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Association between ultrasound findings, tumor type, grade, and biological markers in patients with breast cancer

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Abstract

Background: This prospective study included 65 female patients with primary breast cancer. Ultrasound was performed for all patients. Ultrasound findings were analyzed according to the ACR BI-RADS lexicon 5th edition and correlated with tumor type, grade, and biological markers (ER, PR, HER-2/neu, and Ki67). The purpose of this study is to assess the association between ultrasound findings, tumor type, grade, and the state of biological markers in patients with breast cancer.

Results: Irregular shape and speculated margins are more frequently associated with invasive duct carcinoma than DCIS (p value < 0.001). There were no association between the ultrasound findings (shape, margin, orientation, echopattern, and posterior features) and the tumor grade (p value 1.0, 0, 0.544, 1.0, and 1.0), respectively. Irregular shape is more frequently seen in ER and PR positive breast cancers (p value = 0.036 and 0.026, respectively). Non-circumscribed margins were frequently seen in PR positive breast cancers (p value = 0.068). No statistically significant difference between US descriptors and HER-2/neu-positive cases.

Conclusion: Irregularly shaped tumors with speculated margins are frequently seen in invasive duct carcinoma and also more frequently seen in ER-, PR-, and Ki67-positive cases. No relation between ultrasound descriptors and the tumor grade of invasive duct carcinoma. Also, there were no relation between ultrasound descriptors and the state of HER-2/neu.

Keywords: Ultrasound, Breast cancer, Tumor type, Tumor grade, Biological markers

Background

Breast ultrasound (US) is widely used as a diagnostic modality for evaluating suspected breast abnormalities. Also, it is considered as an effective imaging modality for detecting occult carcinomas in patients with dense breasts [1, 2].

In general, the imaging criteria (tumor shape, margin, and density by mammography, tumor shape, margin, orientation, echo pattern, and posterior features by ultrasound) for diagnosis of breast cancer by various imaging modalities as mammogram, ultrasound, and MRI have been studied for a long time, and this allowed differentiation between benign and malignant breast tumors with some certainty, as outlined in the current imaging criteria used in the BI-RADS (breast-imaging reporting and data system) [3].

The standard prognostic indicators in patients with breast cancer are histological tumor type, tumor grade, and tumor staging [4]. Other prognostic indicators are the biological markers [5]. Common biological markers include estrogen receptor (ER), progesterone receptor (PR), and human epithelial growth factor receptor (HER). ER and PR are present in the nuclei of epithelial cells, and their existence predicts tumor response to hormonal therapy [6]. The HER-2/neu gene is a member in the HER family. It is responsible for organization of normal development of the cell. Trastuzumab usually targets the cells that show HER-2/neu overexpression [7].

Some studies focused on the role of ultrasound to predict tumor type and tumor grade [8–15], also some studies have focused on correlation between US findings and the presence of biological markers [9, 10, 15, 16].

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So, the purpose of this study was to assess if there is an association between ultrasound findings, tumor type, tumor grade, and the state of biological markers in patients with breast cancer.

Methods

Patient's demographic data

This prospective study was performed on 65 female patients with primary breast cancer. Their age ranged from 36 to 85 years with a mean age of 54.95. It was performed during the period from January 2018 till January 2019 and was approved by our institution's ethics committee. All patients gave their informed consent before inclusion in the study.

Inclusion criteria included female patients with primary breast cancer. Exclusion criteria included patients who received neoadjuvant chemotherapy, patients who underwent prior surgery for breast cancer, and patients who refused to participate in the study.

Ultrasound technique

The ultrasound examination was performed using Toshiba Aplio 500. Radial and antiradial scanning of the entire breast and axillary tail of both sides were obtained with image overlap using high-frequency 8–14 MHz linear transducer with B. mode US real-time imaging and Doppler flow mapping. Image depth adjusted on the machine to visualize pectoralis major muscle (at least 4 cm).

Image interpretation

Images were interpreted by an expert radiologist (10 years' experience in breast imaging). Tumor criteria were evaluated according to the ACR BI-RADS atlas 5th edition [3]. The assessed criteria were tumor shape (round or oval versus irregular), margin (circumscribed versus not circumscribed), and "not circumscribed" margins which include indistinct, spiculated, angular or microlobulated margins, orientation (parallel versus non-parallel), echo pattern (hypoechoic or complex versus isoechoic or hyperechoic), and posterior acoustic feature (shadowing or combined posterior acoustic feature versus no posterior acoustic feature or enhancement).

Ultrasound-guided core

Biopsies of the breast were performed for all cases using 14-gauge needle. Multiple core biopsies were taken from different part of lesions to analyze tumor type, grade, and hormonal receptors.

Pathological and immunohistochemical analysis

Histological tumor types of our study were divided into invasive ductal cancers and ductal carcinoma in situ (DCIS). Invasive cancer was graded as grade 1 (well differentiated), grade 2 (moderately differentiated), or grade 3 (poorly differentiated). DCIS cases were classified as group 1 (non-high grade DCIS without comedo-type necrosis), group 2 (non-high grade DCIS with comedo-type necrosis), or group 3 (high-grade DCIS with or without comedo-type necrosis).

Staining was performed for ER, PR, HER/neu-2, and Ki67. ER and PR positivity was defined as the presence of at least 1% positive tumor nucleus in the sample. HER/neu-2 expression was scored as (1+, 2+, or 3+). Tumors with a score of 3+ were classified as HER/neu-2 positive and tumors with scores of 0 or 1+ were classified as HER/neu-2 negative. Ki 67 was reported as the percentage of total number of tumor cells with nuclear staining. A percentage of more than or equal 14% defined positive ki67 status.

Statistical analysis

SPSS (Statistical Package for Social Sciences) version 23.0 was used for data management and data analysis. Qualitative data were expressed as count and percent. Quantitative data were expressed as mean ± standard deviation (SD) if normally distributed or median and interquartile range (IQR) if not. For data comparison, one-sample chi-square test was used for qualitative data for one group. Chi-square test (or Fisher's exact test) was used for qualitative data for two groups (2×2 table). Chi-square test (with Bonferroni method to adjust p values when comparing column proportions) was used for qualitative data for more than two groups (e.g., 2×3 table). For comparing quantitative data between two groups, independent sample t test was used if data were normally distributed in both groups. The non-parametric alternative Mann-Whitney U test was used if not. For any of the used tests, results were considered as statistically significant if p value ≤ 0.050.

Results

This prospective study included 65 female patients with age ranged between 36 and 85 years with a mean age 54.95.

Out of the 65 patients included in this study, there were 52 patients (80.0%) with invasive duct carcinoma and 13 patients (20.0%) with DCIS. The most frequent tumor grade was grade II invasive cancer detected in 30 patients (57, 7%). The most frequent grade of DCIS was grade II detected in 7 patients (53.8%). Fifty-six patients (86.2%) were estrogen receptor positive cases. Forty-seven patients (72.3%) were progesterone receptor-positive cases. Thirty-seven patients (56.9%) were HER-2neu enriched and 48 patients (73.8%) were ki67 index (Table 1).

When correlating the ultrasound findings with tumor type, we found that tumor shape and margins were the

Table 1 Characteristics of 65 patients with malignant breast lesion

		Count	Percent
Tumor type	Invasive cancer	52	80.0
	DCIS	13	20.0
	Total	65	100.0
Tumor grade of invasive cancer	Grade I	18	34.6
	Grade II	30	57.7
	Grade III	4	7.6
	Total	52	100.0
Tumor classification of DCIS	Grade I	3	23.1
	Grade II	7	53.8
	Grade III	3	23.1
	Total	13	100.0
Estrogen receptor	Positive	56	86.2
	Negative	9	13.8
	Total	65	100.0
Progesterone receptor	Positive	47	72.3
	Negative	18	27.7
	Total	65	100.0
HER-2/neu	Positive	37	56.9
	Negative	28	43.1
	Total	65	100.0
KI67	Positive	48	73.8
	Negative	17	26.2
	Total	65	100.0

most important descriptors that can differentiate between invasive carcinoma and DCIS with irregular shape, and non-circumscribed margin were frequently seen in invasive cancer p value (< 0.001) (Table 2) (Figs. 1, 2, and 4). We also found that DCIS usually appeared as a non-mass lesion (area of parenchymal distortion), and this is observed in 46.2% of cases of DCIS included in the study (Table 2) (Fig. 3).

When correlating the ultrasound findings with the tumor grade, we found that ultrasound cannot differentiate between tumor grades of invasive duct carcinoma (Table 3).

When correlating the US findings with biological markers of breast cancer, we reported that irregular shape was more frequent in estrogen- and progesterone-positive cases with significant p value (0.036 and 0.026, respectively) (Tables 4 and 5) (Figs. 1, 2, and 4). Also, we reported that non-circumscribed margins were more frequent in progesterone-positive cases (p value = 0.068) (Table 5) (Figs. 1, 2, and 4). We found that there were no statistically significant difference between US descriptors and HER-2/neu-positive cases (Table 6). Also, we reported that irregular shape and non-circumscribed margin had statistically significant difference in KI67-positive cases (p values 0.050 and 0.047, respectively) (Table 7) (Figs. 1 and 2).

Discussion

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females worldwide [17]. The incidence of breast cancer in Egypt is 32.04% [18]. According to the WHO (World Health Organization), the incidence is 30% and mortality from breast cancer had increased recently in the younger women, so the main issue lies in the screening and early tumor detection to ensure an effective management and better prognosis [19].

Early detection of breast cancer and accurate assessment of lesions are the goals of various imaging modalities to ensure an effective management and better prognosis [20].

The response of breast cancer to therapy is influenced by many factors as tumor type, tumor grade, and the state of biological markers [10], so the aim of this study was to find association between ultrasound findings and tumor type, grade, and the state of biological markers.

In this study, when correlating the US descriptors with the tumor type, we found that the shape and the margin of the mass were the most important US descriptors to differentiate between invasive breast cancer and DCIS (p value < 0.001) with irregular shape, and speculated margin was more frequently seen in invasive cancer (90.4% and 100%, respectively), while most cases of DCIS were characterized by oval/rounded shape and smooth margins (71.4% and 57.1%, respectively) (Fig. 5). This is in agreement with the study done by Marino et al. [8], and they performed a study on 49 breast cancer patients and reported that irregular shape (78.6%) and non-circumscribed margins (100%) were more frequent in invasive cancer than DCIS (p value < 0.005). Our results are also comparable with the study done by An et al. [9]. They performed a study on 52 breast cancer patients and concluded that irregular shape (75.3%) and non-circumscribed margins (61.8%) were more frequent in invasive cancer than DCIS (p value = 0.001).

Our results reported that there was no statistically significant difference in posterior feature descriptor in differentiating between invasive cancers and DCIS (p value = 0.427), and these results are concordant with the study done by Kim et al. [10], who stated that there was no statistical significant difference in posterior features between invasive cancers and DCIS (p value = 0.4552).

We concluded that the other US descriptors (orientation and echopattern) cannot differentiate between invasive cancers and DCIS (p value = 0.604 and 1.000, respectively). This is in agreement with the study done by Scoggins et al. [11], who reported that there was no

Table 2 Association between tumor type and ultrasound findings of the breast cancers

		Tumor type				*p* value
		Invasive cancer		DCIS		
		Count	%	Count	%	
		Mass features				
Mass shape	Oval/round	5	9.6	*5*	*71.4*	< 0.001
	Irregular	*47*	*90.4*	2	28.6	
	Total	52	100.0	7	100.0	
Mass margin	Circumscribed	0	0	4	57.1	< 0.001
	Non-circumscribed	*52*	*100*	3	42.9	
	Total	52	100.0	7	100	
Mass orientation	Parallel	9	17.3	2	18.6	0.604
	Not parallel	*43*	*82.7*	5	81.4	
	Total	52	100.0	7	100.0	
Mass posterior features	No/enhancement	20	38.5	4	57.1	0.427
	Shadowing/ combined	32	61.5	3	42.9	
	Total	52	100.0	7	100.0	
Mass echopattern	Hypoechoic	46	88.5	7	100	1.000
	Heterogeneous	6	11.5	0	0.0	
	Total	52	100.0	7	100.0	
Non-mass features (architectural distortion)		0	0.0	6	100	0.004

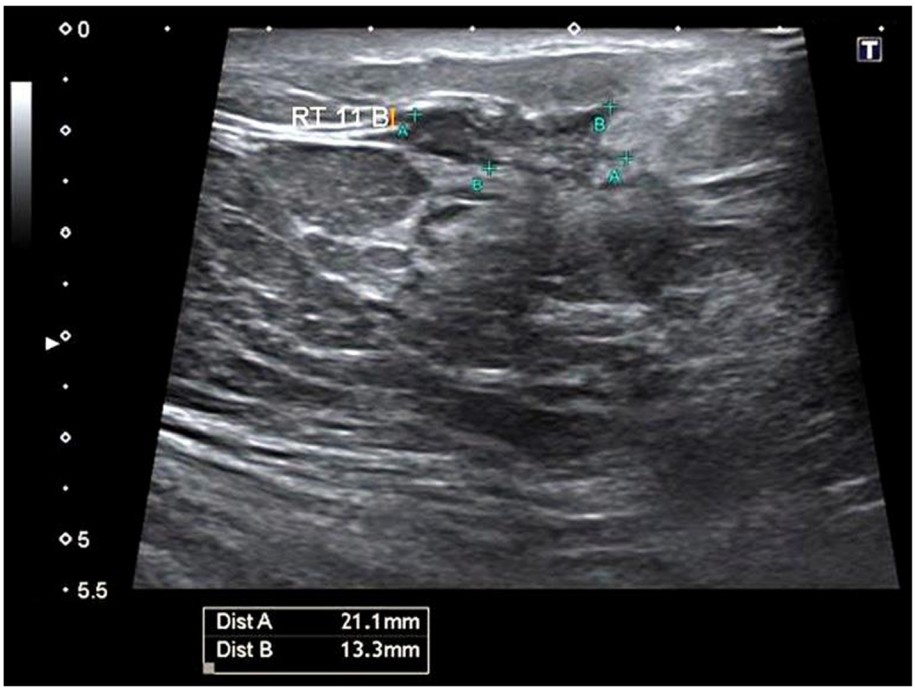

Fig. 1 B-mode US showed an irregular hypoechoic speculated solid mass with posterior shadowing measuring about 27 × 18 mm, assessed as BIRADS 5. Pathology: true cut biopsy revealed invasive ductal carcinoma grade II. Biological markers: ER positive, PR positive, HER/neu-2 negative, and Ki67 positive

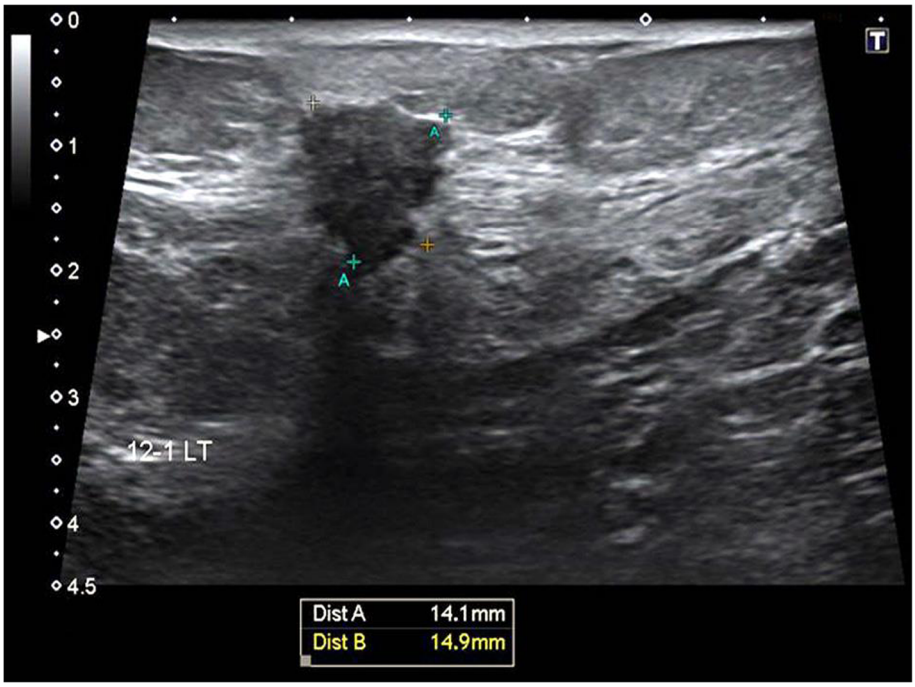

Fig. 2 B-mode ultrasound showed irregular hypoechoic speculated mass with antiparallel orientation and posterior shadowing measuring about (14.1 × 14.9 mm), assessed as BIRADS 5. Pathology: true cut biopsy revealed infiltrating duct carcinoma grade III. Biological markers: ER positive, PR positive, HER/neu-2 negative, and Ki67 positive

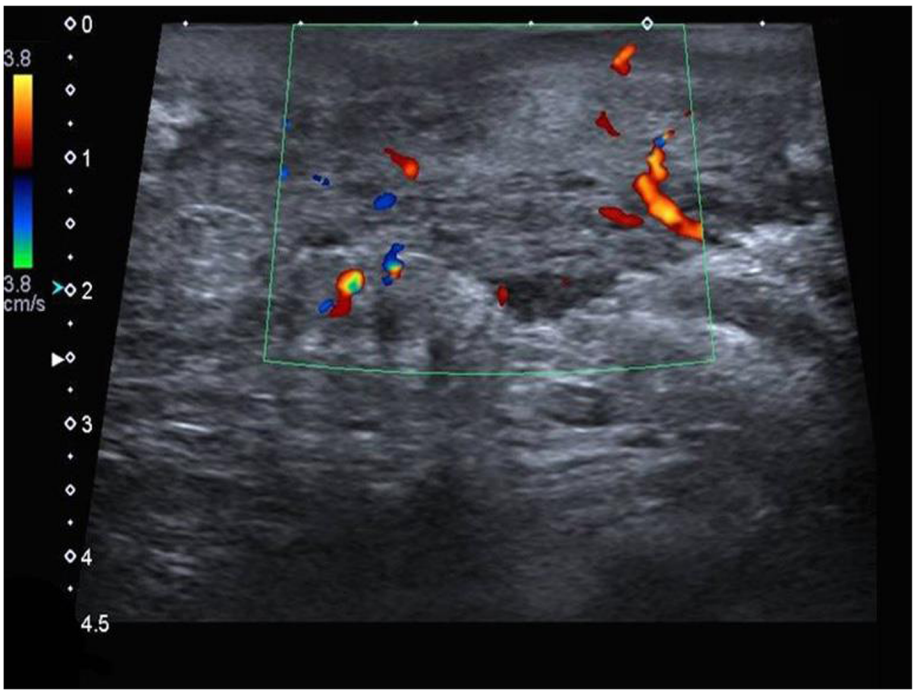

Fig. 3 B-mode ultrasound showed an ill-defined area of parenchymal distortion with marked internal vascularity, no definite masses, assessed as BIRADS 4C. Pathology: DCIS (grade II). Biological markers: ER positive, PR negative, HER/neu-2 positive, and Ki67 positive

Table 3 Association between tumor grade and ultrasound findings of invasive breast cancers

Mass features		Tumor grade				*p* value
		Grade I + grade II		Grade III		
		Count	%	Count	%	
Mass shape	Oval/round	5	10.4	0	0.0	1.0
	Irregular	43	98.6	4	100.0	
	Total	48	100.0	4	100.0	
Mass margin	Non-circumscribed	48	100	4	100.0	–
	Total	48	100.0	4	100.0	
Mass orientation	Parallel	8	16.7	1	25.0	0.544
	Not parallel	40	83.3	3	75.0	
	Total	48	100.0	4	100.0	
Mass posterior features	No/enhancement	19	39.6	1	25.0	1.0
	Shadowing/combined	29	60.4	3	75.0	
	Total	48	100.0	4	100.0	
Mass echopattern	Hypoechoic	42	87.5	4	100.0	1.0
	Heterogenous	6	12.5	0	0.0	
	Total	48	100.0	4	100.0	

Table 4 Association between status of estrogen receptors and ultrasound findings of breast cancers

			Estrogen receptor		*p* value
			Positive	Negative	
Shape	Oval/round	Count	6	4	0.036
		% within	12.0%	44.4%	
	Irregular	Count	44	5	
		% within	88.0%	55.6%	
Margin	Circumscribed	Count	3	1	0.494
		% within	6.0%	11.1%	
	Non-circumscribed	Count	47	8	
		% within	94.0%	88.9%	
Orientation	Parallel	Count	9	2	0.670
		% within	18.0%	22.2%	
	Not parallel	Count	41	7	
		% within	82.0%	77.8%	
Posterior features	No/enhancement	Count	20	4	1.000
		% within	40.0%	44.4%	
	Shadowing/ combined	Count	30	5	
		% within	60.0%	55.6%	
Echopattern	Hypoechoic	Count	46	7	0.224
		% within	92.0%	77.8%	
	Heterogenous	Count	4	2	
		% within	8.0%	22.2%	

Table 5 Association between status of progesterone receptors and ultrasound findings of breast cancer

			Progesterone receptor		*p* value
			Positive	Negative	
Shape	Oval/round	Count	4	6	0.026
		% within PR	9.5%	35.3%	
	Irregular	Count	38	11	
		% within PR	90.5%	64.7%	
Margin	Circumscribed	Count	1	3	0.068
		% within PR	2.4%	17.6%	
	Non-circumscribed	Count	41	14	
		% within PR	97.6%	82.4%	
Orientation	Parallel	Count	7	4	0.713
		% within PR	16.7%	23.5%	
	Not parallel	Count	35	13	
		% within PR	83.3%	76.5%	
Posterior features	No/enhancement	Count	16	8	0.526
		% within PR	38.1%	47.1%	
	Shadowing/ combined	Count	26	9	
		% within PR	61.9%	52.9%	
Echopattern	Hypoechoic	Count	38	15	1.000
		% within PR	90.5%	88.2%	
	Heterogeneous	Count	4	2	
		% within PR2	9.5%	11.8%	

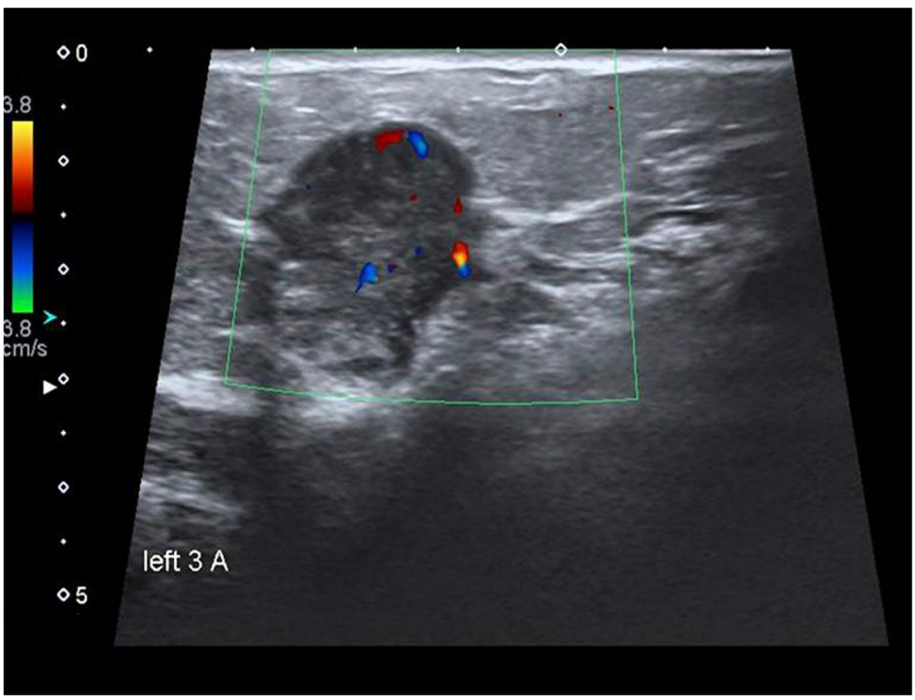

Fig. 4 B mode ultrasound revealed hypoechoic irregular shaped mass with speculated margin, antiparallel orientation, and no posterior features. On CCDI, it shows internal vascularity, assessed as BIRADS 5. Pathology: invasive ductal carcinoma (grade I). Biological markers: ER positive, PR positive, HER/neu-2 negative, and Ki67 negative

Table 6 Association between status of Her-2/neu and ultrasound findings of breast cancer

			Her-2/neu		*p* value
			Positive	Negative	
Shape	Oval/round	Count	5	5	0.510
		% within	14.3%	20.8%	
	Irregular	Count	30	19	
		% within	85.7%	79.2%	
Margin	Circumscribed	Count	3	1	0.639
		% within	8.6%	4.2%	
	Non-circumscribed	Count	32	23	
		% within	91.4%	95.8%	
Orientation	Parallel	Count	5	6	0.299
		% within	14.3%	25.0%	
	Not parallel	Count	30	18	
		% within	85.7%	75.0%	
Posterior features	No/enhancement	Count	14	10	0.898
		% within	40.0%	41.7%	
	Shadowing/ combined	Count	21	14	
		% within	60.0%	58.3%	
Echopattern	Hypoechoic	Count	31	22	1.000
		% within	88.6%	91.7%	
	Heterogenous	Count	4	2	
		% within	11.4%	8.3%	

Table 7 Association between status of Ki67 and ultrasound findings of breast cancer

			K176 receptor		*p* value
			Positive	Negative	
Shape	Oval/round	Count	5	5	0.050
		% within	11.4%	33.3%	
	Irregular	Count	39	10	
		% within	88.6%	66.7%	
Margin	Circumscribed	Count	1	3	0.047
		% within	2.3%	20.0%	
	Non-circumscribed	Count	43	12	
		% within	97.7%	80.0%	
Orientation	Parallel	Count	8	3	1.000
		% within	18.2%	20.0%	
	Not parallel	Count	36	12	
		% within	81.8%	80.0%	
Posterior features	No/enhancement	Count	16	8	0.248
		% within	36.4%	53.3%	
	Shadowing/ combined	Count	28	7	
		% within	63.6%	46.7%	
Echopattern	Hypoechoic	Count	39	14	1.000
		% within	88.6%	93.3%	
	Heterogenous	Count	5	1	
		% within	11.4%	6.7%	

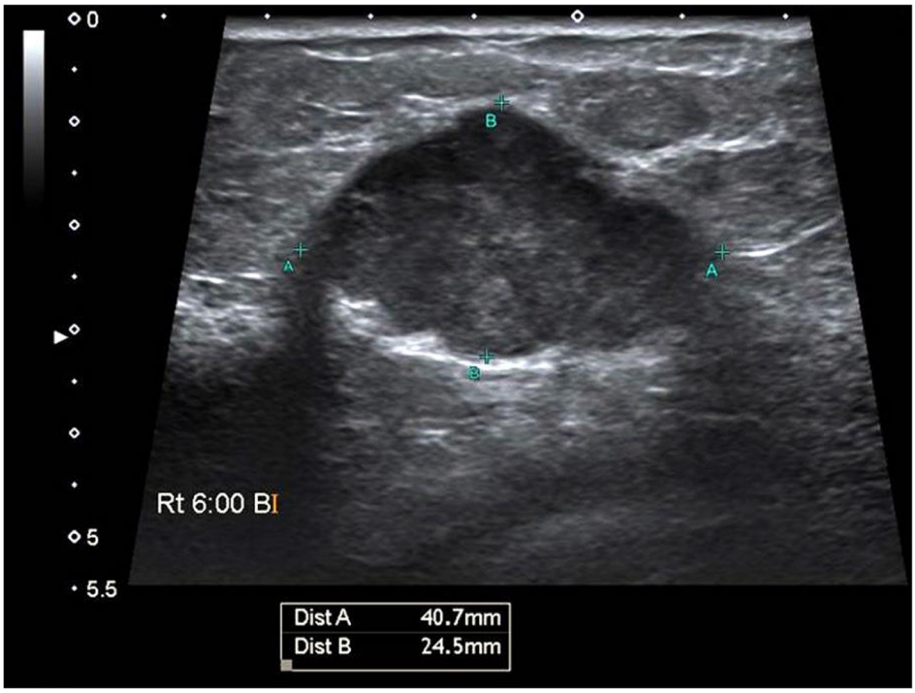

Fig. 5 B mode US shows oval-shaped hypoechoic solid mass with lobulated margin, parallel orientation, and posterior enhancement, and it measures about 40 × 24 mm assessed as BIRADS 4b. Pathology: true cut biopsy revealed DCIS (grade 2). Biological markers: ER positive, PR positive, HER/neu-2 negative, and Ki67 negative

statistically significant difference in orientation and echopattern in differentiating between invasive cancer and DCIS (p value = 1.000 and 0.543, respectively). They reported that irregular shape, non-circumscribed margin, and no posterior features were the most important descriptors in differentiation between tumor types.

Out of the 13 cases of DCIS included in this study, 6 cases were non-mass forming malignancies (parenchymal distortion); in another way, all malignant cases assessed as NMLs were DCIS. Our results are comparable with the study done by Lee et al. [12]. They noted that NMLs were more frequently related with malignancies such as ductal carcinoma in situ (DCIS).

The association between tumor grade of invasive cancer and US findings in previous studies was varied. Watermann et al [13] reported that tumor grading did not significantly influence US descriptors characteristics; on the other hand, Lamb et al. [14] found that high-grade invasive cancer were more likely to demonstrate posterior acoustic enhancement and well-defined margins. Further studies [10, 15] observed that non-circumscribed margin and hypoechoic or heterogeneous echo patterns were more frequent in grade 3 than in grade 1 and 2 invasive cancers. *In our study*, we observed no statistical significant difference between low (Fig. 4)/medium (Fig. 1) and high-grade (Fig. 2) tumor type as regards the examined US descriptors (shape, margin, orientation, posterior feature, and echopattern) (p values 1.0, 0, 0.544, 1.0, and 1.0, respectively). It is likely that the difference between all the previous studies including our results is reliant on the microstructure of the tumors, and this needs further studies.

In this study, we also correlated the US descriptors in breast cancer cases with the biological markers (estrogen, progesterone, HER-2/neu2, and KI 67). As regards the association between the US descriptors and the state of estrogen receptors, we found that irregular shape (88%) was the most important descriptor in estrogen-positive breast cancers (p value = 0.036). Our results reported that there were no statistically significant difference as regard mass margin (p value = 0.494). Our result are comparable with An et al. [9], who reported that irregular shape had a statistically significant difference (p value = 0.005) while there was no statistically significant difference as regards mass margin, posterior features, and echopattern in ER-positive cases (p value 0.83, 1.00, and 0.534, respectively). Our results are in agreement with the study done by Costantini et al. [15], who reported that antiparallel orientation was more frequent in ER-positive breast cancers 41 (82.0%) but with no statistically significant difference. Our results are in disagreement with the study done by Kim et al. [10], who reported that hypoechoic/complex echopattern, shadowing/combined posterior features, and anti-parallel

orientation have statistically significant association in ER-positive cases (p value 0.0033, 0.0566, and 0.0190, respectively).

As regards the association between the US descriptors with the state of progesterone receptors, we found that irregular shape and non-circumscribed margins were the most important descriptor in PR-positive breast cancers (p value = 0.026 and 0.068, respectively) respectively. This is in agreement with Moon et al. [21], who reported that irregular shape is frequently associated with progesterone receptor-positive cases (p value = 0.005) and Costantini et al. [15], who reported that non-circumscribed speculated margins are more frequently associated with progesterone positivity (p value = 0.009). In our study, there were no statistically significant difference in other US descriptor (orientation, echopattern, and posterior features) when correlated with the state of progesterone receptors (p value = 0.713, 0.526, and 1.000, respectively).

As regards the US correlation with the HER-2/neu oncogene expression, we found that there were no statistically significant difference between US descriptors (shape, margin, orientation, echopattern, and posterior features) and HER-2/neu state (p value 0.510, 0.639, 0.299, 0.898, and 1.000, respectively). This is in agreement with Kim et al. [10], who reported that there were no statistically significant difference between us descriptors (shape, margin, orientation, echopattern, and posterior feature) and HER-2/neu state (p value = 0.2521, 0.8243, 0.5334, 0.7620, and 0.2242, respectively). This also was in agreement with Cho et al. [16], who reported that there were no statistically significant difference as regards US descriptors (shape, margin, and orientation) and HER-2/neu state (p value = 0.173, 0.99, and 0.201, respectively).

As regards the US correlation with the ki67-positive breast cancer cases, we found that irregular shape and non-circumscribed margin are more frequent with ki76-positive cases with statistically significant difference (p value = 0.050 and 0.047, respectively). We concluded that there were no statistical significant association between ki76-positive breast cancers and US descriptors (echopattern and posterior feature) (p value = 1.000 and 0.248, respectively). Our results are comparable with Costantini et al. [15]. They concluded that echopattern and posterior features did not attain the level of statistical significance (p value 0.248 and 1.000, respectively).

Conclusion

Finally, we concluded that irregularly shaped tumors with speculated margins were frequently seen in invasive duct carcinoma and also more frequently seen in ER-, PR-, and Ki67-positive cases. No relation between ultrasound descriptors and the tumor grade of invasive duct carcinoma. Also, there were no relation between ultrasound descriptors and the state of HER-2/neu. So, ultrasound may be helpful in prediction of tumor response to therapy and prediction of prognosis in cases of breast cancer.

Abbreviations

ACR: American College of Radiology; BI-RADS: Breast imaging reporting and data system; DCIS: Duct carcinoma in situ; ER: Estrogen receptor; HER: Human epithelial growth factor receptor; IQR: Interquartile range; PR: Progesterone receptor; SD: Standard deviation; SPSS: Statistical Package for Social Sciences; US: Ultrasound; WHO: World Health Organization

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Authors' contributions

SE revised the collected data and the manuscript. DM performed US for all patients; found the correlation between the US findings and tumor type, grade, and state of biological markers; and wrote the manuscript. YA performed the statistical analysis. All authors read and approved the final 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.

Ethics approval and consent to participate

The study was approved by our institution's ethics committee (Mansoura Faculty of Medicine Institutional Research Board) (ethics committee reference number is MS/17. 02. 25), and all patients gave their written informed consent before inclusion in the study.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study. If the patient was less than 16 years old, deceased, or unconscious when consent for publication was requested, written informed consent for the publication of this data was given by their parent or legal guardian.

Competing interests

The authors declare that they have no competing interests.

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