AJR FOCUS ON:

Assessing the Role of Ultrasound in Predicting the Biological Behavior of Breast Cancer

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OBJECTIVE. The purpose of this article is to correlate various ultrasound features of breast cancer with tumor grade, and with estrogen, progesterone, and *ERRB2* (formerly *HER2*) receptor status as well as to assess the predictive value of these features.

MATERIALS AND METHODS. The features of breast cancers found by using ultrasound between January 2010 and June 2011 were reviewed for tumor size, margins, and posterior acoustic features. The tumor margins were classified into spiculated, angular, indistinct, lobulated or microlobulated, and circumscribed. The posterior acoustic features were classified into shadowing, enhancement, mixed pattern, and no change. The individual features were correlated with the estrogen receptor (ER)-progesterone receptor (PR) and *ERRB2* receptor status and tumor grade.

RESULTS. Among 160 patients with breast cancer, 102 (63.8%) were ER-positive/PR-positive, 32 (20.0%) were ER-positive/PR-negative, and 26 (16.3%) were ER-negative/PR-negative (22 were triple-negative). Tumors with posterior shadowing have greater than nine times the odds of having ER-positive findings (95% CI, 2.09–40.81; $p = 0.011$) and greater than 13 times the odds of having a lower-grade tumor (I or II vs III; 95% CI, 4.90–36.54; $p < 0.001$) than those without posterior shadowing. Tumors with posterior enhancement have greater than eight times the odds of having at least one negative receptor (95% CI, 3.97–18.11; $p < 0.001$) and 24 times the odds of having a high-grade tumor (95% CI, 9.91–58.14; $p < 0.001$) than those without posterior enhancement.

CONCLUSION. The presence of posterior shadowing is strongly associated with an ER-positive and low-grade tumor, whereas the presence of posterior enhancement is strongly associated with a high-grade tumor and with moderate risk of being receptor negative.

Keywords: breast cancer, estrogen receptor, progesterone receptor, triple-negative tumor, ultrasound

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Many studies have already established that a distinctive subgroup of breast cancer patients who lack the expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (*ERRB2*, formerly *HER2*) in their tumor cells show a worse prognosis because of the aggressive behavior of this type of cancer [1–4]. This so-called triple-negative breast cancer comprises about 10–27% of all breast cancers [1, 2] and is more common in African American patients [2]. These tumors not only tend to present at younger age [1] but also show higher histologic grade, larger size, higher tendency toward visceral metastasis, and higher recurrence rates, usually within 3–4 years, when compared with non–triple-negative cancers [1–6].

With expanding knowledge of the various biologic factors that affect breast cancer management and prognosis, more attention is needed toward imaging to determine whether certain types of tumor biologic factors can be predicted by imaging. The imaging characteristics of breast cancer in general have been studied for a long time, which has enabled us to differentiate benign from malignant tumors with some certainty, as outlined in the current imaging criteria used in the BI-RADS [7]. However, only limited work has been done on establishing correlations between imaging features and certain types of biologic behavior of these tumors.

Many authors have looked into the imaging features of triple-negative breast cancer [8–19], and a few studies have focused on ultrasound features as well [8–11, 14, 15, 17, 19]. However, limited attention has been paid to the sound-attenuating properties of the tumor (analyzed by acoustic features posterior to the tumor) and tumor margins to assess the biologic behavior of breast cancer. The purpose of our study was to investigate whether ultrasound—a simple and easily operable

tool—can play a valuable role in predicting various important prognostic factors in breast cancers on the basis of certain sonographic tumor features. The main biologic tumor factors correlated in our study were tumor grade, expression of ER and PR, and amplification of *ERRB2* oncogene.

Materials and Methods

Subjects

The study was approved by the institutional review board for human investigation. The breast imaging database was reviewed for ultrasound-guided breast biopsies performed between January 2010 and June 2011. According to our department's protocol, if a lesion is well seen on ultrasound, a core biopsy is almost invariably performed under ultrasound guidance. Among 504 consecutive cases of ultrasound-guided core needle biopsies performed, 166 breast cancers were diagnosed on histopathology and 160 of these cases in which ER/PR status was available were included in this study.

Ultrasound Analysis

All the real-time scanning was performed by one of two trained breast sonographers on a LOGIQ 7 or LOGIQ 9 ultrasound unit (GE Healthcare). A linear transducer (10-15–MHz frequency range) was used for all scanning. During the real-time examination, longitudinal and transverse static images were obtained through all masses. Additionally, in accordance with the protocol of our department, cine clips in transverse and longitudinal orientation were also obtained through the masses. All images and cine clips were stored in a PACS. The ultrasound features, including maximum tumor size, echogenicity, margins, and predominant acoustic features posterior to the tumors, were retrospectively analyzed by two radiologists by reviewing the static images and cine clips. Both radiologists were fellowship-trained breast imagers, one with 11 years and the other with 2 years of experience in breast imaging. The posterior acoustic features were independently analyzed by each radiologist (blinded from the other observer's findings). In cases of interobserver disagreement, a consensus was developed by a joint second reading. The predominant posterior acoustic features were divided into four categories: posterior attenuation or shadowing, posterior enhancement, mixed pattern, and no change. The tumor margins were divided into spiculated, angular, indistinct, microlobulated or lobulated, and circumscribed. The individual features of these tumors were then correlated with histologic tumor grade and hormone receptor status. For the purpose of analysis in this study, the tumors with spiculated and angular margins were grouped together and compared with the tumors having lobulated or microlobulated and circumscribed margins grouped together.

Pathologic Analysis

Formalin-fixed and paraffin-embedded tissue samples were analyzed for tumor type, tumor grade, presence of hormone receptors, and expression of the *ERRB2* oncogene. Tumor grade was classified according to the Nottingham combined histologic grading system –3 for invasive cancers on the basis of gland and tubule formation, nuclear pleomorphism, and mitotic index. For the purpose of this study, grades 1 and 2 were considered lower grade, whereas grade 3 was considered a higher grade. Differentiation between invasive ductal and invasive lobular carcinomas in histologically equivocal cases was made using E-cadherin stains. Estrogen and progesterone receptor status was identified using immunohistochemical stains. On pathology results, the estrogen or progesterone receptor status was classified as positive if nuclear staining was present in > 10%, borderline if nuclear staining was between 1% and 10%, and negative if staining was seen in < 1% of nuclei. For the purpose of this study, the borderline group was considered negative. The *ERRB2/neu* was initially tested by immunohistochemical stains (Hercep Test, Dako) in which membrane staining seen in 0% to < 10% of the invasive tumor cells was scored as 0, partial membrane staining in > 10% of cells was considered 1-positive, complete membrane staining of > 10% of cells was considered as 2-positive, and strong membrane staining of > 30% of cells was considered 3-positive. The scores of 0 and 1-positive were considered unamplified, the score of 2-positive was considered equivocal, and the score of 3-positive was considered positive. The equivocal cases were further assessed by fluorescence in situ hybridization (FISH) test. On FISH, an *ERRB2* gene copy number per chromosome 17 centromere ratio of > 2.2 was consistent with gene amplification and < 1.8 was considered unamplified. A ratio between 1.8 and 2.2 was considered equivocal. The two equivocal cases in our data were considered positive for the purpose of this study and excluded from the analysis of triple-negative tumors.

Statistics and Data Analysis

Demographic and clinical characteristics were tabulated for all subjects as well as stratified by ER/PR receptor status (negative/negative vs others). Group differences for continuous characteristics were assessed using a Wilcoxon rank sums test and for categoric characteristics, a normal (Pearson) chi-square test was used. Cohen kappa was used to measure observer agreement on posterior features. To test the primary hypothesis that ultrasound features are associated with ER/PR status and tumor grade; logistic regression models were developed. Discrimination and classification of each model or predictor were assessed using the concordance statistic (an approximation of the area under the receiver operating characteristic curve [AUC]) as well as the corresponding sensitivity, specificity, and positive and negative predictive values. Multinomial logistic regression models with the number of negative or positive receptors as the outcome were used to assess the probability of ER-negative/PR-negative, ER-positive/PR-negative, and ER-positive/PR-positive findings for specific ultrasound features. All statistical analysis was performed using the SAS System, version 9.2. The type 1 error rate was controlled at 0.05 for all analysis, and p values have not been adjusted for multiple comparisons.

Results

A total of 160 patients had information regarding ER/PR receptor status. Of these, 102 (63.8%) were ER-positive/PR-positive, 32 (20.0%) were ER-positive/PR-negative, and 26 (16.3%) were ER-negative/PR-negative (22 were ER-negative/PR-negative/*ERRB2*-negative, or triple-negative). The average age at ultrasound was 60.1 years (SD = 12.7 years) and 36.3% (n = 58) were African American. The mean tumor size was 1.8 ± 1.2 cm. Among these breast cancer patients, 136 (85.0%) had infiltrating ductal carcinoma not otherwise specified (IDC-NOS), and 18 had invasive lobular carcinoma (ILC). Demographic and ultrasound characteristics are listed for the whole cohort and by ER/PR status in Table 1. Patients with ER-negative/PR-negative findings were more likely to be African American (p = 0.041) compared with patients with at least one positive receptor (ER-positive or PR-positive); thus, all additional models will include race as a covariate.

Two ultrasound readers independently determined the posterior acoustic characteristics for each case. After completing independent characterization, a consensus was developed in each case in which disagreement was found. To determine the reliability of the measure, Cohen kappa was used to assess agreement between the observers. The agreement between the two ultrasound readers was considered moderate to high, with κ = 0.77 (95% CI, 0.69–0.85).

To test the association of ultrasound characteristics with receptor status and tumor grade, separate logistic regression models were fit (Table 2). In tumors with posterior shadowing (n = 62), 96.8% were ER-positive and 91.8% were low-grade tumors. Tumors with posterior shadowing have greater than nine times the odds of having ER-positive findings (95% CI, 2.09–40.81; p = 0.011) and greater than 13

TABLE 1: Demographic and Clinical Characteristics Overall and Stratified by Estrogen Receptor (ER)/Progesterone Receptor (PR) Status

Characteristics	Overall (*n* = 160)	ER-Negative/PR-Negative (*n* = 26)	ER-Positive or PR-Positive (*n* = 134)	*p*
Demographics				
Age (y)	60.1 ± 12.7	57.1 ± 10.0	60.7 ± 13.1	0.185
African American	36.3 (58)	53.9 (14)	32.8 (44)	0.041
Ultrasound features				
Tumor size (cm)	1.80 ± 1.24	2.07 ± 1.38	1.75 ± 1.21	0.213
Tumor size > 1.5 cm	41.9 (67)	46.2 (12)	41.0 (55)	0.629
Tumor margins				0.002
Spiculated	42.5 (68)	15.4 (4)	47.8 (64)	
Angular	20.0 (32)	23.1 (6)	19.4 (26)	
Lobulated or microlobulated	14.4 (23)	26.9 (7)	11.9 (16)	
Indistinct	18.8 (30)	19.2 (5)	18.7 (25)	
Circumscribed	4.4 (7)	15.4 (4)	2.2 (3)	
Posterior tumor features				< 0.001
Enhancement	34.4 (55)	76.9 (20)	26.1 (35)	
Shadowing	38.8 (62)	7.7 (2)	44.8 (60)	
Mixed	7.5 (12)	3.9 (1)	8.2 (11)	
No change	19.4 (31)	11.5 (3)	20.9 (28)	
Other features				
Tumor location				0.711
Right	45.6 (73)	42.3 (11)	46.3 (62)	
Left	54.4 (87)	57.7 (15)	53.7 (72)	
Infiltrating ductal carcinoma	85.0 (136)	88.5 (23)	84.3 (113)	0.768
Tumor grade (*n* = 154)				< 0.001
I	31.2 (48)	4.2 (1)	36.2 (47)	
II	32.5 (50)	4.2 (1)	37.7 (49)	
III	36.4 (56)	91.6 (22)	26.1 (34)	

Note—Data are shown as mean ± SD or percentage (no.) as appropriate. Differences are assessed using a Wilcoxon rank sum test or Pearson chi-square test.

times the odds of having a lower-grade tumor (I or II vs III; 95% CI, 4.90–36.54; $p < 0.001$) than those without posterior shadowing. Tumors with posterior shadowing had a significantly greater probability of having ER-positive/PR-positive status than those without shadowing (probability of ER-positive/PR-positive, 0.77; 95% CI, 0.67–0.88 vs 0.55; 95% CI, 0.45–0.65) (Fig. 1). In tumors showing posterior enhancement ($n = 55$), 36.4% were ER-negative/PR-negative (32.6% were triple-negative) and 76.4% were tumors of grade III.

Tumors with posterior enhancement have greater than eight times the odds of having at least one negative receptor (95% CI, 3.97–18.11; $p < 0.001$) and 24 times the odds of having a high-grade tumor (95% CI, 9.91–58.14; $p < 0.001$) than those without posterior enhancement. Tumors with posterior enhancement had a significantly greater probability of having ER-negative/PR-negative status than those without enhancement (probability of ER-negative/PR-negative, 0.36; 95% CI, 0.24–0.49 vs 0.06; 95% CI, 0.01–0.10) (Fig. 2). When directly comparing tumors with shadowing to tumors with enhancement ($n = 117$), those with posterior tumor shadowing had greater than 16 times the odds of ER-positive findings than those with posterior enhancement (odds ratio [OR], 16.4; 95% CI, 3.6–75.0; $p < 0.001$; AUC, 0.806) and 45 times the odds of being low-grade tumors compared with those with enhancement (OR, 45.4; 95% CI, 14.3–144.1; $p < 0.001$; AUC, 0.885).

Of the masses with either spiculated or angular margins ($n = 98$), 71.4% were low-grade tumors (grade I or II), and in masses with circumscribed or microlobulated margins ($n = 31$), 67.7% were high-grade tumors (grade III). Tumors with circumscribed or lobulated or microlobulated margins were five times more likely to be high-grade tumors (grade III vs I or II; 95% CI, 2.12–12.80) compared with those with spiculated, angular, or indistinct tumor margins. However, those with spiculated tumor margins had a moderate increase in the odds of having a low-grade tumor (grade I or II vs III; OR, 2.4; 95% CI, 1.2–4.8) when compared with all others. When directly comparing tumors with angular or spiculated margins to those with circumscribed and lobulated or microlobulated margins for tumor grade response ($n = 126$ removed tumors with indistinct margins excluded), tumors with angular or spiculated margins were more than five times more likely to have lower-grade tumors than those with circumscribed and lobulated or microlobulated tumor margins (OR, 5.4; 95% CI, 2.2–13.3; $p < 0.001$; AUC, 0.659) and nearly six times more likely to have ER-

TABLE 2: Odds of Specified Estrogen Receptor (ER)/Progesterone Receptor (PR) Status and Tumor Grade for Patients With Posterior Shadowing Versus No Shadowing and Those With Posterior Enhancement Versus No Enhancement

Ultrasound Feature	Outcome Characteristic	Odds of Ultrasound Feature	*p*	AUC
Posterior tumor shadowing vs no shadowing	One or more positive receptors vs double negative	9.24 (2.09–40.81)	0.011	0.723
	Low-tumor grade	13.38 (4.90–36.54)	< 0.001	0.748
Posterior tumor enhancement vs no enhancement	One or more negative receptors vs double positive	8.50 (3.97–18.11)	< 0.001	0.768
	High-grade tumor	24.00 (9.91–58.14)	< 0.001	0.826
Circumscribed or lobulated or microlobulated tumor margins vs all others	High-grade tumor	5.21 (2.12–12.80)	< 0.001	0.646
Spiculated tumor margins vs all others	Low-grade tumor	2.39 (1.19–4.78)	0.014	0.603

Note—Odds data are shown as the odds ratio with associated Wald 95% CI in parentheses. AUC = area under the receiver operating characteristic curve.

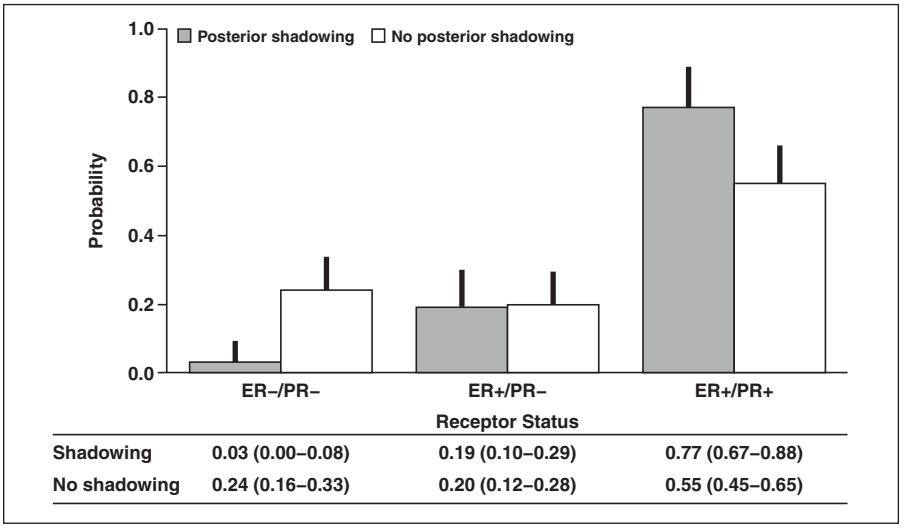

Fig. 1—Probability of receptor status for patients with and without posterior tumor shadowing. Data are shown as probability of receptor status with associated 95% CI in parentheses. ER = estrogen receptor, PR = progesterone receptor, + indicates positive, and – indicates negative. The upper limit of 95% CI is shown as a vertical line over each bar.

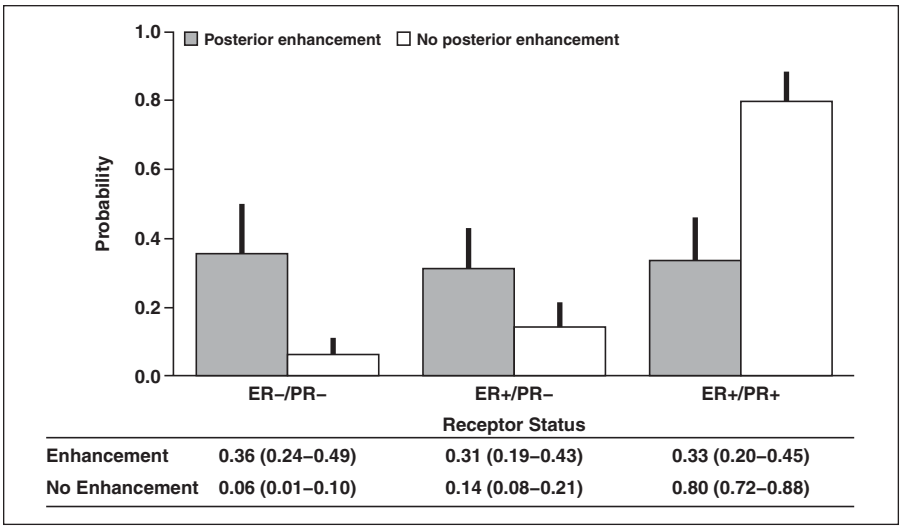

Fig. 2—Probability of receptor status for patients with and without posterior tumor enhancement. Data are shown as probability of receptor status with associated 95% CI in parentheses. ER = estrogen receptor, PR = progesterone receptor, + indicates positive, and – indicates negative. The upper limit of 95% CI is shown as a vertical line over each bar.

positive status (OR, 5.8; 95% CI, 2.1–16.3; $p < 0.001$; AUC, 0.731).

The accuracy of posterior tumor characteristics in use to predict both tumor grade and receptor status was tested using the concordance statistic (Table 2). Posterior tumor shadowing (versus no shadowing) provided fair discrimination for those with at least one positive ER/PR (AUC = 0.723) and for those with low-grade tumors (AUC = 0.748). In addition, posterior tumor enhancement (versus no enhancement) provided fair discrimination for those with at least one negative ER/PR (AUC = 0.768) and good discrimination for those with high-grade tumors (AUC = 0.826). On the basis of the study sample, 97% of tumors with posterior shadowing will be expected to have at least one positive receptor and 92% of these

TABLE 3: Accuracy of Specified Estrogen Receptor (ER)/Progesterone Receptor (PR) Status and Tumor Grade for Patients With Posterior Shadowing Versus No Shadowing and Those With Posterior Enhancement Versus No Enhancement

Ultrasound Feature	Outcome Characteristic	Sensitivity	Specificity	PPV	NPV
Posterior tumor shadowing vs no shadowing	One or more positive receptors vs double negative	0.45 (0.36–0.53)	0.92 (0.82–1.00)	0.97 (0.92–1.00)	0.25 (0.16–0.33)
	Low-tumor grade	0.57 (0.47–0.67)	0.92 (0.84–0.99)	0.92 (0.85–0.99)	0.55 (0.45–0.65)
Posterior tumor enhancement vs no enhancement	One or more negative receptors vs double positive	0.36 (0.24–0.49)	0.82 (0.75–0.90)	0.67 (0.55–0.80)	0.80 (0.72–0.88)
	High-grade tumor	0.27 (0.16–0.38)	0.90 (0.84–0.96)	0.80 (0.70–0.91)	0.85 (0.79–0.92)
Circumscribed or lobulated or microlobulated tumor margins vs all others	High-grade tumor	0.59 (0.45–0.73)	0.88 (0.81–0.95)	0.69 (0.52–0.86)	0.70 (0.61–0.79)
Spiculated tumor margins vs all others	Low-grade tumor	0.49 (0.39–0.59)	0.70 (0.58–0.82)	0.75 (0.64–0.85)	0.45 (0.34–0.55)

Note—Data are shown as the estimated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with the associated 95% CI in parentheses.

tumors will be low grade (Table 3). The accuracy of tumor margin characteristics to predict tumor grade was also assessed. Tumors with circumscribed or lobulated or microlobulated margins (versus all others) provided mostly poor discrimination of tumor grade (AUC = 0.646). Although the measure provided moderate sensitivity (0.59) and high specificity (0.88), the overall discrimination was low.

Discussion

Studies have shown histopathologic grade to be an independent prognostic factor in breast cancer [20, 21]. Clinically, breast cancers that lack the expression of ER, PR, or *ERRB2* show poor outcome, and they currently lack the benefit of certain available systemic therapy, such as tamoxifen and aromatase inhibitors. The molecular profile of breast cancer can be identified into two distinct types [22]: the ER-positive type, comprising the luminal A and B subtypes, and the ER-negative type, which comprises the *ERRB2*-overexpressing subtype and the basal-like subtype (basal-like breast cancer) [21, 23–27]. The tumors in the basal-like breast cancer group frequently lack or show low levels of ER and PR and lack *ERRB2* overexpression and amplification [28–30]. These tumors are frequently called "triple-negative" tumors. Approximately 85% of basal-like breast cancers display *p53* expression by immunohistochemistry or *TP53* mutations [24, 31].

Lack of estrogen and progesterone receptors in breast cancers and presence of high-grade tumor are both considered bad prognostic indicators because these tumors tend to be more aggressive compared with ER-positive/PR-positive or low-grade tumors [32]. Our study showed some strong correlations between the posterior acoustic features and these prognostic factors. In particular, the presence of posterior shadowing was found to be a very strong predictor of a receptor (ER)-positive tumor (about 97% were receptor positive in our study), which in turn almost rules out a triple-negative tumor. Additionally, the presence of shadowing was also strongly associated with a low-grade tumor (about 92% in our study were low grade), which is again an independent good prognostic indicator [32]. We only had two of 22 (9.1%) triple-negative breast cancers that showed posterior shadowing. This confirms the findings of Kojima et al. [10] who only found 8.7% triple-negative breast cancers that showed posterior attenuation in their dataset of 80 patients. They, however, did not have a control group to compare their results with receptor-positive tumors. The reasons for some of these correlations may be explained by the following hypothesis.

Many breast cancers are known to show excessive desmoplastic reaction than others due to excessive collagen deposition [33]. Various growth factors, such as transforming growth factor (TGF)-α, TGF-β, insulinlike growth factor (IGF)-I, and IGF-II have been identified, but platelet-derived growth factor has been postulated as the major initiator in primary breast carcinoma [34]. Although the complexity of the pathophysiology of desmoplastic reaction is not completely understood, it can be hypothesized that low-grade tumors, which are slow growing with lower mitotic rates, may in time induce a stromal reaction that may lead to large differences in the acoustic impedance of tumor interfaces. This may lead to excessive sound reflection or attenuation by the tumor compared with the surrounding tissues, causing shadowing posterior to the tumor (Fig. 3). Conversely, the high-grade tumors, which have higher mitotic rates and are more cellular, may have more uniform internal interfaces or may go through internal necrosis. These tumors are less attenuating to the ultrasound waves compared with the surrounding tissue, leading to brighter signal posterior to the tumors (posterior enhancement) (Fig. 4). Because triple-negative breast cancers are almost always found to be high grade (grade III) at diagnosis (92% in our study), they are more likely to show posterior enhancement, as noted in our study. It seems that the association of posterior shadowing with receptor-positive status could possibly be indirect, secondary to the low tumor grade at the time of diagnosis. This is supported by the fact that the one grade I tumor among the triple-negative breast cancers in our study showed posterior shadowing and the one grade II tumor showed no posterior acoustic change (Fig. 5). Having an indirect link does not diminish the importance of the fact that a receptor-positive tumor can be strongly predicted on the basis of the presence of posterior shadowing.

Among the grade I tumors (n = 48), only four (8.3%) showed posterior enhancement, whereas among grade III tumors (n = 56), 44 (78.6%) showed enhancement and five (8.9%) showed shadowing, whereas the rest showed mixed features or no change. Kim et al. [11] in their study compared the ultrasound features with tumor grade and hormone receptors. However, they grouped tumors with posterior shadowing and mixed posterior features and compared this group with tumors with both enhancement and no change. This most likely was the reason for statistically insignificant correlations in their results.

A similar but weaker correlation was noted between the spiculated or angular margins and a low tumor grade, which again may be explained by the same hypothesis of great-

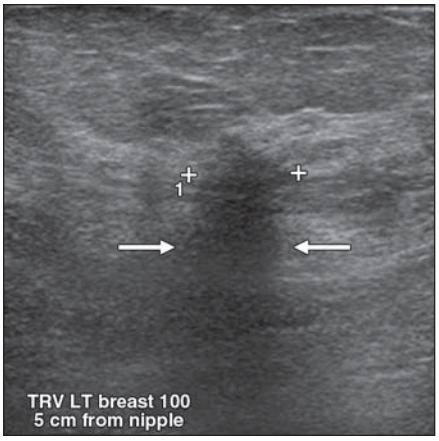

Fig. 3—52-year-old woman who presented with estrogen receptor-positive/progesterone receptor-positive breast cancer. Ultrasound image shows hypoechoic mass (*calipers*) in left upper breast that shows indistinct margins. Predominant posterior acoustic feature noted in this case is posterior shadowing (*arrows*). TRV LT = transverse left.

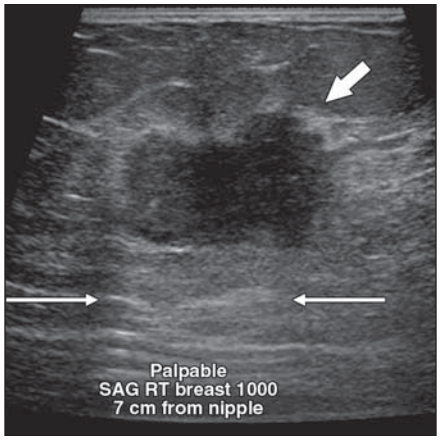

Fig. 4—47-year-old woman with triple-negative breast cancer who presented with palpable mass in upper outer quadrant of right breast. Ultrasound image shows markedly hypoechoic mass with angular margins (*short arrow*). Predominant feature posterior to mass is acoustic enhancement (*long arrows*). SAG RT = sagittal right.

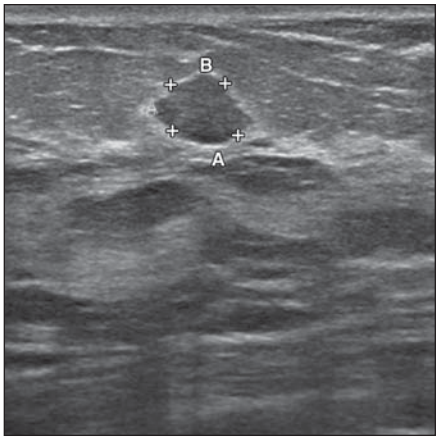

Fig. 5—41-year-old woman with estrogen receptor-positive/progesterone receptor-positive breast cancer who was evaluated for mammographic density in left breast. Ultrasound image shows slightly hypoechoic mass (*calipers*) with relatively circumscribed margins. Predominant feature posterior to mass is no acoustic change.

er desmoplastic reaction in these leading to noncircumscribed tumor margins. The triple-negative tumors, on the other hand, which are mostly grade III, are mostly cellular and rapidly growing, forming relatively circumscribed margins.

The correlations were observed to be similar between ductal and lobular cancers. Among the 18 ILC, 14 (77.8%) showed shadowing, and three (16.7%) showed enhancement. All the shadowing lobular cancers were ER-positive and low grade. Furthermore, 14 (77.8%) lobular cancers showed spiculated or angular margins whereas four showed indistinct margins. No lobular cancer was categorized to have circumscribed or lobulated margins. Only one ILC was triple negative and grade III. Although we did not find a pure mucinous or papillary carcinoma in our study, it is known that these less-common types of tumors are more likely to show relatively defined margins and posterior enhancement despite their low grade. This is probably due to their tendency to be more cystic in nature even at a lower grade compared with the more common forms of IDC and ILC.

In our view, certain findings in our results may have global implications. Although breast cancer is the most common cancer in women worldwide, it should be realized that some of the sophisticated laboratory tests (used to identify aggressive biologic tumor behavior) that are available in the developed world are either not readily available or not cost-effective in many parts of the world. On the other hand, ultrasound is a relatively inexpensive, easily operable, and widely accessible tool worldwide that can play a valuable role in predicting various important prognostic factors in breast cancers. Knowing the predictive values of certain sonographic features of breast cancer may help various practices around the world to stratify their patients who may or may not have biologically aggressive tumors and manage them according to their own available resources. For example, our study shows that > 95% of tumors with shadowing are ER-positive. For practices with limited access to sophisticated receptor testing, it might be feasible to empirically start ER-targeted therapy for these kinds of tumors. On the other hand, tumors with enhancement may be selectively tested for receptors because they have a greater chance of being receptor negative. Additionally, increased diagnostic confidence in imaging can always help to develop cost-effective strategies for practices at home and around the world. If further studies show similar results, the cost-effectiveness will be subject to further analysis.

The limitations of our study include a relatively small sample size and retrospective design. Larger studies, including larger number of receptor-negative tumors, will show a better correlation. The interobserver agreement was moderate to high in our study, but we only used two observers. It remains to be seen if results may be affected by using more observers.

In conclusion, certain tumor features on ultrasound show strong correlation with tumor grade and receptor status of breast cancer. These findings may help to expand the scope of ultrasound in predicting with confidence certain biologic tumor characteristics that are currently beyond the scope of ultrasound BI-RADS.

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