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Original Research Article

Correlative study of sonological appearance of BI-RADS 4 and above breast lumps with histopathology and immunohistochemistry markers

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ABSTRACT

Background: Breast cancer is clinically categorized into 4 major subtypes, ER (+), PR (+), Her2 (+), and TNBC. Although the correlation between sonographic features of breast cancer and immunohistochemistry markers expression is found, it is not still very clear; thus, this study aimed to investigate the ultrasound features of breast cancer and analyze the correlation between them.
Methods: This was a prospective study, in which patients with breast lumps were sonologically categorized as BI-RADS 4 and above. Percutaneous biopsy was done. Histopathology and immunohistochemistry markers were correlated with ultrasound findings.
Results: ER (+), PR (+) tumors were associated with irregular shape. ER (+), PR (+), and Her2 (+) tumors were associated with indistinct margin. TNBC tumor was associated with microlobulated margin. TNBC cases had more posterior acoustic enhancement.
Conclusions: Young female with ultrasound features of oval/round shape, micro-lobulated margin, abrupt tumor interface, showing posterior acoustic enhancement, absence of microcalcification was significantly associated with TNBC. Tumor with an irregular shape, indistinct margin, hyperechoic halo, no change in posterior acoustic feature, and presence of microcalcification were significantly associated with ER (+) cancers. Tumor with irregular shape, indistinct margin, and no change in the posterior acoustic feature was significantly associated with PR (+) cancers. Tumour with indistinct margin, and hyperechoic halo is significantly associated with Her2 (+) cancers. Tumor with irregular shape, indistinct margin, hyperechoic halo, and no posterior acoustic feature was associated with NTNBC.

Keywords: Breast cancer, Immunohistochemical markers, Non triple negative breast cancer, Triple negative breast cancer

INTRODUCTION

Breast cancer is one of the top cancers in women both in the developed and the developing world. The incidence of breast cancer is increasing in developing countries due to an increase in life expectancy, increased urbanization, and the adoption of Western lifestyles.[1] It is estimated that worldwide over 508,000 women died in 2011 because of breast cancer (Global Health Estimates, WHO 2013). The chance of getting breast cancer is increased by a factor of two or three if there is a family history of breast cancer. Breast cancer risk is greatly increased by mutations, especially in the p53, BRCA1, and BRCA2 genes. But these mutations are uncommon, and they only contribute a small amount to the global burden of breast cancer. One of the most significant risk factors for the development of breast cancer is reproductive factors, such as early menarche, late menopause, and late age at

first childbirth, which are linked to prolonged exposure to endogenous estrogen. Exogenous hormones also exert an increased risk for breast cancer. Oral contraceptive and hormone replacement therapy users are at higher risk for developing breast cancer than non-users. Breastfeeding has a protective effect.[1] Breast cancer is the most common cancer in women in India and it accounts for 27% of all cancers in women. According to Globocan 2012 data, new cases were registered: 1,44,937 and deaths: 70,218. Approximately, 1 in 28 women is likely to develop breast cancer during her lifetime. In rural areas, 1 in 60 women develops breast cancer in her lifetime as compared to in urban areas where 1 in 22 women are likely to develop breast cancer during her lifetime.[2] Ultrasound is usually the first line of investigation and is an important complement to both clinical examination and mammography in the evaluation of breast lesions. Radiologic imaging has a very important role in the diagnosis, staging, treatment, and follow-up of breast cancer patients, and it may also help to predict the molecular subtypes of breast cancer patients for guiding treatment.[3] Breast cancer is a highly heterogeneous disease with a variety of morphological and clinical manifestations, which results in a variety of responses after the treatment. Recently, targeted therapies based on the genetic, hormonal, or immunohistochemical (IHC) subtypes of breast cancer have been used.[4] Tumor size, lymph node status, histologic type, histologic grade, and estrogen receptor (ER), or progesterone receptor (PR) or human epidermal growth factor receptor 2 (HER2) expression status by immunohistochemistry (IHC) analysis are established as prognostic and predictive factors for breast cancers.[5] But the correlation between ultrasonic imaging features in breast cancer and the expression of ER, PR, and HER-2 is not still very clear, thus this study aimed to investigate the ultrasonic imaging features of breast cancer, and analyze its correlation between ER, PR, and HER-2 to provide a strong basis for clinical diagnosis and treatment and judging the prognosis.[6]

Aims and objectives

To correlate and characterize sonological features of BI-RADS 4 and above breast lumps with ER, PR, HER-2, TNBC, and NTNBC status. To correlate sonological features of BIRADS 4 and above breast lumps with various histological subtypes of breast cancer.

METHODS

A prospective study of patients with breast lumps from November 2018 to May 2020 were subjected to ultrasound examination of the breast and classified according to the BI-RADS lexicon. 72 patients with BIRADS 4 and above lesions were taken into the study. This was a prospective cross-sectional study done in Victoria Hospital attached to Bangalore Medical College and Research Institute, Bangalore. A total of 72 patients were studied from November 2018 to May 2020

Inclusion criteria

All BIRADS 4 and above breast lumps patients who were not on any chemotherapy or radiotherapy treatment.

Exclusion criteria

BIRADS III and below lesions. Patients on chemotherapy and radiotherapy treatment.

Technique of examination

Ultrasound analysis

All the real-time scanning was performed using PHILIPS Affiniti 50G, PHILIPS clearvue 350 ultrasound machines. Patients were examined in the supine position on the table in the ultrasound room. For all scanning, a linear transducer with a frequency range of 10-15 MHz was utilized. Transverse and longitudinal images were acquired through all masses during the real-time examination. An analysis was conducted on the ultrasound features, which included the maximum tumor size, margins, echogenicity, and predominant acoustic features posterior to the tumors. Four categories were identified based on the predominant posterior acoustic features: mixed pattern, no change, posterior enhancement, and posterior attenuation or shadowing. Tumor margins were classified as circumscribed, angular, spiculated, indistinct, micro-lobulated or lobulated. Breast lumps were staged according to BIRADS US description.[7] For each patient with BIRADS 4 and above the result of histopathological examination, tumor grading, ER, PR, and HER2 were considered. Percutaneous ultrasound-guided biopsy was done for BIRADS 4 and above breast lumps after explaining the procedure to the patients and informed written consent was taken from all the patients.

Pathologic analysis

Formalin-fixed and paraffin-embedded (FFPE) breast tissue samples were analyzed for tumor type, grade, and presence of hormone receptors. Tumor grade was classified according to the Nottingham combined histologic grading system-3 for invasive cancers based on gland and tubule formation, nuclear pleomorphism, and mitotic index.[8] Grade 1 was considered a low grade, grade 2 was considered a moderate grade, whereas grade 3 was considered a higher grade. Immunohistochemical stains were used to determine the status of the estrogen and progesterone receptors. Nuclear staining was categorized as positive in histopathology results if it was present in >10% of nuclei, borderline in nuclei between 1% and 10%, and negative in less than 1% of nuclei. The borderline group was viewed negatively in this study. The initial test for the Her2 was performed using immunohistochemical stains. Membrane staining observed in 0% to <10% of the invasive tumor cells was scored as 0, partial membrane staining in >10% of cells

was regarded as 1-positive, complete membrane staining in >10% of cells were regarded as 2-positive, and strong membrane staining in >30% of cells was regarded as 3-positive. A score of 0 or 1+ was regarded as unamplified, a score of 2+ as ambiguous, and a score of 3+ as positive. Ultrasound features were compared with histopathologic features, Grade and ER, PR, HER 2, and TNBC status.

Sample size estimation

Based on a previous study conducted by Yang et al, the mean invasive tumor size was 2.33±1.63 cm.[9] The sample size calculation was done as

$$n = \frac{Z_{\alpha}^{2}\sigma^{2}}{d^{2}}$$

From the above formula, the sample size was 50.

Statistical analysis

Data was entered into a Microsoft Excel data sheet and was analyzed using SPSS 22 version software. The chi-square test was used as a test of significance for qualitative data.

P value of <0.05 was considered statistically significant.

RESULTS

Although our sample size was 72, many tumors had more than one hormone receptor positivity.

Table 1: Mean age of the patients.

Hormone receptors	Mean age in years	SD	Minimum	Maximum
ER (+)	61.62	9.317	39	78
PR (+)	62.41	9.578	35	78
HER2 (+)	61.16	10.846	39	76
TNBC	54.21	10.886	35	73
NTNBC	61.85	9.528	35	78

The result was statistically significant between TNBC and NTNBC. The mean invasive tumor size was 2.29 cm for ER (+) cancers, 2.07 for PR (+), 2.17 cm for HER2 (+) cancers, 2.40 cm for TNBC cases, and 2.1 cm for NTNBC cases. The result was not statistically significant. ER (+), PR (+), and Her2 (+) cancers were more commonly associated with grade 2 tumors. The result was significant in ER (+) (54.1%) and PR (+) (56.2%) cancers. Tumor grade was more commonly grade 3 among TNBC cancers (63.2%) and more commonly grade 2 among NTNBC cases (54.7%). The result was statistically significant. If we consider grades 1 and 2 as low grade and grade 3 as high grade, then the high-grade tumor was significantly associated with TNBC (63.2%), and, the low-grade tumor was significantly associated with ER (+) (78.4%) and PR (+) (81.2%) tumors. ER (+) was found in 51.4% of cancers, PR (+) was found in 44.4% of cancers, Her2 (+) positivity was found in 34.7% of cancers and TNBC was found in 26.38% of cancers. Among 72 breast cancer cases, 19 (26.38%) were TNBC and 53 (73.61%) were non-TNBC cases.

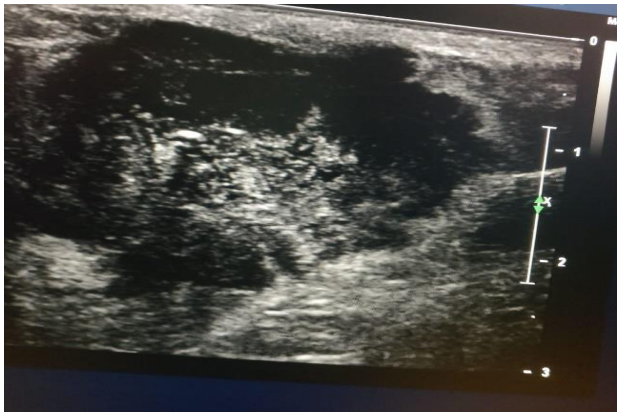

Figure 1: B mode ultrasound image of a 59-year-old female with a breast lump.

Showing well defined hypoechoic lesion measuring 4.9x4.2cm with parallel orientation with an irregular shape, indistinct margin, hyperechoic tumor halo, no obvious posterior acoustic feature and presence of microcalcification assessed as BIRADS 4C. Histologic diagnosis: invasive ductal carcinoma. Immunohistochemical diagnosis: ER (+) and PR (+) cancer.

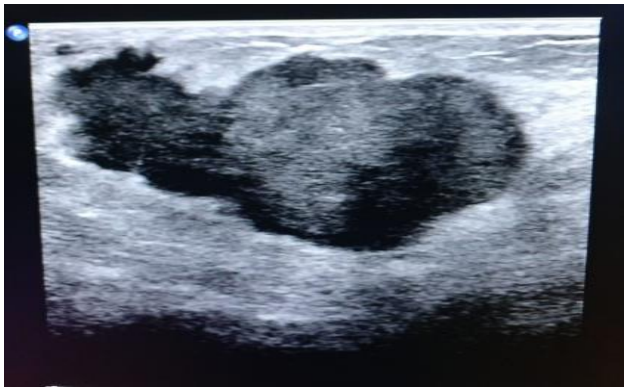

Figure 2: B mode ultrasound image of a 51-year-old female with a breast lump.

Showing well defined hypoechoic lesion measuring 5.1x3.2cm with parallel orientation with oval shape, micro-lobulated margin, with abrupt tumor interface, mild posterior acoustic enhancement, with absence of microcalcification, assessed as BIRADS 5. Histologic diagnosis: invasive ductal carcinoma. Immunohistochemical diagnosis: triple-negative breast cancer.

Pathologically invasive ductal carcinoma was the most common histologic type in ER (+) cancer, PR (+) cancer, HER2 (+) cancer, and TNBC cases. Ductal carcinoma in situ was found in ER (+) cancer (13.5%, 5 of 37), PR (+) cancer (15.6%, 5 of 32), and HER2 (+) cancer (28.0%, 7 of 25). Whereas it was not seen with TNBC, the result was statistically significant. Invasive lobular carcinoma was found in one of the ER (+) cancers (2.7%, 1 of 37). There were two medullary cancers among the TNBC

group (10.5%, 2 of 19). Mucinous carcinoma was found in ER (+) cancer (2.7%, 1 of 37), and Her2 (+) cancer, (4.0%, 1 of 25). The mass shape was more commonly irregular in ER (+) cancers (81.1%) and PR (+) cancers (81.4%). The result was statistically significant. The mass shape was more commonly irregular in NTNBC (77.4%) when compared to TNBC (47.4%). The result was statistically significant. The mass margin was more common with indistinct margin in ER (+) (56.8%), PR (+) (53.1%), HER2 (+) (68%), and NTNBC (62.3%). The result was statistically significant. All cases described in sonography as micro-lobulated margins were proved to be TNBC. The indistinct margin was significantly less commonly associated with TNBC (21.1%) than NTNBC (62.3%). The result was statistically significant. Hyper-echoic halo lesion boundary was commonly found in ER (+), PR (+), and HER2 (+) cancers. The result was statistically significant in HER2 (+) (60%) cases. Lesion boundary was an abrupt interface in TNBC cancers (84.2%). The result was statistically significant. ER, (+), and PR (+) tumors were significantly associated with no characteristic posterior acoustic features (46.8%, and 56.2% respectively). Posterior enhancement was more commonly seen in TNBC (63.2%) than in NTNBC (35.8%). No change was more commonly seen in NTNBC (43.4%) than in TNBC (10.5%). The result was statistically significant. Microcalcification was more commonly present in ER (+) cancers. Microcalcification was more commonly absent in TNBC (84.2%) than in NTNBC. There was no statistical significance between mass orientation and the tumoral subtypes. Echo pattern was more commonly hypoechoic in Her2 (+) cancers (72.0%) The result was statistically significant. No statistically significant Echo pattern was found in ER (+), PR (+), TNBC, and NTNBC cases. No statistical significance between mass shape, mass margin, lesion boundary, echo pattern, posterior acoustic features, and microcalcification with different histologic subtypes.

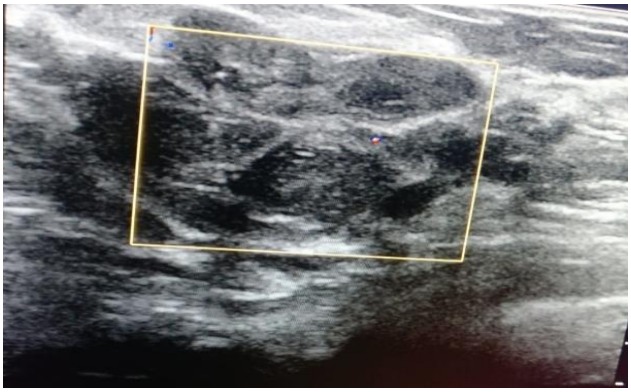

Figure 3: B mode ultrasound image of a 62-year-old female with a breast lump.

Showing an ill-defined hypo-isoechoic lesion measuring 3.9x2.8 cm with parallel orientation, irregular shape, indistinct margin, hyperechoic halo, no obvious posterior acoustic features and absence of microcalcification, assessed as BI-RADS 5. Histologic diagnosis: invasive ductal carcinoma. Immunohistochemical diagnosis: ER (+), PR (+), HER2 (+).

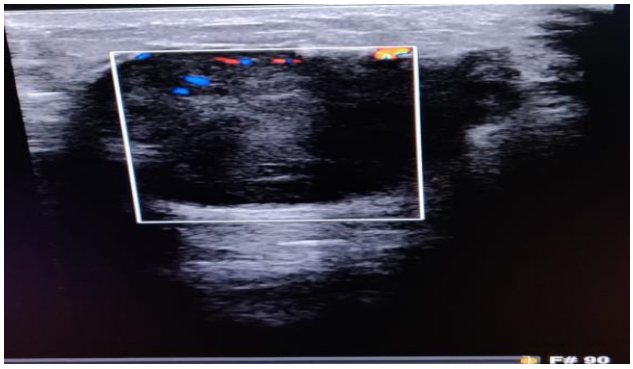

Figure 4: Well-defined hypoechoic lesion with round shape, micro-lobulated margin, abrupt tumor interface, posterior acoustic enhancement, with the absence of microcalcification.

Histologic diagnosis: medullary cancer. Immunohistochemical diagnosis: Triple-negative breast cancer.

DISCUSSION

Breast cancer is one of the top cancers in women both in the developed and the developing world. Breast cancer is the most common cancer in women in India and it accounts for 27% of all cancers in women. Ultrasound is usually the first line of investigation. The present study was undertaken with the aim of correlating and characterizing sonological features of BI-RADS 4 and above breast lumps with ER, PR, Her2, and TNBC status, and also with various histological subtypes of breast cancer. The mean age of patients among TNBC in the present study was significantly younger- 54.2 years compared to 61.8 years among the NTNBC group. This is similar to the study conducted by Wojcinski et al showed the mean age was 53.9 years among TNBC and 63.6 years among NTNBC cancers and the study conducted by Du et a, which showed it was 49 years among TNBC and 54 years among NTNBC.[10,11] The study conducted by Wojcinski et al showed mean tumor size was significantly larger (2.8 cm) among TNBC and smaller (2.0 cm) among NTNBC cases.[10] However, there was no significant association was found in the present study and also in the study conducted by Du et al.[11] In the present study, grade 3 (high grade) tumor was significantly associated with TNBC (63.2%) than NTNBC (28.3%) cases. Similar to the study conducted by Wojcinski et al and Du et al, grade 3 tumor was significantly associated with TNBC (80.8%; 80.0%) than NTNBC (22.1%; 21.9%) cases respectively.[10,11] Mass with irregular shape was significantly seen in ER (+), (81.1%); and PR (+) (76%). But no significant association was found in HER2 (+). This is similar to study the conducted by Elsaeid et al.[12] Similarly, Yang et al showed irregular shape was associated with ER (+), (80.8%); and HER 2 (+) (70.7%) cancers.[9] In the present study, TNBC cases were less commonly associated with irregular shape (47.4%) than TNBC (52.7%). This is similar to the study conducted by Du et al, which showed NTNBC cases are more commonly associated with irregular shape (77.0%) than TNBC (33.3%).[11] This is contrary to the study conducted

by Wojcinski et al, who showed no association between mass shape and TNBC/NTNBC, whereas Yang et al showed irregular margin is more commonly associated with TNBC (70.7%).[9,10] The present study showed that indistinct margin was significantly associated with ER (+) cancers (56.8%), PR (+) cancers (53.1%), and HER2 (+) cancers (68.0%). A similar study conducted by Yang et al showed no significant association between margin and tumor subtypes.[9] The present study showed all cases described in sonography as micro-lobulated margins were proved to be TNBC and TNBC cases were significantly associated with micro-lobulated margins (52.6%). Whereas a study conducted by Yang et al and Wojcinski et al showed there is no significant between tumor margin and tumor subtypes.[9,10] The present study showed ER (+) and HER (+) cancers are significantly associated with hyperechoic halo lesion boundary. None of the studies have done this ultrasound correlation with ER and HER 2 markers. The present study showed TNBC cases significantly associated with the abrupt interface (84.2%). This is similar to the study conducted by Costantini et al, who showed all TNBC cases associated with abrupt tumor interface.[13] Whereas the study conducted by Du et al did not show any association between tumor boundary and TNBC cases.[11] The present study showed, only ER (+) tumor was significantly associated with the presence of microcalcification (54.1%) in the mass. A similar study conducted by Yang et al showed both ER (+) and ER (+) tumors are associated with microcalcification.[9] The present study showed that TNBC was significantly associated with an absence of microcalcification (84.2%). It is similar to the study conducted by Yang et al and Du et al where it was 80.5% and 64.4% respectively.[9,11] The present study showed, there is no significant association between tumor orientation and tumor subtypes. This is similar to the study conducted by Du et al and Wojcinski et al.[10,11] The present study showed ER (+) and PR (+) tumors were significantly associated with no characteristic posterior acoustic features (46.8%, and 56.2% respectively). Whereas a similar study conducted by Yang et al showed no such significant correlation among tumour markers.[9] The present study showed that TNBC cases are significantly associated with posterior acoustic enhancement. Even a study conducted by Wojcinski et al and Du et al also showed similar findings.[10,11] However, a study conducted by Yang et al showed no such significant correlation seen in TNBC cases.[9] The present study showed invasive ductal carcinoma was most commonly the histological type in ER (+), HER2 (+), and TNBC (81.1%, 68.0%, 89.5%) respectively. Similar to the present study, Yang et al showed invasive ductal carcinoma was most commonly the histological type in ER (+), Her2 (+), and TNBC (79.0%, 68.2%, 85.4%) respectively.[9] Similar to the present study (0%), a lower incidence of ductal carcinoma in situ was found in the study conducted by Yang et al, (7.4%).[9] The present study showed invasive ductal carcinoma was the most common histologic type among TNBC (89.5%), and NTNBC (79.2%). Similar to the present study, invasive ductal carcinoma was the most common histologic type among TNBC (88.5%), and NTNBC (79.3%) in the conducted by Wojcinski et al.[10] Our study showed that there was no statistical significance between mass shape and margin with the different histologic subtypes. In contrast to the study conducted by Elsaeid et al showed that irregular shape and speculated margins were more frequently associated with invasive duct carcinoma than DCIS.[12] The present study showed there was no statistical significance between mass shape, tumor orientation, and echo pattern with the different histologic subtypes. However, a study conducted by Kim et all showed Invasive cancers displayed more frequently an irregular shape, a not parallel orientation, and a hypoechoic or complex echo pattern than carcinoma in situ cases.[14]

Summary

In our study total of 72 patients were evaluated for ultrasound features of breast cancer using a linear transducer. Percutaneous ultrasound-guided biopsy of the lesions were done and the specimen was sent for histopathologic and immunohistochemistry analysis. It was found that young age with ultrasound features of oval/round shape, micro-lobulated margin, abrupt tumor interface, posterior acoustic enhancement, and absence of microcalcification was significantly associated with TNBC. Tumor with an irregular shape, indistinct margin, hyperechoic halo around the lesion, no obvious posterior acoustic feature, and absence of microcalcification was significantly associated with ER (+) cancers. Tumor with an irregular shape, indistinct margin, and no obvious posterior acoustic feature were significantly associated with PR (+) cancers. Tumor with indistinct margin, and hyperechoic halo lesion boundary was significantly associated with HER2 (+) cancers. Tumor with an irregular shape, indistinct margin, hyperechoic halo, and no posterior acoustic feature was associated with NTNBC. No significant ultrasound features were found to distinguish various histologic subtypes of breast cancer. Hence correlation was found between ultrasound features and the immunohistochemical status of breast cancer. This needs meta-analysis to find whether ultrasound can replace immunohistochemical laboratory analysis which will be time effective and cost effective and which will help the patient therapeutically

There are few limitations also. The sample size was small. Imaging features of the TNBC at different cancer stages were not analyzed, which might influence the imaging features at the diagnosis. Although ultrasound can predict the immunohistochemical subtypes, it still needs further confirmation because of the uncertain and complex biological mechanism involved in triple-negative breast cancer.

CONCLUSION

The present study was aimed at the correlation of ultrasound features of BIRADS 4 and above breast

lesions with the immunohistochemistry markers (ER, PR, HER2, TNBC). This was done by describing the various ultrasound features of the lesion and later comparing it with the immunohistochemical markers. Patients with TNBC are significantly younger when compared to NTNBC. The mean size of the tumor was larger in TNBC when compared to NTNBC. ER (+) and PR (+) tumors were significantly associated with low-grade (grade 1 and 2) tumors and TNBC was significantly associated with high-grade (grade 3) tumors. HER2 (+) tumor was associated with low-grade (grade 1 and 2) tumors. ER (+), and PR (+) tumors were significantly associated with irregular shape. TNBC tumor was more commonly associated with round/oval shape. HER2 (+) tumor was commonly associated with irregular shape. ER (+), PR (+), and HER2 (+) tumors were significantly associated with indistinct margins. TNBC tumor was significantly associated with micro-lobulated margin. NTNBC cases had more commonly indistinct and spiculated margins than TNBC. Hyperechoic halo around the mass was significantly associated with ER (+) and Her2 (+) cancers. In contrast, lesion with abrupt interface was significantly associated with TNBC. The posterior acoustic feature was most commonly no change in ER (+) and PR (+) cancers. TNBC cases had more significant posterior acoustic enhancement. Microcalcification was associated with ER (+) cancers. At the same time, the absence of microcalcification was significantly associated with TNBC. ER (+), PR (+), HER2 (+) and TNBC cases had more commonly nonparallel orientation. HER2 (+) cancers had significantly hypoechoic mass. Whereas ER (+), PR (+), and TNBC also had more commonly hypoechoic mass patterns. Invasive ductal carcinoma (NST) had a more common hypoechoic pattern, irregular shape, indistinct margin, abrupt tumor interface, posterior acoustic enhancement, and absence of microcalcification. Ductal carcinoma in situ had a more common hypoechoic pattern, irregular shape, indistinct margin, and hyperechoic halo around the mass, showing no significant posterior acoustic features.

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