Sonographic features of invasive ductal breast carcinomas predictive of malignancy grade

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Abstract

Context: Assessment of individual sonographic features provides vital clues about the biological behavior of breast masses and can assist in determining histological grade of malignancy and thereby prognosis. Aims: Assessment of individual sonographic features of biopsy proven invasive ductal breast carcinomas as predictors of malignancy grade. Settings and Design: A retrospective analysis of sonographic findings of 103 biopsy proven invasive ductal breast carcinomas. Materials and Methods: Tumor characteristics on gray-scale ultrasound and color flow were assessed using American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) Atlas Fifth Edition. The sonographic findings of masses were individually correlated with their histopathologic grades. Statistical Analysis Used: Chi square test, ordinal regression, and Goodman and Kruskal tau test. Results: Breast mass showing reversal/lack of diastolic flow has a high probability of belonging to histological high grade tumor (β 1.566, P 0.0001). The masses with abrupt interface boundary are more likely grade 3 (β 1.524, P 0.001) in comparison to masses with echogenic halos. The suspicious calcifications present in and outside the mass is a finding associated with histologically high grade tumors. The invasive ductal carcinomas (IDCs) with complex solid and cystic echotexture are more likely to be of high histological grade (β 1.146, P 0.04) as compared to masses with hypoechoic echotexture. Conclusions: Certain ultrasound features are associated with tumor grade on histopathology. If the radiologist is cognizant of these sonographic features, ultrasound can be a potent modality for predicting histopathological grade of IDCs of the breast, especially in settings where advanced tests such as receptor and molecular analyses are limited.

Key words: BI-RADS; breast malignancy; histological grade; invasive ductal carcinoma; ultrasound

Introduction

Ultrasound is used as a first line modality of imaging for breast masses in patients less than 35 years and as an adjunct to mammography in older patients.[1-4] The purpose of this study was to investigate whether high resolution ultrasound is able to predict the likelihood of histological grade of invasive ductal breast carcinomas. This study aims to find out which sonographic features based on American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) Atlas Fifth Edition help in predicting

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the histological grade of tumor. This information may be useful to pick up high risk patients for nodal metastasis on ultrasound. To our knowledge, no report has correlated gray scale and vascularity findings in invasive ductal breast carcinomas that were analyzed according to BI-RADS Fifth Edition with histological grades.

Materials and Methods

This study was conducted using a retrospective case record review design. A total of 394 solid breast masses were evaluated by ultrasound in the department of radiodiagnosis from May 2013 to September 2016. Out of these, we identified 103 biopsy proven invasive ductal breast carcinomas [Figure 1]. Each of these masses was assessed based on sonographic findings and color flow as per ACR BI-RADS Atlas Fifth Edition. The study was approved by the institutional review board and ethics committee of the institution. The study group comprised of patients which were positive for invasive ductal carcinoma (IDC) of breast on core needle biopsy and had both sonographic images and histopathological data available. The age of the patients ranged from 31 years to 78 years.

Sonographic analysis

Ultrasound examination of breast masses was done on a Philips ultrasound machine unit (HD7/Clearvue 650) using linear, high frequency (3–12 MHz), and curvilinear (2–5 MHz) transducers. Each breast mass was assessed and given a BI-RADS grade based on its sonographic features as per ACR BI-RADS Atlas Fifth Edition by two radiologists with experience of 10 or more years. Each mass was characterized on sonography based on its shape, orientation, margin, echo pattern, posterior features, calcifications, presence of associated features if any, and color flow [Table 1]. “Lesion boundary” though has been eliminated in the ACR BI-RADS Atlas Fifth Edition, was additionally used in this study to describe the breast mass, since review of literature suggested a significant association between boundary zone and low/high grades of tumor.

Histopathological analysis

The histopathological study of each breast mass was performed by the department of pathology in our institution. The biopsy specimens were received in 10% buffered formalin. All specimens were routinely processed for histological examination. The related pathology reports were obtained from the department of pathology.

Table 1: Descriptors on ultrasound for characterization of each solid mass

| Sonographic feature | Sonographic descriptor |
|---------------------|-----------------------|
| Shape               | Oval, Round, Irregular |
| Orientation         | Parallel, Not parallel |
| Margin              | Circumscribed, Not circumscribed, Indistinct, Angular |
| Echo pattern        | Anechoic, Hyperechoic, Complex cystic and solid, Hypoechoic, Isoechoic, Heterogeneous |
| Posterior features  | No posterior features, Enhancement, Shadowing, Combined pattern |
| Calcifications      | Absence of suspicious calcifications, Presence of suspicious calcifications, Calcifications in a mass, Intraductal calcifications |
| Associated features | No features, Architectural distortion, Duct changes, Skin changes, Thickening, Retraction, Retraction, Edema |
| Vascularity         | Internal vascularity absent, Internal vascularity present with no reversal/inversion of diastolic flow, Internal hypervascularity present with reversal/inversion of diastolic flow |

Figure 1: Sample included in the study analysis
using graded alcohols, cleared in xylene and embedded in paraffin wax and 4–6 micron thickness sections were cut. All sections were stained with hematoxylin and eosin stain. The histopathological grading was performed with modified Bloom Richardsons' scoring for grading invasive ductal breast carcinomas.[6,7] Three factors were taken into consideration—gland formation, nuclear features, and mitotic activity. A score of 1–3 was given to each factor and then each score was added to give a final total score ranging from 3 to 9. The total score was used to determine the grade [Table 2]. Cancers with score of 3–5 were graded as 1, cancers with a score of 6–7 were graded as 2 and cancers with a score of 8–9 were graded as 3.

Table 2: Scoring system for histological grading of invasive ductal carcinoma (IDC)-breast

| Bloom Richardsons' score | Grade |
|--------------------------|-------|
| 3-5                      | 1     |
| 6-7                      | 2     |
| 8-9                      | 3     |

**Statistical analysis**

The results for qualitative data was presented in frequency and percentage. Chi-square test was used to find association between histological grades of IDC (dependent parameter) and their sonographic features (independent parameters) [Table 3]. Ordinal regression was used to predict the contribution of each independent parameter to arrive at the final histological grade, which happens to be the dependent parameter in our study [Table 4]. Ordinal regression is a multivariate statistical analytical method which is applied for ordinal dependent variables, in our case the histological grade of IDC. It is more advantageous than logistic and multinomial regression as it treats the dependent variable as an ordinal variable and gives estimates of regression coefficients. The regression coefficients have to be interpreted as the chance of moving from the lowest grade of IDC to the highest grade with shift in the category of the ultrasound finding from the lowest to the highest in the predictability of histological grade.

**Table 3: Distribution of histological grade by sonographic feature category**

| Ultrasound characteristics            | Histological grade on biopsy | Total n (%) |
|---------------------------------------|------------------------------|-------------|
|                                       | 1 n (%) | 2 n (%) | 3 n (%) |                      |
| Shape                                 |          |          |          | 0.006**              |
| Oval                                  | 3 (7.1%)| 7 (19.4%)| 4 (16%)  | 14 (13.6%)           |
| Round                                 | 1 (2.4%)| 7 (19.4%)| 0%       | 8 (7.8%)             |
| Irregular                              | 38 (90.5%)| 22 (61.1%)| 21 (84%)  | 81 (78.6%)           |
| Margin                                |          |          |          | 0.79                 |
| Circumscribed                         | 5 (11.9%)| 3 (8.3%)  | 3 (12%)  | 11 (10.7%)           |
| Indistinct                            | 16 (38.1%)| 17 (47.2%)| 9 (36%)  | 42 (40.8%)           |
| Angular                               | 1 (2.4%)| 3 (8.3%)  | 1 (4%)   | 5 (4.9%)             |
| Microlobulated                        | 11 (26.2%)| 7 (19.4%)  | 9 (36%)  | 27 (26.2%)           |
| Spiculated                            | 9 (21.4%)| 6 (16.7%)  | 3 (12%)  | 18 (17.5%)           |
| Echo pattern                          |          |          |          | 0.236                |
| Complex cystic and solid              | 1 (2.4%)| 4 (11.1%)  | 3 (12%)  | 8 (7.8%)             |
| Hypoechoic                            | 41 (97.6%)| 32 (88.9%)| 22 (88%)| 95 (92.2%)           |
| PAF                                   |          |          |          | 0.488                |
| No features                           | 16 (38.1%)| 15 (41.7%)| 9 (36%)  | 40 (38.8%)           |
| Enhancement                           | 13 (31%)| 9 (25%)  | 11 (44%) | 33 (33%)             |
| Shadowing                             | 10 (23.8%)| 6 (16.7%)  | 4 (16%)  | 20 (19.4%)           |
| Combined pattern                      | 3 (7.1%)| 6 (16.7%)  | 1 (4%)   | 10 (9.7%)            |
| Suspicious calcification              |          |          |          | 0.385                |
| Absent                                | 25 (59.5%)| 25 (68.4%)| 15 (60%)  | 65 (65%)             |
| Intra mass calcification              | 15 (35.7%)| 8 (22.2%)  | 7 (28%)  | 30 (29.1%)           |
| Intramass and Intra ductal           | 1 (2.4%)| 0.00%    | 2 (8%)   | 3 (2.9%)             |
| Intra ductal calcification            | 1 (2.4%)| 3 (8.3%)  | 1 (4%)   | 5 (4.9%)             |
| Doppler                               |          |          |          | 0.0001***            |
| Absence of internal vascularity      | 20 (47.6%)| 19 (52.8%)| 8 (32%) | 47 (45.6%)           |
| Internal vascularity present with no reversal/inversion of diastole | 21 (50%)| 8 (22.2%) | 6 (24%) | 35 (34%)             |
| Internal vascularity present with reversal/inversion of diastole | 1 (2.4%)| 9 (25%)  | 11 (44%) | 21 (20.4%)           |
| Boundary                              |          |          |          | 0.0001***            |
| Echogenic halo                        | 37 (88.1%)| 20 (55.6%)| 10 (40%) | 67 (65%)             |
| Abrupt interface                      | 5 (11.9%)| 16 (44.4%)| 15 (60%) | 36 (35%)             |

NS: Not Significant, ***Highly significant. Pearson χ² test was used.
The statistical analysis was done using SPSS 21.0 in our study. The significance level was used at $P \leq 0.05$.

**Results**

The analysis included 103 invasive ductal breast carcinomas diagnosed on core biopsy in 101 patients (100 females and 1 male). Bilateral cancer was present in two patients. The bivariate analysis of the sonological characteristics of masses with histological grading is shown in Table 3. Multivariate ordinal regression analysis and the regression coefficients with 95% confidence intervals are depicted in Table 4.

**Echopattern:** Based on the prior studies, most malignant masses are hypoechoic with some showing complex solid cystic mass with heterogeneous echotexture. In our study, 95 (92.2%) masses were hypoechoic and eight (7.8%) masses had complex solid cystic mass with heterogeneous echotexture [Table 3; Figures 2 and 3]. No masses had hyperechoic, isoechoic, or anechoic echotexture. The ordinal regression results in our study revealed that complex solid cystic IDCs with heterogeneous echotexture have greater chance of having histological grade 3 as compared to masses having hypoechoic echotexture ($\beta 1.146$, $P 0.04$) [Table 4; Figure 4].

**Vascularity:** Fifty six (54.4%) masses out of 103 depicted one or more suspicious features of malignancy on color flow: internal hypervascularity with tortuous and irregular vessels, central distribution, presence of penetrating artery [Figure 5A] [Table 3]. Out of 56 masses showing internal vascularity, 21 (20.4%) masses depicted presence of reversal/lack of diastolic flow—a unique vascular finding [Figure 5B and C] [Table 3]. All 21 masses which depicted presence of reversal/lack of diastolic flow were correlated with their histological grades [Figure 5B and C]. 11 (52%) masses belonged to histological grade 3, 9 (43%) belonged to histological grade 2, and only 1 (5%) mass having reversal/lack of diastolic flow belonged to histological grade 1. A strong association of reversal/lack of diastolic flow with high histological grade of tumor was noted ($P 0.0001$) [Table 3]. Ordinal regression statistics depicted that masses with reversal/lack of diastolic flow had a greater chance of belonging to histological grade 3 tumor as compared to masses without it ($\beta 1.566$, $P 0.001$) [Table 4].

**Boundary:** An echogenic halo boundary zone is a prominent feature to suggest malignancy in a breast mass and was seen in 67 (65%) masses in our study. Thirty six (35%) masses had abrupt interface with surrounding breast parenchyma. We assessed the occurrence of both boundary zones in histological grade 3 tumors and found that 15 (60%) masses had abrupt interface and 10 (40%) masses had echogenic halos [Table 3]. In histological grade 1 IDCs, 37 (88%) masses had echogenic halos, and five (12%) masses had abrupt interfaces [Figures 2 and 6]. Ordinal regression statistics depicted that masses with reversal/lack of diastolic flow had a greater chance of belonging to histological grade 3 tumor as compared to masses without it ($\beta 1.566$, $P 0.001$) [Table 4].
results suggested that mass had a greater chance of belonging to histological grade 3 when boundary zone was “abrupt interface instead of echogenic halo” ($\beta$ 1.524, $P$ 0.001) [Table 4; Figure 7].

Calcifications: In this study suspicious calcifications suggestive of malignancy were present in only 38 (36.9%) masses, located inside the breast mass and/or inside the dilated duct/s adjacent to it [Table 3]. IDCs which had calcifications present both within the mass and ducts showed a greater chance of having grade 3 tumor as compared to masses without it ($\beta$ 1.847, $P$ 0.039) [Table 4; Figure 8].

Margin: Indistinct margin was seen in 42 (40.8%) IDCs making it the commonest margin in our study, followed by microlobulated margins in 27 (26.2%) and spiculated margins in 18 (17.5%) masses. Spiculated margins were present in 21.4% of histological grade 1 IDCs, 16.7% of grade 2, and 12% of grade 3 IDCs [Table 3]. The histological grade 3 tumors had indistinct margins in 9 (36%), microlobulated margins in 9 (36%), circumscribed margins in 3 (12%), spiculated margins in 3 (12%), and angular margins in 1 (6%) mass [Table 3]. Ordinal regression results, however, suggested that margin of a mass did not contribute significantly to the prediction of histological grade in this study.

Shape: Irregular shape of a mass is a suspicious feature of malignancy, as was also observed in our study. Of all IDCs, 81 (78.6%) masses had irregular shapes, followed by oval shape in 14 (13.6%) and round shape in 8 (7.8%) masses [Table 3]. The histological grade 1 IDCs had irregular shape in 81 (90%) masses on ultrasound. The shape of the mass depicted statistically significant association with histological grade of tumor ($P$ 0.006) [Table 3]; however, ordinal regression results showed that shape does not predict the histological grade of IDC ($P$ 0.119) [Table 4].
Posterior features: The most common posterior feature in our study was masses showing neither posterior enhancement nor posterior shadowing, seen in 40 (38.8%) IDCs. The posterior enhancement was present in 33 (32%) masses and posterior shadowing (either alone or in combination with enhancement) in 30 (29.8%) masses ($P=0.488$) [Table 3]. Review of literature suggested an association of posterior enhancement with high-grade tumor and posterior shadowing with low-grade tumor; however, we found no statistically significant association between posterior features and grade of tumor ($P=0.63$, Table 5).

Orientation: The orientation of a breast mass perpendicular to the longitudinal plane of the breast is a very important diagnostic sign of malignancy. In our study, 65 (63.1%) masses had antiparallel orientation with no statistically significant distribution noted to suggest any association with grades of malignancy [Table 5].

Discussion

Ultrasound is a safe and widely available imaging modality for diagnostic evaluation of breast lesions, in addition to mammography.$^{[12-23]}$. Primarily, breast ultrasound has been used to differentiate benign and malignant lesions.$^{[4,5,8]}$. However, many studies have also looked at utilizing the tissue information available with ultrasound to differentiate various grades of malignancy in breast carcinomas.$^{[9-11]}$. BI-RADS lexicon use facilitates quality assurance, communication, research, and patient care.$^{[4,5,8]}$. In the present study, we used the latest (Fifth) Edition of ACR BI-RADS Atlas to individually assess ultrasound descriptors of breast masses for prediction of histological grade of IDC.$^{[5]}$. The role of vascularity within the mass was also assessed.$^{[12-14]}$. This study depicted a strong association of presence of reversal/lack of diastolic flow with histologically high grades of IDCs [Figure 9].

Features of masses on ultrasound as abrupt interface of tumor, complex solid cystic mass with heterogeneous echotexture, and presence of suspicious calcifications located intraductally and within the mass were shown to have a mild to moderate association with histologically high grades of IDCs.

The management of breast malignancies and its prognosis is guided largely by its histological grade. The prognosis of a breast malignancy depends largely on the histological grade and biological markers as estrogen receptor, progesterone receptor, and human epithelial growth factor receptor.$^{[15-18]}$. In many countries, advanced modalities and tests such as receptor analyses are not widely available and therefore ultrasound is often the primary modality of imaging of a breast mass. The detection of cancer is the primary goal of breast imaging. Several prior studies have established that the major ultrasound features characterizing a malignant mass include hypoechoic or complex echotexture of the mass, irregular shape, and antiparallel orientation.$^{[5,11,17]}$. Additionally, if we also describe the sonographic features of the mass that suggest high aggressiveness of that malignant lesion, that information can be very useful to the referring surgeon in management of the patient. This particular information can be specifically used to identify the high-risk patient for lymph node metastasis.$^{[19,20]}$. Previous studies have indicated that there is evidence of ultrasound features and pathological tumor grade correlation in breast malignancies.$^{[19-11,15-17]}$. Some prior studies found that sonographic features of posterior enhancement and well circumscribed margins of a mass are features commonly

Figure 7 (A and B): A 47-year-old female patient with left breast mass. (A) Gray scale ultrasound image demonstrating sonographic features of abrupt interface surrounding the hypoechoic mass. (B) Histological sections revealed composition of cells arranged in sheets (asterisk) with nuclear pleomorphism and increased mitotic activity (arrow) more than 15 per 1 hpf proving to be grade 3 IDC. 400×, Hematoxylin and Eosin stain

Figure 8 (A and B): A 34-year-old female patient with right breast mass—gray scale ultrasound image demonstrating sonographic features of presence of intra-mass calcifications (lines in A) and ductal dilatation (DD) with intra ductal calcifications (B). This mass was proven to be grade 3 invasive ductal carcinoma (IDC) on histopathology

Figure 9 (A and B): A 55-year-old female patient with right breast mass. (A) Spectral Doppler image demonstrating presence of reversal of diastolic flow. (B) Histological sections showing composition of cells arranged in tubules (arrow) and in sheets (asterisk) with nuclear pleomorphism and mitotic activity between 8 and 14 per 10 hpf proving to be grade 2 invasive ductal carcinoma (IDC). 400×, Hematoxylin and Eosin stain
Table 5: Degree of strength of sonographic features in relation to histological grades

| S. no | Sonographic features | \( \tau \) | \( P \) |
|-------|---------------------|----------|-------|
| 1     | Margin              | 0.012    | 0.772 |
| 2     | Echotexture         | 0.028    | 0.239 |
| 3     | Boundary            | 0.176    | 0.068 |
| 4     | Shape               | 0.077    | 0.003**|
| 5     | Orientation         | 0.005    | 0.781 |
| 6     | PAF                 | 0.014    | 0.636 |
| 7     | Suspicious calcification | 0.014 | 0.633 |
| 8     | Doppler             | 0.081    | 0.002**|

Figure 10: A 40-year-old female patient with left breast mass—gray scale ultrasound image demonstrating sonographic features of ductal dilatation (DD) and intraductal calcifications (marked by lines) on ultrasound.
The color flow findings when used in association with gray-scale features can provide useful information in differentiating benign and malignant breast masses.[12‑14] ACR BI‑RADS Atlas Fifth Edition used three descriptors of color flow to describe the vascularity of mass: absent, internal vascularity, and vascularity in rim.[15] Features as internal vascularity with irregular vessels and a central distribution, with or without an observable penetrating artery, high RI greater than 0.8 and Pulsatility index greater than 0.4 are suggestive signs of malignancy on color Doppler.[12‑14] The presence of reversal/lack of diastolic flow is known to be a specific (specificity up to 99% and positive predictive value up to 97%) sign of malignancy.[12] In this study, the presence of reversal/lack of diastolic flow was the strongest predictor to suggest histologically high grade of tumor ($\tau = 0.081, P = 0.002$) [Table 5]. A larger previous study of 826 breast lesions found that though infrequently seen (14% in their study), sign of inversion/lack of diastolic flow when present, was suggestive of high aggressiveness of lesion.[13] Our study found a strong association between reversal/lack of diastolic flow and histological high grades of tumor ($P = 0.0001$) [Table 3]. The presence of reversal/lack of diastolic flow was infrequently seen in our study (20.4%), and found significant association with histologically high grade of IDCs ($\beta = 1.566, P = 0.001$) [Table 4].

There are a few limitations in our study. Due to retrospective nature, analysis was based on some selected images of the case rather than evaluating the masses in real-time. A possible source of bias in the study is that the radiologists were aware that the study comprises of only biopsy proven breast masses and this may have affected their observation of ultrasound features. We tried to minimize bias by selecting all biopsy proven cases of IDC within a given time frame. Another limitation of our study is a relatively small sample size. Despite these limitations, our study provides valuable information about sonographic features of breast masses that correlate with high malignancy grade. Further work with larger studies is needed to elucidate the full potential of sonography for predicting the histological grade of tumor.

Conclusion

In conclusion, our study confirms that histological grades of invasive ductal breast carcinomas determine differences in ultrasound imaging. The masses with complex solid cystic mass with heterogeneous echotexture, abrupt interfaces, calcifications and/or presence of reversal/lack of diastolic flow may suggest high grade of tumors. The finding of reversal/lack of diastolic flow in a breast mass was the strongest predictor of high grade of tumor in our study and warrants early lymph nodal sampling.

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Conflicts of interest
There are no conflicts of interest.

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