the absence of nodal metastasis is the strongest independent predictor of LA subtype (OR = 5.4) Thus, LN status could help to differentiate between these two subtypes that share certain SS as described, so its absence predicts

with confidence the LA subtype, while its presence excludes LA subtype and increases the possibility of LB subtype.

In a study done by Seo et al. [22] found that the TN subtype is more likely than the other subtypes to have microlobulated margins, regular shape, and posterior acoustic enhancement and is less likely to have echogenic halo, spiculated margin, and calcifications. Similarly, in our study, the predictive SS of the TN subtype are the circumscribed or lobulated margin, oval or round shape, posterior enhancement or no posterior change, abrupt interface of the tumor boundary, and parallel orientation. Also, the absence of nodal metastases is a predictive SS of TN subtype that agrees with the study done by Yang et al. [23] who reported that the basal subtype (ER- and PR- and HER-2-) which represent the TN subtype in our

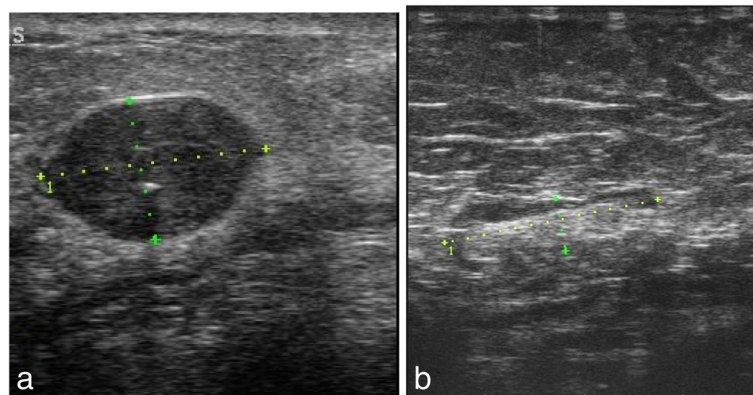


Fig. 4 **a** Ultrasound of right breast and **b** right axilla in 56years old women shows **a** mass with oval shape, circumscribed margin, parallel orientation, and abrupt interface of the tumor boundary with no posterior changes. **b** Benign featuring right axillary lymph nodes. The mass proved to be high grade invasive ductal carcinoma with no nodal infiltration and TN subtype pathologically

Table 4 Univariate and multivariate logistic regression analysis

Subtype	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	Predictive SS	OR (95% C.I.)	P value	Independent predictors	OR (95% C.I.)	P value
Luminal A subtype	Echogenic halo	7.46 (3.69–15.07)	< 0.001*	Echogenic halo	3.56 (1.46–8.69)	0.005*
	Posterior shadowing	6.72 (3.30–13.66)	< 0.001*	Posterior shadowing	4.60 (1.78–11.89)	0.002*
	Angular or spiculated margin	4.65 (2.37–9.12)	< 0.001*	Angular or spiculated margin	1.65 (0.66–4.16)	0.287
	No nodal metastasis	4.10 (2.11–7.97)	< 0.001*	No nodal metastasis	5.40 (2.24–14.02)	< 0.001*
	Unifocal mass	4.03 (1.80–9.04)	< 0.001*	Unifocal mass	2.36 (0.91–6.08)	0.076
Luminal B subtype	Nodal metastasis	9.54 (3.11–29.30)	< 0.001*	Nodal metastasis	2.54 (0.91–7.09)	0.075
	Irregular shape	3.65 (1.38–9.65)	0.006*	Irregular shape	8.04 (2.58–25.07)	< 0.001*
HER2 subtype	Nodal metastasis	5.43 (2.04–14.41)	< 0.001*	Nodal metastasis	4.17 (1.42–12.29)	0.010*
	Unifocal mass	5.35 (2.20–13.00)	< 0.001*	Unifocal mass	2.90 (1.04–8.14)	0.043*
	Abrupt interface	5.09 (1.92–13.52)	< 0.001*	Abrupt interface	2.73 (0.87–8.53)	0.084
	Posterior enhancement or no posterior change	5.03 (1.64–15.38)	0.002*	Posterior enhancement or no posterior change	3.45 (0.95–12.55)	0.060
	Calcification	3.06 (1.29–7.28)	0.009*	Calcification	2.76 (1.02–7.46)	0.045*
TN subtype	Circumscribed or lobulated margin	23.73 (5.37–104.93)	< 0.001*	Circumscribed or lobulated margin	8.21 (1.41–47.83)	0.019*
	Oval or rounded shape	18.92 (4.29–83.44)	< 0.001*	Oval or rounded shape	6.90 (1.29–36.83)	0.024*
	Posterior enhancement or no posterior change	11.65 (2.65–51.25)	< 0.001*	Posterior enhancement or no posterior change	3.67 (0.60–22.51)	0.160
	Abrupt interface	8.95 (2.92–27.46)	< 0.001*	Abrupt interface	1.38 (0.28–6.68)	0.691
	Parallel orientation	3.56 (1.42–8.96)	0.005*	Parallel orientation	2.01 (0.61–6.59)	0.251
	No nodal metastasis	3.14 (1.19–8.31)	0.017*	No nodal metastasis	2.09 (0.62–7.03)	0.233

Predictive SS sonographic signs

*Result with statistically significant difference $P < 0.05$

study is less likely to show nodal involvement than the other subtypes.

The predictive SS of the HER2 subtype in our study are posterior acoustic enhancement or no posterior change, nodal metastases, calcification, unifocal mass, and abrupt interface of the mass boundary. Similar to our results, calcifications and post-acoustic enhancement were shown to be characteristics of the HER2 subtype by Yang et al. [23]. The HER2 subtype was also found to have more calcifications (80%) than the TN subtype (28%) and luminal (A or B) subtypes (41%) by mammography in the study done by Ko et al. [15]; this might be explained by the probability that HER2 breast cancers are more often accompanied by ductal carcinoma in situ. In agreement with our result, Yang et al. [23] observed higher frequency of nodal metastases in the HER2 followed by LB subtype (mostly HER2 positive) than in TN and LA subtype. Wiechmann et al. [16] found a higher frequency of multicentric or multifocal disease in HER2 subtype than other subtypes. On the contrary, our results showed that unifocal mass is one of the predictors SS of HER2 subtype. This could be explained by the big difference between the number of the patients of

HER2 subtype in both studies ($n = 16$ in our study and $n = 368$ in Wiechman's study).

This study demonstrated that most of the high grades were TN subtype followed by HER2 subtype (44% and 36%, respectively) and sonographically tend to have circumscribed or lobulated margin, posterior enhancement or no posterior change, and abrupt interface of the tumor boundary. This was also described by Kim et al. [24]. The mechanism of their formation attributed to the high mitotic rates and increased cellularity with less stromal and desmoplastic reaction.

Among the previous, predictive SS of HER2 subtype nodal metastasis are the strongest independent predictor of HER2 subtype (OR = 4.17). As TN and HER2 subtypes share certain SS, thus presence of nodal metastasis strongly predicts the HER2 subtype, and its absence excludes HER2 and predicts with great confidence the TN subtype.

There are some limitations of this study; small sample size in LB subtype may have limited the statistical significance of the data obtained. Using a combination of imaging modalities, including mammography, Doppler, and ultrasonographic elastography, may improve the diagnostic accuracy. There is no correlation between the

presence of ductal carcinoma in situ and the molecular subtypes.

Conclusions

Ultrasonographic imaging features, including the tumor shape, margin, boundary, posterior features, multiplicity, orientation, and calcification, are significant predictive sonographic signs of different molecular subtypes. Nodal metastasis is the strongest independent predictor for the HER2 when present and for LA when absent. So nodal status used as a tool in differentiating between each two subtypes has to some extent similar sonographic features; accordingly, it can differentiate firstly between LA and LB subtypes and secondly, between HER2 and TN subtypes. So the sonographic features of the mass and the LN status can expand the scope of the ultrasound in predicting with confidence the molecular subtypes of the breast cancer that are currently beyond the scope of ultrasound BI-RADS. We recommended correlating the BIRADS Ultrasound lexicon with each molecular subtype aiming to change the description of each category of the BIRADS and put the LN status as a separate item in each category of the BIRADS.

Abbreviations

SS: Sonographic signs; IDC: Invasive ductal breast cancer; LA: Luminal A; LB: Luminal B; HER2: Human epidermal growth factor receptor; TN: Triple negative; ER: Estrogen receptor; PR: Progesterone receptor; US: Ultrasound; HR: Hormonal receptor; OR: Odds ratio; CI: Confidence interval; BIRADS-US: Breast Imaging Reporting and Data System Ultrasound; ACR: American College of Radiology; FISH: Fluorescence in situ hybridization

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Guarantor

The scientific guarantor of this publication is Dr. Lamiaa M.R Khalaf.

Authors' contributions

Corresponding author: LMRK. Dr. Lamiaa was responsible for the study design, revision and interpretation of the sonographic images for all the patients who enrolled in this study, analysis and interpretation of the data, statistical analysis, editing, drafting and submission of the manuscript, and guarantor of integrity of the entire study. Co-author: RAH was responsible for diagnosis of all the pathological specimen after surgery or biopsy and writing the pathological part of the manuscript. All authors have approved and read the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors whose names are listed on the title page and shared in the Manuscript entitled "Role of Ultrasound in predicting the molecular subtypes of Invasive Breast Ductal Carcinoma," certified that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers, membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony; or patent/licensing arrangements) or non-financial interest

(such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethics approval and consent to participate

This prospective study was approved by the Research Ethics Committee of the Faculty of Medicine at Assiut University in Egypt (its number is 17100016). Written informed consent was obtained from each patient after receiving information about the details of the study.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study

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