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Ultrasound Assessment of Invasive Breast Cancer:
Correlation with Histologic Grade[1]

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Purpose: To correlate the final assessment of ultrasound and histologic grade in patients with invasive breast cancer.

Materials and Methods: The study consisted of one hundred eighty-six women with breast masses that were evaluated by ultrasound and subsequently found to have invasive ductal carcinoma not previously diagnosed. Two radiologists prospectively analyzed the results of the ultrasounds and issued an American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) assessment category which indicates the probability of malignancy. The histologic grade of the 186 invasive ductal carcinomas were separated as follows, low grade in 22 lesions (9%), intermediate grade in 91 lesions (50%), and high grade in 73 lesions (41%).

Results: In the 186 invasive ductal carcinomas not previously diagnosed, a circumscribed margin was seen in 4% (three of 73) of high-grade tumors compared to none in intermediate-grade and low-grade tumors. A spiculated margin was seen in 59% (13 of 22) of low-grade tumors compared, to 20% (18 of 91) in intermediate-grade and 7% (five of 73) in high-grade tumors. Posterior acoustic enhancement was seen in 33% (24 of 73) of high-grade tumors compared, to 20% (18 of 91) in intermediate-grade and none in low-grade tumors. Posterior acoustic shadowing was seen in 59% (13 of 22) of low-grade tumors compared, to 34% (31 of 91) in intermediate-grade and 15% (11 of 73) in high-grade tumors. The final BI-RADS assessment of the 186 cases separated as follows, three lesions (2%) were category 3 probably benign, 115 lesions (62%) were category 4 suspicious, and 68 lesions (37%) were category 5 highly suggestive of malignancy. The three cases misclassified as probably benign were high-grade tumors.

Conclusion: Breast cancer showing a spiculated margin and posterior acoustic shadowing on ultrasound were mainly low-grade tumors whereas breast cancer showing benign features were high-grade tumors.

Index words : Breast neoplasms, diagnosis
Breast neoplasms, ultrasound

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In addition to distinguishing a cyst from sold breast tumors, gray-scale ultrasonography (US) can be used to help differentiate benign from malignant solid lesions. To improve the specificity of US interpretation, Stavros et al. (1) used a strict classification scheme to predict the benignity of 750 solid breast masses detected by US. Of the 424 masses that were predicted to be benign, only two, one invasive ductal carcinoma and one metastatic lung cancer, proved to be malignant with 99.5% (424 of 426) negative predictive value and 98.4% (123 of 125) sensitivity. This study suggests that a short interval follow-up is a reasonable alternative to the biopsy of lesions that are probably benign on the basis of US results. However, these results were not consistently achieved by other investigators.

Circumscribed cancers can be misclassified as probably benign, American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) category 3 lesions (2 - 5). Parker et al. (2) evaluated 124 solid breast nodules with US before core needle biopsy and provided a BI-RADS final assessment category to indicate the probability of malignancy. Of the 54 category 3 lesions, one was noted to be a 9-mm high-grade invasive ductal carcinoma. In a study of 162 solid breast nodules, one out of three reviewers interpreted one medullary and three invasive ductal carcinomas as benign at US (3). To our knowledge, the relationship between the level of suspicion at US and the histologic grade in patients with invasive ductal carcinoma has not been investigated.

The purpose of this study was to correlate the final assessment at US and histologic grade in patients with invasive breast cancer.

Materials and Methods

Between December 1999 and January 2002, 600 women (age range, 27 - 74 years; median age, 52 years) with breast masses detected clinically, mammographically, or ultrasonographically and scheduled for US-guided needle biopsy ($n=559$) or surgery ($n=41$) were prospectively examined with gray-scale US. US-guided needle biopsy or surgery in the 600 women revealed 261 cancers (234 cases of invasive cancers and 27 cases of ductal carcinomas in situ) and 339 benign lesions. Of the 234 patients with invasive cancers, 186 patients (age range, 27 - 71 years; median age, 51 years) were invasive ductal carcinomas not previously diagnosed and composed our study population. Of the 186 patients with breast cancer, 110 (59%) presented with a palpable mass and ten presented with bloody nipple discharge.

The histologic grade of the 186 invasive ductal carcinomas were classified as follows, 22 (9%) low grade lesions, 91 (50%) intermediate grade lesions, and 73 (41%) high grade lesions. The Elston-Ellis method of tumor grading was used for histologic grading (6), in which a score of 1 - 3 was assigned for (a) tubule formation, (b) pleomorphism, and (c) mitotic count. The total score could range from 3 to 9, with a total of 3 - 5 representative of grade 1, a total of 6 or 7 representative of grade 2, and a total of 8 or 9 representative of grade 3. The histologic diameter of the lesions were 0.4 - 5.9 cm (mean, 1.7 cm). Axillary lymph node involvement was found in 56 (30%) patients. Approximately 97% (180 of 186) of the cases were interpreted by one pathologist without information about imaging results.

On the mammograms, the breast cancers were seen as a mass in 79 cases; a mass with microcalcifications in 56 cases, asymmetric density in 23 cases and architecture distortion in four cases. In 24 (13%) patients no mammographic abnormalities were found. Of the 186 patients, 21 (11%) had entirely fatty breasts (grade 1), 36 (19%) had scattered fibroglandular tissues in fatty breasts (grade 2), 67 (36%) had heterogeneously dense breasts (grade 3), and 62 (33%) had extremely dense breasts (grade 4).

All US examinations were performed by two experienced radiologists with knowledge of clinical and mammographic findings. A 10- or 12-MHz linear array probe (HDI 3000 and HDI 5000; Advanced Technology Laboratories, Bothell, Wash, U.S.A.) was used in 128 patients and a 13-MHz linear array probe (LOGIQ 700; GE Medical Systems, Milwaukee, Wis, U.S.A.) was used in 58 patients. US examinations were performed with the patient in the supine position with arms raised. Scanning was done in radial and antiradial planes as well as longitudinal and transverse planes. The examinations took approximately 20 minutes (range, 15 - 35 minutes).

All US images were prospectively analyzed and assessed in consensus by two radiologists prior to biopsy and a BI-RADS final assessment category was issued to indicate the probability of malignancy. On the US, the size of the mass was measured at the location of the greatest dimension. The lesions were described according to the shape as oval, round, or irregular; according to the orientation as wider than tall or taller than wide; according to the margin as circumscribed, microlobulated,

ill-defined, or spiculated; according to the echogenicity compared to the subcutaneous fat as hyperechoic, isoechoic, mildly hypoechoic, or markedly hypoechoic; according to the echotexture as homogeneous or heterogeneous; according to the acoustic transmission as enhancement, normal, or shadowing; according to the boundary echo as absent or echogenic halo; and according to the calcifications as absent or present (1, 7). On the US, the criteria for classification of a tumor as malignant were, findings of irregular shape, tumor height greater than width, non-circumscribed margins, marked hypoechogenicity, a heterogeneous internal echo, posterior acoustic shadowing, a thick boundary echo, and calcifications (1). A BI-RADS assessment was provided based on the cumulative findings from mammography and US in each case. In breast cancers classified as probably benign lesions at US, a retrospective analysis of imaging findings was performed by the same radiologists who interpreted the US examination to investigate the reason for misclassification.

Table 1. US Findings of 186 Invasive Breast Cancers Not Previously Diagnosed

US Findings	Low Grade ($n=22$)	Intermediate Grade ($n=91$)	High Grade ($n=73$)
Shape			
Oval	0	0	2
Round	1	3	5
Irregular	21	88	66
Orientation			
Wider than tall	12	57	50
Taller than wide	10	34	23
Margin			
Circumscribed	0	0	3
Microlobulated	2	13	11
Ill-defined	7	60	54
Spiculated	13	18	5
Echogenicity			
Hyperechoic	0	0	0
Isoechoic	1	5	3
Mildly hypoechoic	15	63	46
Markedly hypoechoic	6	23	24
Echotexture			
Homogeneous	4	13	25
Heterogeneous	18	78	48
Acoustic transmission			
Enhancement	0	18	24
Normal	9	42	38
Shadowing	13	31	11
Boundary echo			
Absent	15	79	56
Echogenic halo	7	12	17
Calcifications			
Absent	21	63	58
Present	1	28	15

The imaging findings and the final assessment category of US were compared with histologic grade. The Spearman rank correlation coefficient was used to assess the correlation between the final assessment category of US and the histologic grade in patients with invasive ductal carcinoma not previously diagnosed using a statistical software system (SAS for Windows, version 6.12; SAS Institute, Cary, NC). Statistically significant correlations ($p < .05$) were considered substantial when the correlation coefficient (r value) was at least 0.700 (8).

Results

US results of 186 invasive breast cancers not previously diagnosed are summarized in Table 1. The mean lesion size at US was 1.7 cm (range, 0.4 - 5.2 cm, median, 1.6 cm). Seventy-seven (41%) were 1.5 cm or smaller and 109 (59%) were larger than 1.5 cm.

On the US, an irregular shape ($n=175$), ill-defined margin ($n=121$), mild hypoechogenicity ($n=124$), and heterogeneous echotexture ($n=144$) were the predominant findings, but an oval shape ($n=2$), circumscribed margin ($n=3$), and isoechogenicity ($n=9$) were also seen

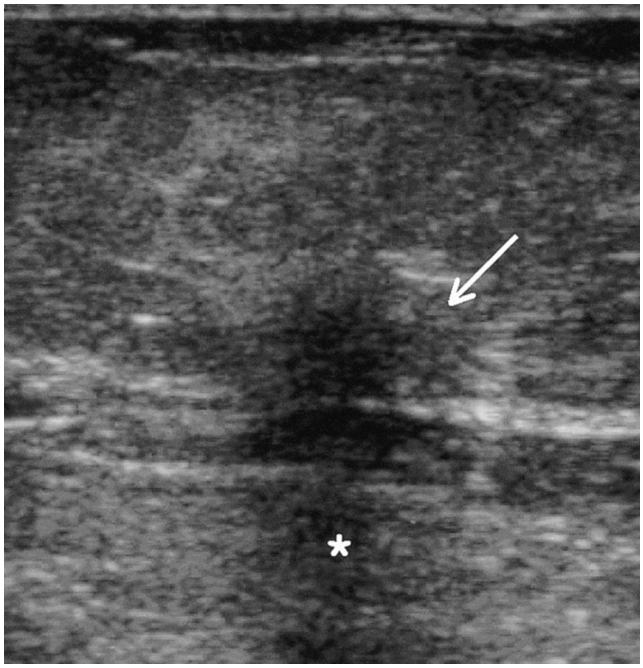

Fig. 1. Low-grade invasive ductal carcinoma, in a 56-year-old woman. Radial US scan shows a 1.1-cm irregular hypoechoic mass with spiculated margin (arrow) and posterior shadowing (asterisk) in the left breast. The final assessment prior to biopsy was BI-RADS category 5, highly suggestive of malignancy.

in invasive breast cancers (Figs. 1 - 3). Posterior acoustic enhancement was seen in 42 (23%) of the 186 cancers, whereas posterior acoustic shadowing was seen in 55 (30%) cancers. A circumscribed margin was seen in 4% (three of 73) of high-grade tumors compared to none in intermediate-grade and low-grade tumors. A spiculated margin was seen in 59% (13 of 22) of low-grade tumors compared to 20% (18 of 91) in intermediate-grade and 7% (five of 73) in high-grade tumors. Posterior acoustic enhancement was seen in 33% (24 of 73) of high-grade tumors compared to 20% (18 of 91) in intermediate-grade and none in low-grade tumors. Posterior acoustic shadowing was seen in 59% (13 of 22) of low-grade tumors compared to 34% (31 of 91) in intermediate-grade and 15% (11 of 73) in high-grade tumors. Statistically significant correlations were noted ($r = 0.516$, $p = 0.005$).

With US, the final assessment of the 186 cancers were three (2%) category 3 (probably benign), 115 (62%) category 4 (suspicious) and 68 (37%) category 5 (highly suggestive of malignancy). All breast cancers misclassified as probably benign category were high-grade tumors. One of the three cancers was palpable and two were nonpalpable. Typical benign breast mass characteristics such as oval shape ($n = 2$), circumscribed margin ($n = 3$), homogeneous echotexture ($n = 2$), and posterior acoustic enhancement ($n = 2$) were seen in these cancers (Fig. 3).

Of the 22 low-grade tumors, none were assessed as category 3, 14 (64%) were assessed as category 4, and eight (36%) were assessed as category 5. Of the 73 high-grade tumors, three (4%) were assessed as category 3, 44 (60%) were assessed as category 4 and 26 (36%) were assessed as category 5. Of the 91 intermediate-grade tumors, none were assessed as category 3, 57 (63%) were assessed as category 4, and 34 (37%) were assessed as category 5. The correlation between the final assessment on US and histologic grade was not significant ($r = -0.101$, $p = 0.06$).

Retrospectively, misinterpretation of the mass margins was the reason for the classification of breast cancers as probably benign on US in one of three cases. The margins of the masses were originally interpreted as circumscribed in all cases. In retrospect, one mass did not strictly meet the criterion of circumscribed margin. The margin of the mass was regarded as partially circumscribed and partially ill-defined (Fig. 3). No remarkable errors were found in the interpretation of other imaging findings such as shape, orientation, echogenicity, echotexture, acoustic transmission, boundary echo, and calcifications.

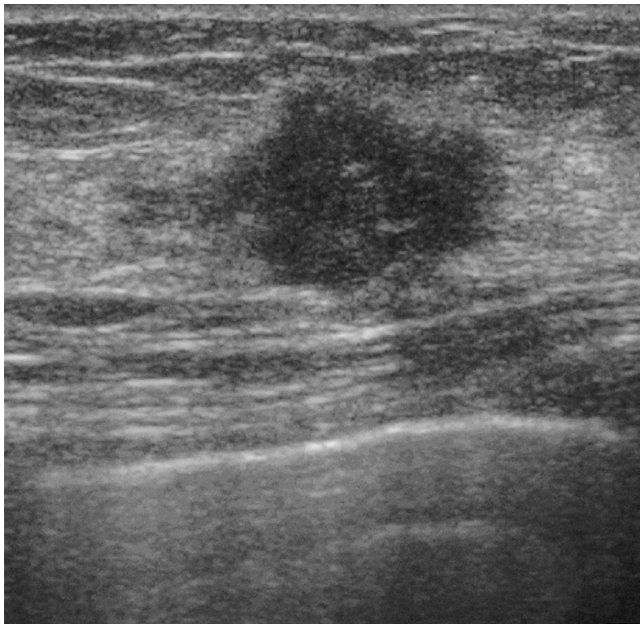

Fig. 2. Intermediate-grade invasive ductal carcinoma, in a 45-year-old woman. Antiradial US scan shows a 2.1-cm ill-defined hypoechoic mass in the right breast. The final assessment prior to biopsy was BI-RADS category 5, highly suggestive of malignancy.

Fig. 3. High-grade invasive ductal carcinoma, in a 53-year-old woman. Radial US scan shows a 1.1-cm ovoid hypoechoic mass with circumscribed margin and posterior acoustic enhancement (asterisk) in the left breast. The final assessment prior to biopsy was BI-RADS category 3, probably benign.

Discussion

This study and others (9 - 11) have shown that the classical appearance of a malignant breast mass as a spiculated mass on mammogram associated with posterior acoustic shadowing on US is more typical of a low-grade tumor. In comparison, high-grade tumors are more likely to demonstrate posterior acoustic enhancement, and a proportion has a circumscribed margin on US. In this study, a spiculated margin and posterior acoustic shadowing on US was seen in 59% (13 of 22) of low-grade tumors compared to 7% (five of 73) in high-grade tumors. Posterior acoustic enhancement at US was seen in 33% (24 of 73) of high-grade tumors compared to none in low-grade tumors. Three (4%) of the 73 high-grade tumors had a circumscribed margin. Previous studies which have examined the relationship between US characteristics and pathological features of breast cancer have attributed particular importance to the presence of fibrous connective tissue in those cases that demonstrate posterior acoustic shadowing, the so-called desmoplastic reaction (12, 13). Conversely it has been suggested that those tumors which demonstrate posterior acoustic enhancement are more cellular and have more hyaluronic acid in the extracellular matrix (14). High-grade tumors or typical medullary carcinomas tend to be more cellular and tend to incite lymphoplasmacytic rather than fibroelastotic host response compared to low-grade tumors or tubular carcinomas.

The results of this study suggest that high-grade invasive ductal carcinomas may display similar imaging features to benign breast masses. Three (2%) of the 186 invasive breast cancers were prospectively misclassified as probably benign at US based on typical benign characteristics such as oval shape, circumscribed margin, isoechogenicity, homogeneous echotexture, and posterior acoustic enhancement. These cases did not show typical features of malignancy; however, one of the three cancers did not meet all of the criteria of benignity defined in the strictest sense when reviewed with knowledge of the biopsy result. In retrospect, the malignant mass had partially ill-defined margins. The criteria for differentiating benign from malignant solid masses should be strictly applied, as emphasized by Stavros et al (1).

It has been reported in anecdotal cases that power Doppler US reveals prominent tumor vessels in breast lesions otherwise considered to be probably benign at gray-scale US and mammography (15 - 17). Circumscribed cancers such as medullary, papillary, and metastatic cancers often show hypervascularity at power Doppler US whereas spiculated cancers such as tubular carcinomas or invasive lobular carcinomas are avascular in the majority of the cases (18, 19). Further study is needed to determine whether power Doppler US has the potential to reduce false-negative rates in gray-scale US.

ACR BI-RADS US lexicon was published recently with illustrated examples (20, 21). Application of this standardized US lexicon would be helpful to decrease interobserver variability in US interpretation. Lack of uniformity among observer's use of descriptive terms for solid breast masses has been known to be the cause of inconsistent diagnoses (22).

In conclusion, breast cancers showing a spiculated margin and posterior acoustic shadowing on US were mainly low-grade tumor whereas breast cancers showing benign US features were high-grade tumors.

References

1. Stavros AT, Thickman D, Rapp CL, Dennis MA, Parker SH, Sisney GA. Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. *Radiology* 1995;196:123-134
2. Parker SH, Klaus AJ, McWey PJ, Schiling KJ, Cupples TE, Duchesne N, et al. Sonographically guided directional vacuum-assisted breast biopsy using a handheld device. *AJR Am J Roentgenol* 2001;177:405-408
3. Rahbar G, Sie AC, Hansen GC, Prince JS, Melany ML, Reynolds HE, et al. Benign versus malignant solid breast masses: US differentiation. *Radiology* 1999;213:889-894
4. Sickles EA. Periodic mammographic follow-up of probably benign lesions: results in 3,184 consecutive cases. *Radiology* 1991;179: 463-468
5. American College of Radiology. *Breast imaging reporting and data system (BI-RADS™)*. 3rd ed. Reston, Va: American College of Radiology, 1998
6. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* 1991; 19:403-410
7. Moon WK, Noh DY, Im JG. Multifocal, multicentric, and contralateral breast cancers: bilateral whole-breast US in the preoperative evaluation of patients. *Radiology* 2002;224: 569-576
8. Norman GR, Streiner DL. *Regression and correlation*. In: Norman GR, Streiner DL, eds. *Biostatistics: the bare essentials*. 2nd ed. Hamilton, Ontario, Canada: Decker, 2000;118-126
9. Kasumi F, Fukami A, Kuno K, Kajitani T. Characteristic echographic features of circumscribed cancer. *Ultrasound Med Biol* 1982;8:369-375
10. Stavros AT. *Malignant solid breast nodules: specific types*. In: Stavros AT, ed. *Breast ultrasound*. 1st ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2004;597-688
11. Lamb PM, Perry NM, Vinnicombe SJ, Wells CA. Correlation be-

tween ultrasound characteristics, mammographic findings and histological grade in patients with invasive ductal carcinoma of the breast. *Clin Radiol* 2000;55:40-44
12. Kobayashi T. Diagnostic ultrasound in breast cancer: analysis of retrotumorous echo patterns correlated with sonic attenuation by cancerous connective tissue. *J Clin Ultrasound* 1979;7:471-479
13. Kossoff G. Causes of shadowing in breast sonography. *Ultrasound Med Biol* 1988;14:211-215
14. Vignal P, Meslet MR, Romeo JM, Feuilhade F. Sonographic morphology of infiltrating breast carcinoma: relationship with the shape of the hyaluronan extracellular matrix. *J Ultrasound Med* 2002;21:532-538
15. Cosgrove DO, Kedar RP, Bamber JC, al-Murrani B, Davey JB, Fisher C, et al. Breast diseases: color Doppler US in differential diagnosis. *Radiology* 1993;189:99-104
16. Raza S, Baum JK. Solid breast lesions: evaluation with power Doppler US. *Radiology* 1997;203:164-168
17. Mehta TS, Raza S, Baum JK. Use of Doppler ultrasound in the evaluation of breast carcinoma. *Semin Ultrasound CT MR* 2000;21:297-307
18. Moon WK, Im JG, Noh DY, Han MC. Nonpalpable breast lesions: evaluation with power Doppler US and a microbubble contrast agent-initial experience. *Radiology* 2000;217:240-246
19. Birdwell RL, Ikeda DM, Jeffrey SS, Jeffrey RB. Preliminary experience with power Doppler imaging of solid breast masses. *AJR Am J Roentgenol* 1997;169:703-707
20. American College of Radiology. *Breast imaging reporting and data system (BI-RADS™) ultrasound*. Reston, Va: American College of Radiology, 2003
21. Mendelson EB, Berg WA, Merritt CR. Toward a standardized breast ultrasound lexicon, BI-RADS. *Semin Roentgenol* 2001;36:217-225
22. Baker JA, Kornguth PJ, Soo MS, Walsh R, Mengoni P. Sonography of solid breast lesions: observer variability of lesion description and assessment. *AJR Am J Roentgenol* 1999;172:1621-1625

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침윤성 유방암의 초음파 평가: 조직학적 등급과의 상관관계[1]

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목적: 침윤성 유방암 환자에서 초음파 검사의 최종평가와 조직학적 등급과의 상관관계를 분석하고자 했다.
대상과 방법: 유방종괴로 초음파를 시행하고 침윤성 유방암 일반형으로 확진된 186명을 대상으로 하였다. 두명의 방사선과 의사가 전향적으로 초음파 소견을 분석하고 암의 가능성을 미국대학방사선과 Breast Imaging Reporting and Data System에 따라 평가했다. 침윤성 유방암의 조직학적 등급은 저등급 22예(9%), 중등급 91예(50%), 고등급 73예(41%)이었다.
결과: 186예의 침윤성 유방암 중 국한형 변연은 고등급 종양의 4%(3/73)에서 보였으나 중등급이나 저등급 종양에서는 한예도 없었다. 침윤형 변연은 저등급 종양에서는 59%(13/22)에서 보였으나 중등급 종양에서는 20% (18/91), 고등급 종양에서는 7%(5/73)에서 보였다. 후방음영증가는 고등급 종양의 33%(24/73)에서 보였으나 중등급 종양에서는 20%(18/91)에서 저등급 종양에서는 한예도 관찰되지 않았다. 후방음영감쇄는 저등급 종양의 59%(13/22)에서 보였으나 중등급 종양에서는 34%(31/91)에서 고등급 종양에서는 15%(11/73)에서 관찰되었다. 초음파에서 유방암의 최종평가는 양성추정 병변이 3예(2%), 악성의심 병변이 115예(62%), 악성가능성이 높음병변이 68예(37%) 였다. 양성추정 병변으로 잘못 평가된 3예는 모두 고등급 침윤암이었다.
결론: 초음파에서 침윤성 변연이나 후방음영감쇄를 보이는 유방암은 조직학적으로 저등급 침윤암이 많았고 양성소견을 보이는 유방암은 모두 고등급 침윤암이었다.