The Association Between Ultrasound Features and Biological Properties of Invasive Breast Carcinoma Is Modified by Age, Tumor Size, and the Preoperative Axilla Status

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Objectives—To investigate the value of ultrasound (US) feature-based models in predicting the proliferation and invasiveness of invasive breast cancer (IBC) and to compare the performance of models based solely on US features with models that combined US features, patient age, tumor size, and axilla status from US.

Methods—With ethical approval, 746 patients with a pathologic diagnosis of IBC were reviewed for preoperative clinical, US, and postoperative pathologic data. The proliferation and invasiveness properties of the IBC included the histologic grade and Ki-67 status and lymphovascular invasion (LVI) and axillary lymph node metastasis (ALNM), respectively. Logistic regression analyses were used to identify independent risk factors for tumor proliferation and invasiveness.

Results—Posterior echo enhancement, calcification, a tumor size larger than 2 cm, and suspicion of ALNM from axillary US were independent risk factors for a high histologic grade and high Ki-67 expression of IBC (\(P < .05\)). A posterior echo shadow, patient age younger than 45 years, and suspicious findings on axillary US imaging were independent variables for predicting the presence of LVI and ALNM in IBC (\(P < .05\)). Calcification was the independent factor for predicting LVI (\(P = .013\)). The predictive performance of the combined models was improved compared with the US feature-based models, with a higher accuracy rate and negative predictive value. The area under curve of the combined models was also significantly higher than that of the single models (\(P < .05\)).

Conclusions—Compared with the US feature-based models, the combined models yielded better predictive performance. This may provide a more robust model to predict the tumor biological properties of IBC before surgery.

Key Words—invasive breast cancer; invasiveness; proliferation; ultrasound features

Breast cancer is a complex disease with varied therapeutic responses and clinical outcomes due to its heterogeneity. Current clinical practice for breast cancer management is generally based on histologic and molecular criteria. Therefore, it is important to expand the knowledge of the various histologic and molecular characteristics of this disease, which is a focus of ongoing research by clinicians, pathologists, and biologists. Meanwhile, the radiographic appearance of malignant tumors...
might also be influenced by the histologic and molecular characteristics of the breast cancer.\(^5\) It has been proved that imaging features in multiple modalities such as ultrasound (US), mammography, magnetic resonance imaging, and positron emission tomography–computed tomography are associated with the biological properties of breast cancers.\(^5\)–\(^9\)

These imaging data are usually acquired before biopsy or surgery. The characterization of biological properties of breast cancers based on imaging features may therefore assist in developing personalized treatment planning and prognosis prediction at an early stage.\(^4\)

Breast US has now evolved as a standard protocol followed by most hospitals as an effective and important diagnostic tool in addition to mammography in the evaluation of clinically or radiologically suspicious abnormalities of breasts.\(^10\) However, the current clinical application of US is mainly limited to distinguishing malignant breast lesions from benign ones. In fact, biomedical images contain hidden information on histologic and molecular characteristics of tumor lesions.\(^11\)–\(^12\) Several studies have determined the association between US features and biological behaviors of breast cancers.\(^13\)–\(^15\) Our preliminary results have shown that the proliferation and invasiveness of invasive breast cancer (IBC) were associated with the US features derived before surgery.

Patient age, tumor size, and the preoperative axilla lymph node status from US are parameters considered prognostic indicators in breast cancer\(^16\) and can also be acquired before surgery. We hypothesized that these characteristics might have added value in predicting the proliferation and invasiveness of IBC when combined with US features. The purpose of this study was to investigate the value of US feature-based models in predicting the proliferation and invasiveness of IBC and to compare the predictive performance of the models based solely on US features with models that combined US features, patient age, tumor size, and the axilla node status from US.

**Materials and Methods**

**Patient Enrollment**

The study protocol was approved by the Institutional Review Board of Fudan University Shanghai Cancer Center (number 1802181-22-NSFC), and informed consent was waived because of the retrospective design of the study. From July 2014 to August 2018, a total of 952 consecutive female patients who had a diagnosis of IBC by surgical pathologic examinations at our center were collected. All patients underwent a routine preoperative US examination for the evaluation of breast lesions and the status of axillary lymph nodes. Patients with nonmass breast cancer \((n = 23)\), bilateral or multifocal masses \((n = 59)\), recurrence or large mass lesions involving the whole breast \((n = 39)\) and patients who had received neoadjuvant therapy \((n = 67)\) and had poor-quality US images \((n = 18)\) were excluded. Finally, 746 female patients were included in this study. To evaluate the effect of age on the tumor proliferation and invasiveness, patients were sub grouped into those younger than 45, 45 to 60, and older than 60 years.

**Ultrasound Examination and Image Analysis**

A US examination was performed with high-end US equipment including Mylab90 (Esaote SpA, Genoa, Italy), iU22 (Philips Healthcare, Andover, MA), Aixplorer (SuperSonic Image, Aix-en-Provence, France), LOGIQ E9 (GE Healthcare, Wauwatosa, WI), and Apio 500 (Toshiba Medical Systems, Tokyo Japan). All machines were equipped with high-frequency (5–14 MHz) linear array transducers. Ultrasound images of breast lesions and axillary lymph nodes were recorded and saved as the Digital Imaging and Communications in Medicine format for a double-blind review. Two dedicated radiologists with greater than 5 years of clinical experience in breast US and the Breast Imaging Reporting and Data System lexicon\(^17\) reviewed these images independently. Disagreements between the radiologists were solved by a joint review to reach a consensus.

According to the Breast Imaging Reporting and Data System lexicon,\(^17\) US features of the breast masses were assessed in terms of orientation (parallel or not parallel), shape (regular or irregular), margin (circumscribed or not circumscribed), spiculated/angular margin (yes or no), acoustic pattern (hypoechoic, mixed solid echo, complex cystic, or solid echo), posterior acoustic pattern (shadow, enhancement, combined pattern, or no posterior features), and the presence of calcification on US images (yes or no). The lesion size was measured by US in 3 dimensions in accordance with the Breast Imaging
Reporting and Data System benchmark. The length at the maximum dimension was defined as the tumor size and was subgrouped into smaller than 2 cm and 2 cm or larger.

Ultrasound parameters used for identifying suspicious lymph nodes included irregular shape, eccentric cortical thickening (>3 mm), absence of the fatty hilum, hypoechogeticity, and a noncircumscribed margin. Lymph nodes with 3 or more US parameters were considered highly suspicious. In contrast, lymph nodes with less than 3 US parameters were considered of low suspicion. Lymph nodes with none of these criteria were described as normal. The US evaluation of the axillary lymph nodes was classified as normal findings, high suspicion of metastasis, or low suspicion of metastasis.

Pathologic and Immunohistochemical Analyses
Breast specimens were routinely fixed in formalin, embedded with paraffin, and subsequently subjected to hematoxylin-eosin staining. The tumor characteristics of pathologic type, histologic grade, lymphovascular invasion (LVI), and axillary lymph node metastasis (ALNM) were assessed by reviewing hematoxylin-eosin–stained slices from postoperative paraffin wax specimens. Based on the Nottingham histologic grade, breast specimens were categorized into 3 groups: I (high differentiation), II (moderate differentiation), and III (poor differentiation). Considering the limited number of the highly differentiated breast carcinoma, grades I and II were combined to be low grade, whereas grade III was high grade.

Positive expression of Ki-67 was defined as brown-stained particles in the nucleus after a standardized immunohistochemical staining procedure. The Ki-67 index was scored as high expression when 20% or more of the nucleus was immunostained; otherwise, it was considered low expression.

Clinical- and US Feature-Based Predictive Model for IBC Proliferation and Invasiveness
To predict the tumor proliferation and invasiveness characteristics of IBC including the histologic grade and Ki-67 status and LVI and ALNM, logistic regression models based on US features of tumor lesions solely and the combination of US features, age, tumor size, and axillary ultrasound (AUS) were established. The performance of these models was compared.

Statistical Analyses
Statistical analyses were performed with SPSS version 23.0 software for Mac (IBM Corporation, Armonk, NY). Continuous and categorical variables were presented as mean ± standard deviation and frequency (percent), respectively. Categorical variables were compared by a $\chi^2$ test. Binary univariate and multivariate logistic regression analyses were used to determine the independent risk factors that were correlated with tumor proliferation and the invasiveness of IBC; those with $P < .05$ were further considered in the multivariate logistic regression analysis. Odds ratios with 95% confidence intervals were recorded to quantify the correlations between covariates and outcomes. Receiver operating characteristic curves were plotted to assess the predictive performance of the independent risk factors based on the multivariate model (MedCalc version 15.8 software; MedCalc, Ostend, Belgium). The differences between predictive models were compared by the area under the curve using the DeLong test. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were also calculated to evaluate the performance of predictive models. Two-tailed $P < .05$ was considered statistically significant.

Results
In total, there were 746 patients in this study, with a mean age of 52.4 ± 11.6 years (range, 24–90 years) at diagnosis, and the mean tumor size measured by US was 2.3 ± 0.9 cm (range, 0.5–8.2 cm). Among them, 9 patients (1.2%) had histologic grade I; 331 patients (44.4%) had grade II; and 383 patients (51.3%) had grade III. The remaining 23 patients (3.1%) with an unknown histologic grade in the pathologic report were excluded from the analysis for the tumor proliferation assessment.

The US and clinical characteristics of IBC and their associations with tumor proliferation (histologic grade and Ki-67 status) and invasiveness (LVI and ALNM) are summarized in Table 1. The orientation, morphologic characteristics, spiculated/angular margin, posterior acoustic pattern, calcification, AUS staging, and tumor size were significantly associated with the histologic grade and Ki-67 level ($P < .05$). Ki-67 expression was also correlated with patient age ($P = .018$) and the acoustic pattern ($P = .042$) of IBC. The
| Parameter                        | Grade | OR (95% CI) | Grade | OR (95% CI) | Grade | OR (95% CI) | Grade | OR (95% CI) |
|---------------------------------|-------|-------------|-------|-------------|-------|-------------|-------|-------------|
| Orientation                     |       |             |       |             |       |             |       |             |
| Parallel                        | 1.02  | (.95 - 1.09)| 0.98  | (.91 - 1.06)| 1.01  | (.95 - 1.07)| 1.02  | (.95 - 1.09)|
| Not parallel                    | .01   | (.00 - 1.00)| .02   | (.00 - 1.02)| .05   | (.01 - 1.09)| .09   | (.01 - 1.00)|
| Morphologic characteristics     |       |             |       |             |       |             |       |             |
| Regular                         | 1.00  | (0.87 - 1.14)| 1.00  | (0.87 - 1.13)| 1.00  | (0.87 - 1.13)| 1.00  | (0.87 - 1.13)|
| Irregular                       | .49   | (.25 - 0.93)| .53   | (.28 - 1.00)| .53   | (.28 - 1.00)| .53   | (.28 - 1.00)|
| Margin                          | .40   | (.26 - 0.62)| .40   | (.26 - 0.62)| .40   | (.26 - 0.62)| .40   | (.26 - 0.62)|
| Acoustic pattern                | .63   | (.39 - 1.01)| .63   | (.39 - 1.01)| .63   | (.39 - 1.01)| .63   | (.39 - 1.01)|
| Calci                           | .01   | (<.001 - 1.00)| .01   | (<.001 - 1.00)| .01   | (<.001 - 1.00)| .01   | (<.001 - 1.00)|
| No posterior features           |       |             |       |             |       |             |       |             |
| Size, cm                        |        |             |        |             |        |             |        |             |
| AUS                             |         |             |         |             |         |             |         |             |
| High suspicion of ALNM          | .22   | (.03 - 1.70)| .22   | (.03 - 1.70)| .22   | (.03 - 1.70)| .22   | (.03 - 1.70)|
| Low suspicion of ALNM           | 1.00  | (0.87 - 1.13)| 1.00  | (0.87 - 1.13)| 1.00  | (0.87 - 1.13)| 1.00  | (0.87 - 1.13)|
| Reference                       | 1.00  | (0.87 - 1.13)| 1.00  | (0.87 - 1.13)| 1.00  | (0.87 - 1.13)| 1.00  | (0.87 - 1.13)|
| OR                              | 0.99  | (.95 - 1.03)| 0.99  | (.95 - 1.03)| 0.99  | (.95 - 1.03)| 0.99  | (.95 - 1.03)|

CI indicates confidence interval; and OR, odds ratio.
tumor shape, posterior acoustic pattern, AUS staging, tumor size, and patient age were found to be significantly associated with LVI and ALNM ($P < .05$). Lymphovascular invasion was also correlated with the presence of calcification ($P = .003$).

The independent US and clinical features for a high histologic grade and Ki-67 level and the presence of LVI and ALNM were identified, as shown in Tables 2 and 3. In the single model based on US features, posterior echo enhancement and calcification were independent US features of high cellular proliferation of IBC (Table 2; $P < .05$), whereas an irregular shape and a posterior echo shadow were independent US characteristics for predicting both LVI and ALNM.

### Table 2. Multivariate Analysis of Correlative US for Higher Tumor Proliferation and Invasiveness Properties of IBC

| Parameter                  | $B$  | SE  | $P$   | OR (95% CI)     |
|----------------------------|------|-----|-------|-----------------|
| Predictive factors for a higher tumor grade |       |     |       |                 |
| Posterior echo enhancement | 1.16 | 0.23 | <.001 | 3.20 (2.04–5.01) |
| Calcification              | 0.41 | 0.17 | .014  | 1.51 (1.09–2.10) |
| Predictive factors for a higher Ki-67 index |       |     |       |                 |
| Posterior echo enhancement | 1.91 | 0.38 | <.001 | 6.75 (3.20–14.23) |
| Calcification              | 0.89 | 0.21 | <.001 | 2.43 (1.62–3.64) |
| Predictive factors for LVI |       |     |       |                 |
| Irregular shape            | 0.49 | 0.21 | .021  | 1.63 (1.08–2.46) |
| Posterior echo shadow      | 0.52 | 0.22 | .016  | 1.68 (1.10–2.57) |
| Calcification              | 0.50 | 0.16 | .002  | 1.65 (1.20–2.26) |
| Predictive factors for ALNM |       |     |       |                 |
| Irregular shape            | 0.51 | 0.22 | .018  | 1.66 (1.09–2.53) |
| Posterior echo shadow      | 0.49 | 0.21 | .021  | 1.64 (1.08–2.49) |

CI indicates confidence interval; and OR, odds ratio.

### Table 3. Multivariate Analysis of correlative US and Clinical Features for Higher Tumor Proliferation and Invasiveness Properties of IBC

| Parameter                  | $B$  | SE  | $P$   | OR (95% CI)     |
|----------------------------|------|-----|-------|-----------------|
| Predictive factors for a higher tumor grade |       |     |       |                 |
| Posterior echo enhancement | 1.15 | 0.23 | <.001 | 3.17 (2.01–4.98) |
| Calcification              | 0.36 | 0.17 | .035  | 1.44 (1.03–2.02) |
| Size $\geq$ 2 cm           | 0.41 | 0.17 | .016  | 1.51 (1.08–2.12) |
| High suspicion of ALNM     | 1.03 | 0.21 | <.001 | 2.80 (1.86–4.21) |
| Low suspicion of ALNM      | 0.69 | 0.22 | .002  | 1.99 (1.28–3.08) |
| Predictive factors for a higher Ki-67 index |       |     |       |                 |
| Posterior echo enhancement | 1.78 | 0.38 | <.001 | 5.92 (2.79–12.57) |
| Calcification              | 0.77 | 0.21 | <.001 | 2.16 (1.43–3.26) |
| Size $\geq$ 2 cm           | 0.57 | 0.19 | .003  | 1.77 (1.22–2.58) |
| High suspicion of ALNM     | 0.74 | 0.25 | .003  | 2.10 (1.28–3.48) |
| Predictive factors for LVI |       |     |       |                 |
| Posterior echo shadow      | 0.65 | 0.25 | .009  | 1.91 (1.18–3.10) |
| Calcification              | 0.45 | 0.18 | .013  | 1.57 (1.10–2.23) |
| Age $\leq$ 45 y            | 1.00 | 0.25 | <.001 | 2.72 (1.68–4.39) |
| High suspicion of ALNM     | 2.24 | 0.21 | <.001 | 9.42 (6.20–14.32) |
| Low suspicion of ALNM      | 0.80 | 0.22 | <.001 | 2.23 (1.45–3.43) |
| Predictive factors for ALNM |       |     |       |                 |
| Posterior echo shadow      | 0.61 | 0.25 | .016  | 1.84 (1.12–3.01) |
| Age $\leq$ 45 y            | 0.64 | 0.25 | .012  | 1.90 (1.15–3.12) |
| High suspicion of ALNM     | 2.97 | 0.24 | <.001 | 19.43 (12.06–31.30) |
| Low suspicion of ALNM      | 0.53 | 0.23 | .020  | 1.71 (1.09–2.68) |

CI indicates confidence interval; and OR, odds ratio.
Table 4. Predictive Performance of US Feature-Based and Combined Models

| Biological Characteristic | Method   | Accuracy, % | Sensitivity, % | Specificity, % | PPV, %   | NPV, %   | AUC (95% CI)     |
|--------------------------|----------|-------------|----------------|----------------|----------|----------|-----------------|
| High grade               | US-based | 62.8        | 56.7           | 69.7           | 67.8     | 58.8     | 0.67 (0.63–0.70) |
|                          | Combined | 69.2        | 72.3           | 65.6           | 70.3     | 67.8     | 0.73 (0.70–0.77) |
| High Ki-67               | US-based | 62.4        | 58.5           | 75.4           | 87.7     | 37.8     | 0.72 (0.69–0.75) |
|                          | Combined | 74.9        | 72.8           | 68.5           | 87.3     | 45.7     | 0.75 (0.71–0.79) |
| LVI                      | US-based | 59.4        | 48.3           | 66.3           | 47.1     | 67.3     | 0.59 (0.56–0.63) |
|                          | Combined | 74.4        | 59.1           | 83.9           | 69.6     | 76.7     | 0.77 (0.73–0.80) |
| ALNM                     | US-based | 49.7        | 76.6           | 33.8           | 40.7     | 70.9     | 0.58 (0.55–0.62) |
|                          | Combined | 78.6        | 59.4           | 90.0           | 77.8     | 78.8     | 0.79 (0.76–0.83) |

AUC indicates area under the curve; CI, confidence interval; NPV, negative predictive value; and PPV, positive predictive value.

Figure 1. Receiver operating characteristic curves of US and combined methods for the prediction of a higher histologic grade (A), Ki-67 positivity (B), LVI (C), and ALNM (D).
Discussion

An accurate evaluation of the histologic and molecular characteristics of IBC before further diagnostic steps might be beneficial for treatment selection as well as for the assessment of the prognosis. Hence, it is of importance to develop a clinically applicable method to preoperatively evaluate the biological characteristics of IBC. In our experience, US features have a correlation with the proliferation and invasiveness of IBC. However, the performance of US features in predicting the biological behavior of IBC was less satisfactory. In addition, not all cases of IBC show the typical US features indicated for certain biological characteristics, and variations may occur depending on the patient’s individual characteristics. In the literature, it was reported that the tumor size, patient age, and nodal status were significantly associated with the biological characteristics of tumors. For instance, a tumor size larger than 2 cm was more common in human epidermal growth factor receptor 2 and triple-negative subtypes of IBC; patients younger than 50 years showed more hormone receptor–negative cancers compared with older patients; and nodal metastases were more frequent in patients with the human epidermal growth factor receptor 2 subtype. Therefore, when evaluating the biological properties of tumors, these preoperative clinical parameters should be taken into consideration. To our knowledge, this is the first study that established a prediction model for the biological behavior of IBC using preoperative US, clinical, and AUS features. Compared with the models based solely on US features, the combined prediction models based on the US features, patient age, tumor size, and preoperative axilla status from AUS achieved higher predictive performance for tumor proliferation and invasiveness.

An advanced histological grade and the Ki-67 status were associated with a high proliferation rate of malignant breast tumors. In this study, we found that posterior echo enhancement and calcification were independent US features for predicting tumor proliferation. Tumors with a high histological grade and high Ki-67 expression are expected to have a high mitotic rate and short doubling time. The tumors are prone to be homogeneous with intensive cellularity, leading to less US wave attenuation and enhanced through-transmission, which result in posterior echo enhancement. Meanwhile, a higher proliferation rate suggests rapid tumor growth and a more active metabolism. When nutrition and oxygen inside the tumor are insufficient, local ischemic necrosis and calcium deposition occur, which result in the observation of calcification on US images.

We also found that a larger tumor size and suspicion of ALNM from AUS were the independent predictors of a higher tumor proliferation rate. This finding was in agreement with previous studies showing that the breast tumor size increased with an upgrade of the tumors, and the maximum tumor diameter was significantly associated with high Ki-67 expression. Axillary US is a simple test, which is routinely applied for assessing the axilla nodal status in patients with breast cancer. Previous studies reported an association between highly suspicious lymph node metastasis from AUS and the incidence of a high histologic grade. In addition, Dihge et al reported that the findings from AUS were significantly related to the Ki-67 expression level. These previous studies provided robust support of our finding that suspicion of ALNM from AUS is capable of indicating a higher tumor proliferation rate.

The presence of LVI and ALNM was associated with the invasive characteristics of breast cancer and was a factor on which to base the treatment plan.
In agreement with a previous report, our results showed that US features of an irregular shape and a posterior echo shadow were independent predictors of LVI and ALNM. The irregular shape of breast cancer indicated the inconsistent tumor edge resulting from the uniform invasion of cancer cells into surrounding breast tissues. The invasion also results in fibrosis, which leads to sound attenuation that forms a posterior acoustic shadow. Additionally, calcification was also an independent predictor of LVI, which was similar to the result obtained in the work of Gajdos et al. In addition, patients younger than 45 years and suspicious AUS findings had independent value for predicting ALNM and LVI. Similar results have indicated that the positivity of LVI and ALNM drops in younger (<50 years) patients. Since the menstrual status is age related, both a hormonal effect and time-dependent exposure might be reasonable explanations. It was reported that suspicious lymph nodes from AUS were the strongest predictor of ALNM. Since LVI was the highest risk factor for ALNM, the abnormal AUS findings might also be able to suggest LVI.

An irregular shape, a posterior echo shadow, and calcification are well-acknowledged typical US features of malignant breast tumors. Breast lesions with these features tend to have a high risk of lymphovascular involvement. Posterior echo enhancement is an indicator of a benign tumor; however, it may also occur in highly proliferative tumors. False classification may result in harmful consequences for patients. Therefore, it is essential for US physicians to be aware of the variations in US morphologic characteristics of breast cancer and the potential association with biological properties. Since a preoperative AUS examination is always a part of a conventional US examination for patients with breast cancer in most Chinese cancer centers, tumor size and age information are routinely available before surgery, and this combined model might offer clinical physicians a new way to predict the biological behavior of IBC. In addition, considering the heterogeneity of the breast cancers, the model based on clinical, US, and AUS findings may shed light on the development of radiomics and artificial intelligence by incorporating all preoperative variables rather than focusing on the image itself. A prospective study using a combined model based on high-throughput US features and other preoperative data to predict biological properties of breast cancers has been initiated at our center.

Our study had some limitations. First, in this retrospective study, only breast lesions with a complete data archive were included, which resulted in an unavoidable selection bias. The stiffness of a breast lesion is also an important US feature. However, US elastography is not routinely performed at our center. Therefore, we did not include elastographic data in this study. Lesion stiffness can be considered in future research. Second, the assessment of US features was based on a review of stored still images. This might have caused misinterpretation or missing information. A prospective study with a video loop stored for image evaluation has been initiated at our institute. Third, our results may not be applicable to non-IBC cases as well as patients who have accepted neoadjuvant chemotherapy before surgery.

In conclusion, US features of IBC were found to be correlated with the tumor proliferative and invasive characteristics. The predictive performance of the US feature-based models was improved when incorporating preoperative variables such as the patient age, tumor size, and axilla status from AUS. This may offer clinical physicians a more robust model to accurately predict the biological properties of IBC before surgery.

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