Asian Oncology Research Journal

Volume 6, Issue 1, Page 46-53, 2023; Article no.AORJ.98631

Correlation of Ultrasonography Features of Breast Masses with Hormone Receptor Status and Molecular Subtypes of Breast Cancer

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/98631

Original Research Article

Received: 13/02/2023
Accepted: 15/04/2023
Published: 22/04/2023

ABSTRACT

Objectives: The purpose of the study is to inquire the possibility of predicting tumour subtypes of breast cancer based on imaging features of breast lesions on ultrasonography.
Methodology: This cross-sectional study was conducted on 55 patients who were referred to the department of Radiodiagnosis of K.S.Hegde Medical Academy who were diagnosed or suspected to have breast cancer. USG features of breast lesions were characterised based on BIRADS lexicon. After histopathological confirmation and Immunohistochemistry (IHC) analysis, lesions were classified into molecular subtypes. Association of the USG features of lesions with molecular subtypes and hormone receptor status were assessed statistically.
Results: Majority of the tumours belonged to Luminal B (LB) subtype followed by Triple negative breast cancer (TNBC), human epidermal growth factor receptor 2/neu (Her 2 Neu) enriched and Luminal A (LA) subtypes in descending order. Majority of LA subtype showed non parallel orientation, posterior acoustic shadowing, calcifications and vascularity. Most of the Her 2 neu

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enriched subtype showed non-parallel orientation, lesion calcifications and none showed posterior acoustic features. Non parallel orientation and increased vascularity were also observed in TNBC lesions. Posterior acoustic enhancement was seen in only TNBC subtype lesion. Lesions showing posterior acoustic shadowing were associated more with Hormone receptor (HR) positive status.
Conclusion: Though most of the subtypes of malignant breast tumours showed similar features on USG , the combination of features would help in predicting the molecular subtype to some extent.

Keywords: Ultrasonography; molecular subtypes; breast cancer; hormone receptor.

1. INTRODUCTION

Breast cancer is the most common malignant tumour and the major cause of death from cancer among women worldwide. It constitutes a diverse group of diseases with variable natural history, histopathological subtypes, biological and molecular characteristics [1]. The risk factors of breast cancer include genetic (BRCA 1 /BRCA 2 mutations), family history (especially in first degree relatives), reproductive (early menarche, early age of first pregnancy, late menopause and low parity), modern lifestyles and extremely dense breast [2].

The traditional classification of breast cancer was based on their histopathological features which determines the treatment type and prognosis of breast cancer. However, this classification is not sufficient to demonstrate the tumour heterogeneity.

A detailed molecular classification is the requirement for appropriate treatment and management as the latest anticancer drugs are based on these biological mechanisms. The St. Gallen International Expert Consensus recent classification on breast cancer was based on tumour markers like: estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2/neu (HER2 neu) and Ki-67. This classification system categorizes breast cancer into 5 molecular subtypes- Luminal A (LA), Luminal B (LB) with HER2/neu negative, Luminal B with HER2/neu positive, HER2/neu-enriched and Basal-like (Triple negative). Immunohistochemistry (IHC) is used as the gold standard for detecting ER/PR, HER2 neu status and Ki-67 levels [3].

Mammography and ultrasonography (USG) of the breast are used as common imaging techniques in the diagnosis of breast cancer throughout the world [4]. Various imaging characteristics of breast cancer were being studied on different modalities since long time with differentiation of tumours based on BIRADS (Breast Imaging Reporting And Database System). An effective method for the reduction of breast cancer mortality rates is to diagnose the disease at an early stage. With the knowledge of the effect of various biologic factors on breast cancer management and prognosis, more attention is needed towards diagnosis of molecular subtypes of breast cancer in addition to imaging diagnosis of benign vs malignant lesions. If imaging modalities can predict certain tumour subtypes it would help the clinicians and the patients for the management of disease accordingly with the resources available.

2. MATERIALS AND METHODS

This prospective cross-sectional study was conducted from April 2021 to September 2022 on 55 patients referred to the department of Radiodiagnosis of K.S.Hegde Medical Academy who were either diagnosed or suspected to have breast cancer. Patients who received neoadjuvant chemotherapy, who were on treatment during the study and who came for follow-up were excluded from the study. Informed consent of the patients were obtained prior to imaging.

Ultrasound was performed on all patients using Philips Affinity 70 ultrasound machine with linear array probe (7-12 MHz frequency). On USG, the breast mass features like echopattern, size, shape, orientation, margins, calcifications, posterior acoustic features and vascularity were assessed. The final assessment was made according to the BIRADS score, biopsy and histopathological examination of the breast masses. Following this, patients were evaluated for hormonal status of the breast lesions by IHC-ER, PR, HER2/neu and Ki 67 levels and the lesions were classified following St Gallen classification into molecular subtypes of LA, LB, HER2/neu-enriched and Triple negative. Tumours positive for either ER or PR or both were considered HR (Hormone receptor) positive tumours. The imaging features were then compared with hormonal status and molecular

subtypes of breast cancer. The data was analysed using SPSS version 22.0. Tests of significance between variables and within variables were tested with Chi-square tests. A *P-value* less than 0.05 was considered statistically significant.

3. RESULTS

The mean age of the participants in the study was 56.2 years with age range of 40-78 years. Scattered fatty and fibroglandular pattern (heterogenous echotexture) of breast parenchyma was the most common type observed in 58.2% of the participants followed by 27% of participants with fibroglandular pattern and 15% with fatty parenchyma. Invasive lobular carcinoma was the highest and was seen in 40% of the patients, followed by 36% of patients with invasive ductal carcinoma and 23% had invasive carcinoma of no special type. 60% of the patients showed HR positive status and the remaining 40% patients had HR negative status. 60% of the breast tumours showed Estrogen receptor positivity, while 38% showed Progesterone receptor positivity and 32% showed the presence of Her 2 Neu receptors. Majority of the tumours (52%) in the study were Luminal B subtype, 27% were TNBC, 13% were Her 2 Neu enriched type and 7% were Luminal A subtype (Fig. 1).

Among HR positive and HR negative tumours, the features observed in similar frequency (60%) were microlobulations and spiculated margins either in combination or alone, lesions with non-parallel orientation (>80%) and hypervascularity of the lesions (>70%). Lesions with calcifications within were also seen in similar frequency in HR positive and HR negative tumours. Statistically significant association was seen between posterior acoustic features of the lesion and HR status. Lesions showing posterior acoustic shadowing (42.4%) were associated more with HR positive status compared to HR negative status (Table 1).

In our study, all of the Luminal A subtype tumours and 50-60% of Luminal B and TNBC subtype tumours were observed in patients with scattered fatty and fibroglandular parenchyma (heterogenous echotexture). More than 50% of the lesions of all the subtypes showed spiculated margins or a combination of microlobulations and spiculated margins.

All of the Luminal A and Her 2 neu enriched tumour subtypes, 86% of Luminal B and 73% TNBC tumour subtypes showed non parallel orientation of the lesions. Posterior acoustic shadowing was observed in 75% of Luminal A subtype. Among all, TNBC subtype lesion alone showed posterior acoustic enhancement. All of the Her 2 neu enriched (100%) subtypes and

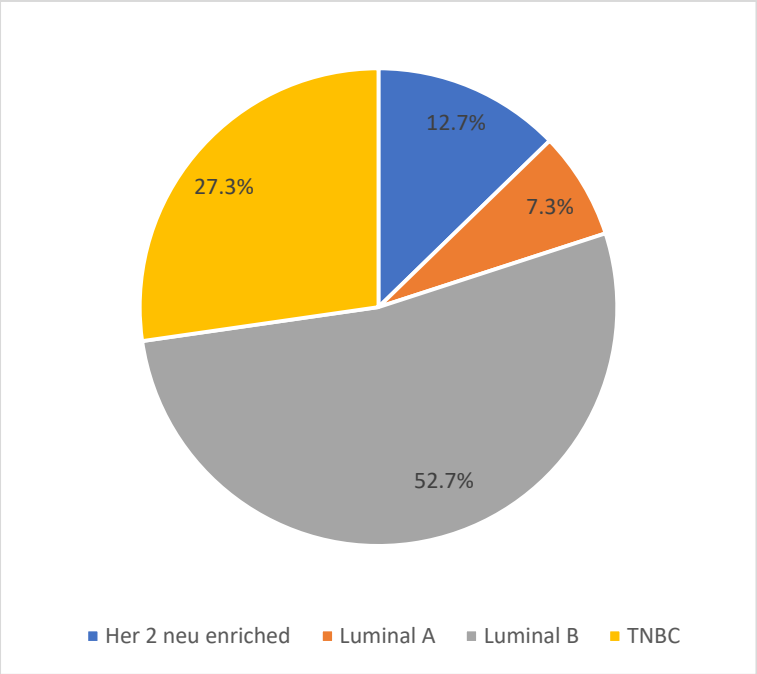

Fig. 1. Distribution based on the molecular subtype

Table 1. Association between USG features and HR status

HR status	USG features			Total	*P value*
	• **Lesion Orientation**				
	Non parallel [N (%)]	Parallel [N (%)]			
Negative	18 (81.8%)	4 (18.2%)		22	.53
Positive	29 (87.9%)	4 (12.1%)		33	
Total	47 (85.5%)	8 (14.5%)		55	
HR status	• **Lesion- Posterior features**				
	Enhancement	No features	Shadowing		
Negative	1 (4.5%)	19 (86.4%)	2 (9.1%)	22	.017*
Positive	0 (0.0%)	19 (57.6%)	14 (42.4%)	33	
Total	1 (1.8%)	38 (69.1%)	16 (29.1%)	55	
HR status	• **Lesion calcifications**				
	Nil [N (%)]	Present [N (%)]			
Negative	10 (45.5%)	12 (54.5%)		22	.82
Positive	14 (42.4%)	19 (57.6%)		33	
Total	24 (43.6%)	31 (56.4%)		55	
HR status	• **Lesion vascularity**				
	Absent [N (%)]	Present [N (%)]			
Negative	5 (22.7%)	17 (77.3%)		22	.70
Positive	9 (27.3%)	24 (72.7%)		33	
Total	14 (25.5%)	41 (74.5%)		55	

80% of the TNBC subtype showed no specific posterior acoustic features. Calcification within the lesion was observed in 71% of Her 2 neu enriched and 75% of Luminal A subtypes. All of the Luminal A subtype lesions and most of the TNBC (86%) and Luminal B (69%) subtypes showed hypervascularity (Table 2).

4. DISCUSSION

Even though the diagnostic features of malignant breast lesions on various imaging modalities were studied in the past with expanding knowledge of various biological factors implicated in breast cancer it is required to understand the possible role of imaging in differentiating the biological subtypes.

The grey scale ultrasonography features favouring malignancy in our study were irregular hypoechoic lesions(100%) in non-parallel orientation (86% of the lesions) with non-circumscribed margins and increased vascularity (75% of the lesions) which were similar to many other published studies, like Stavros et al [5] who described in their study that marked hypoechogenicity in malignant masses and another study by Choi et al's [6] who mentioned that non parallel orientation could be considered as an independent factor for malignant lesions. In a study conducted by Okello et al [7], it was mentioned that irregular shape of the lesion pointed towards inconsistent growth with advancement of lesion edge which was predictive of malignant outcome. 69% of the lesions in our study showed no characteristic posterior acoustic features. Posterior acoustic shadowing was observed in 29% of the lesions and only <2% showed posterior acoustic enhancement. Similar features were observed by Barman et al [8] in their study in which majority of the lesions (58%) showed no posterior features while posterior shadowing was seen in 34% and enhancement in 7.41%. It is mentioned in the literature that posterior attenuation of malignant breast masses is due to collagen fibres within or necrotic bleeding or calcification. Majority (75%) of the lesions in our study were hypervascular. Hypervascularity of the lesions was also reported by Kanika Gupta et al [9] in their study where in 77% of malignant breast masses showed hypervascularity. Tumour angiogenesis in malignant lesions is responsible for the increased vascularity [10].

Majority of LA subtype tumours in our study showed non parallel orientation (100%), posterior acoustic shadowing (75%), calcifications (75%) and vascularity (100%). Our findings are partly supported by a study conducted by Gopal R Vijayaraghavan et al [11] who mentioned that ER positive tumours were associated with nonparallel orientation, spiculated margins and posterior acoustic shadowing. Similarly, most of the Her 2 neu enriched subtype showed non parallel orientation (100%) and tumour

Table 2. Association between USG features and molecular subtypes

Molecular subtypes	USG features			Total	*P value*
	1.Lesion Orientation				
	Non parallel [N (%)]	Parallel [N (%)]			
Her 2 neu	7 (100.0%)	0 (0%)		7	.30
LA	4 (100%)	0 (0%)		4	
LB	25 (86.2%)	4 (13.8%)		29	
TNBC	11 (73.3%)	4 (26.7%)		15	
Total	47 (85.5%)	8 (14.5%)		55	
Molecular subtypes	**2. Lesion- Posterior features**				
	Enhancement	No features	Shadowing		
Her 2 neu	0 (0%)	7 (100.0%)	0 (0%)	7	.05
LA	0 (0%)	1 (25%)	3 (75%)	4	
LB	0 (0%)	18 (62.1%)	11 (37.9%)	29	
TNBC	1 (6.7%)	12 (80%)	2 (13.3%)	15	
Total	1 (1.8%)	38 (69.1%)	16 (29.1%)	55	
Molecular subtypes	**3. Lesion calcifications**				
	Nil [N (%)]	Present [N (%)]			
Her 2 neu	2 (28.6%)	5 (71.4%)		7	.61
LA	1 (25%)	3 (75%)		4	
LB	13 (44.8%)	16 (55.2%)		29	
TNBC	8 (53.3%)	7 (46.7%)		15	
Total	24 (43.6%)	31 (56.4%)		55	
Molecular subtypes	**4. Lesion vascularity**				
	Absent [N (%)]	Present [N (%)]			
Her 2 neu	3 (42.9%)	4 (57.1%)		7	.24
LA	0 (0.0%)	4 (100%)		4	
LB	9 (31%)	20 (69%)		29	
TNBC	2 (13.3%)	13 (86.7%)		15	
Total	14 (25.5%)	41 (74.5%)		55	

calcifications (71%). However, none of the lesions of Her 2 neu enriched subtype showed any posterior acoustic features and no association was observed with vascularity of the lesions. These features were also partly supported by a study conducted by Algazzar MAA et al [12] in which HER2/neu subtype lesions were significantly associated with calcifications and no significant association was seen with regard to posterior features.

Non parallel orientation and increased vascularity were also observed in most of the TNBC subtype lesions in our study. But compared to the other subtypes the association was relatively less. Even though the majority (80%) of TNBC subtype showed no posterior acoustic features, 6.7% of them showed posterior acoustic enhancement which was not observed in any other subtype. This was in concordance with Tandon et al's [13] study in which TNBC were associated with posterior acoustic enhancement, high vascularity and large size.

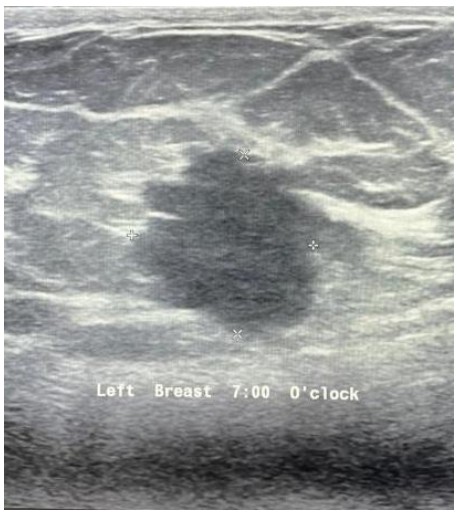

Fig. 2. USG image of a 66 year old female with lump in left breast showing irregular hypoechoic lesion with spiculated and angular margins. Histopathologically proven as Invasive carcinoma No special type and of Luminal B molecular subtype

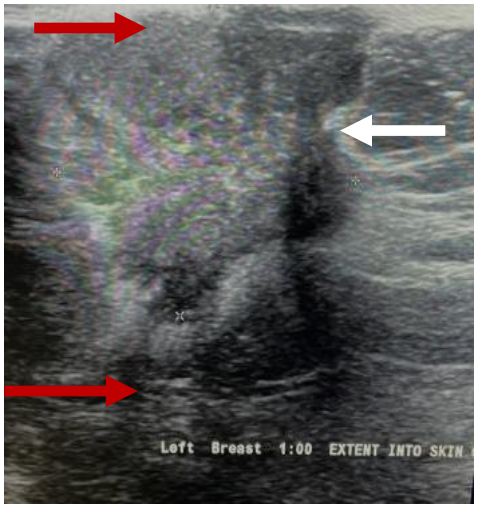

Fig. 3. 44 year old female with lump in left breast. USG images show a heterogeneously hypoechoic lesion with ill-defined margins, lobulations (white arrow) with extension into muscular plane posteriorly and into the skin anteriorly (Red arrows). Histopathologically proven as Invasive carcinoma - No special type and belonged to Luminal B subtype

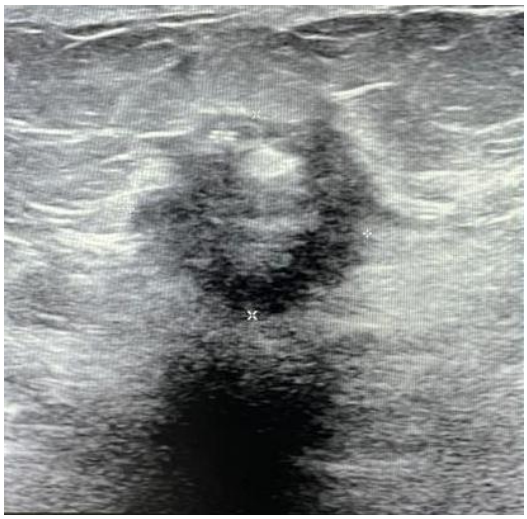

Fig. 4. 66 year old female- USG image shows an irregular hypoechoic lesion with spiculated margins and calcific foci within with posterior acoustic shadowing. Histopathologically proven to be invasive lobular carcinoma. Molecular subtype was Luminal A subtype

None of the HR positive lesions showed posterior acoustic enhancement in our study. Lesions showing posterior acoustic shadowing were more associated with HR positive status than HR negative status in our study and this association was statistically significant. This was concordant with the studies conducted by Irshad A et al [14] and Algazzar MAA et al [12]. Even though our study could not establish statistically significant association between molecular subtypes and grey scale USG features except HR status and posterior acoustic features of the lesions, most of our study results were matching with previous studies.

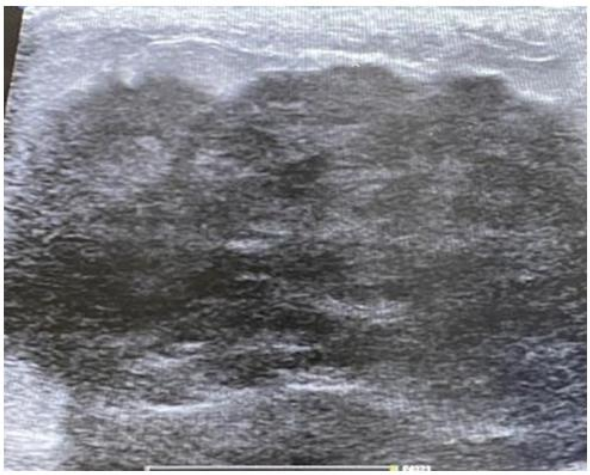

Fig. 5A

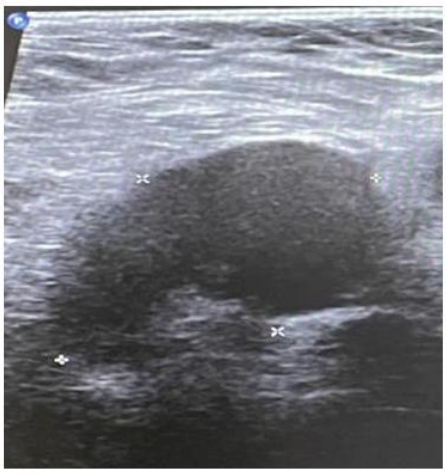

Fig. 5B

Fig. 5A and 5B. 53 year old female with right breast lump. USG images shows multilobulated hypoechoic lesion with posterior extension into muscular plane (Fig. 5A) and enlarged axillary lymphnodes (Fig. 5B). Histopathologically proven as Invasive ductal carcinoma and belonged to Triple negative biological subtype

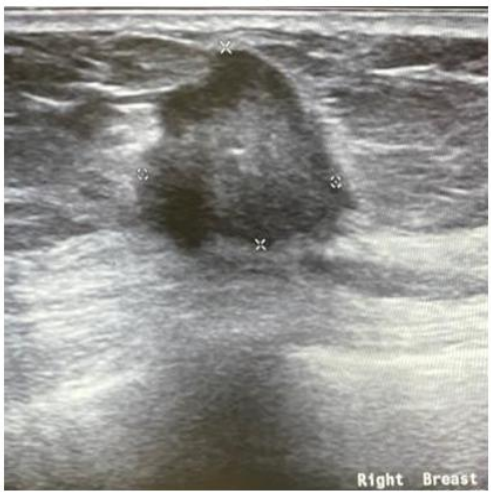

Fig. 6A

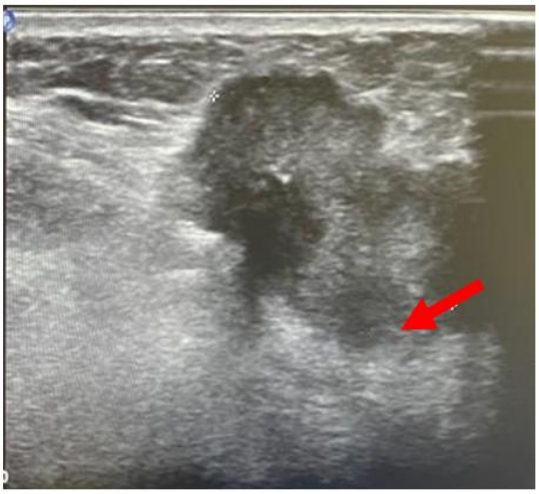

Fig. 6B

Fig. 6A and 6B. 60 year old female with lump in the right breast. USG images shows an irregular microlobulated hypoechoic lesion (Fig. 6A) with extension into underlying muscular plane (Red arrow in Fig. 6B). Histopathologically proven as Infiltrating ductal carcinoma and belonged to TNBC subtype

5. CONCLUSION

Evaluation of the USG features of breast lesions can help the radiologist to identify the malignant potential of the lesions. In our study, posterior acoustic shadowing is seen to be more associated with HR positive status. Features of non-parallel orientation, posterior acoustic shadowing, calcifications and hypervascularity of the lesion in combination can favour LA subtype lesion whereas lesions with non-parallel orientation, posterior enhancement or no posterior acoustic features and increased vascularity could suggest a TNBC subtype lesion. In addition, none of the subtypes other than TNBC showed posterior enhancement. Her 2 neu enriched subtype showed presence of calcification and no posterior features. Even though the grey-scale and Doppler features of the malignant lesions appeared to be common to all subtypes, based on the combination of the features it is possible to predict the subtypes. Since the major limitation of our study was the small sample size and lack of inclusion of all the imaging features of BIRADS lexicon of USG further similar studies on larger population is recommended.

ACKNOWLEDGEMENTS

No external funding was required for the study.

CONSENT

Written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

The study was approved by the Local Ethics Committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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https://www.sdiarticle5.com/review-history/98631