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ORIGINAL ARTICLE

Three-dimensional ultrasonography for the prediction of breast cancer prognosis

Guang Xu[1*], Ting Han[2*], Ming-Hua Yao[1], Juan Xie[1], Hui-Xiong Xu[1], Rong Wu[1]

[1]*Department of Ultrasound in Medicine, and* [2]*Department of Clinical Nutrition, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China*

**These authors contributed equally to this work.*

Summary

Purpose: *To determine the value of three-dimensional (3D) ultrasonography findings in the prediction of breast cancer prognosis.*

Methods: *The findings of 3D ultrasonography of 221 breast tumors were compared with pathologic prognostic factors, including tumor diameter, axillary lymph node status, histologic grade, estrogen receptor (ER) and progesterone receptor (PR) status, human epidermal growth factor receptor 2 (C-erb-B2), Ki-67 (cell proliferation marker) and p53 expression.*

Results: *The convergence sign was correlated to the tumor diameter, axillary lymph node status, histologic grade, ER and PR status. The convergence sign was found significantly more frequently in the small tumor group (diameter ≤2 cm; p=0.001), in breast tumors associated with axillary lymph node metastases (p=0.034), in lower histologic grade (grade I and II) (p=0.011) and in positive ER and PR expression group (p=0.049; p=0.023, respectively). The appearance of tumor margins was correlated to axillary lymph node status and C-erb-B2 expression, with most breast tumors associated with axillary lymph node metastases and negative C-erb-B2 expression exhibiting irregular margins on 3D ultrasonography (p=0.000; p=0.039). The homogeneity of the tumor boundary was detected significantly more frequently in breast tumors without axillary lymph node metastases (p=0.037).*

Conclusion: *The 3D ultrasonographic characteristics of breast tumors, especially the convergence sign, may be used to predict breast cancer prognosis and provide a basis for making more accurate therapeutic decisions.*

Key words: *breast cancer, convergence sign, prognosis, three-dimensional ultrasonography*

Introduction

In 2012 in the United States, there were 229,060 new cases of breast cancer and 39,920 deaths [1]. Mammography is an evidence-based screening modality for breast cancer [2]. However, in women with dense breasts, the performance of mammography is poor [3,4]. Magnetic resonance imaging has been shown to have high sensitivity in the detection of breast cancer [5], but it is more expensive and less accessible. In contrast, ultrasonography is an important, non-invasive and relatively convenient tool to diagnose breast cancer. B-mode imaging has been used to differentiate benign from malignant lesions on the basis of spectral information or morphological features, with modest improvements in sensitivity and specificity [6,7]. In the past decade, advances in 3D ultrasonography have led to the widespread use of this technology for the diagnosis of breast diseases, and its advantages in the diagnosis of early breast cancer have become increasingly apparent. The main advantages offered are the imaging of multiple planes, especially the coronal plane, which cannot be generated using two-dimensional (2D) ultrasonography, and the acquisition of precise information for the diagnosis of breast cancer.

Correspondence to: Rong Wu, PhD. Department of Ultrasound in Medicine, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China. Tel/Fax: +86 21 66307539, E-mail: huixiongxudoc@163.com
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Rahbar et al.[2] reported that on conventional ultrasonography, breast cancer lesions appeared irregular, lobulated and spiculated or crab-like. Clinical experience and research data show that the following characteristics are the most useful for diagnosis of breast cancer on 3D ultrasonography [8-11]: convergence sign, appearance of tumor margins (smooth vs irregular) and echotexture of tumor boundary (homogeneous vs heterogeneous). The convergence sign is a type of retraction phenomenon observed in coronal sections on 3D ultrasonography and is defined as follows: a mass surrounded by a funicular radiation of alternating iso- and hyperechoic tissue. This sign is also called "coronal spiculation" [12].

In this study, we aimed to determine the relationship between the 3D ultrasonographic characteristics and conventional prognostic indicators of malignant breast tumors.

Methods

Study population

The study involved 221 women with a total of 221 breast tumors who underwent preoperative ultrasonography and surgical resection along with unilateral or bilateral axillary lymph node dissection between January 2010 and November 2012 in our hospital. In all patients, the diagnosis was confirmed by histopathological examination.

Instruments and methods

Ultrasonography was performed using a Voluson 730 Pro (GE Healthcare, Milwaukee, Wl, USA). With the patient lying in supine position and the arms extended overhead, each breast was scanned to localize the mass. Relevant grey-scale and color Doppler data related to the mass were collected and stored.

The selected volume of interest (the mass plus a 3-5 mm area surrounding it) was analyzed with high-frequency volume probes (RSP 5-12 MHz, GE Healthcare, Milwaukee, Wl, USA) at a volume angle of 15°-29°. The probe was kept steady, the 3D mode was switched on and 3D ultrasound volume imaging was generated by the automated mechanical movements of the ultrasound transducer. Three planes were simultaneously displayed on the monitor. The intercept line and centre point could be moved to any section plane. Optimal images of the three orthogonal planes and the reconstructed coronal plane were selected. The 3D imaging procedure was repeated twice. The 3D (coronal section and space stereo) imaging data thus obtained was stored on a removable computer disk. The results of ultrasonography and pathological examinations were compared to obtain complete diagnostic data.

Image analysis

Image analysis was performed independently by two sonographers who were experienced in breast ultrasonography and were blinded to the results of the pathological examination. The convergence sign was recorded when both sonographers agreed on the existence of the retraction phenomenon in coronal sections (Figure 1). Similarly, echotexture of tumor boundary (homogeneous vs heterogeneous) was determined when both sonographers agreed that in coronal sections, there was a (integrity vs non-uniform) circle of a medium or strong echo interface around the mass.

Statistics

Quantitative data were expressed as mean±standard deviation (SD) and, using the chi-square test, the characteristics of breast cancer on 3D ultrasonography were compared with pathologic prognostic factors, including tumor diameter, axillary lymph node status, histologic grade, ER and PR status and C-erb-B2, and Ki-67 expression. When evaluating the associations between 3D ultrasonographic characteristics of breast cancer and p53 expression, we analysed only 155 breast tumors in which p53 expression was identified by immunohistochemical staining. A p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS 17.0 software (SPSS Inc, Chicago IL).

Results

The mean age of the 221 patients was 57.0±12.3 years (range 25-86), and the diameter of the breast tumors was 19.9±8.7 mm on average (range 5-48 mm).

The cancers were histologically characterized according to the 2003 World Health Organization histological classification of breast tumors [13]. Of the breast tumors in which p53 expression was identified by immunohistochemical staining (155/221;70.1%) intraductal carcinoma was present in 7 (3.2%) patients, ductal carcinoma *in situ* in 7 (3.2%), invasive lobular carcinoma in 8 (3.6%), infiltrating ductal carcinoma in 185 (83.7%), mucinous carcinoma in 11 (5.0%) and medullary carcinoma in 3 (1.4%) (Table 1). The association of each of these tumor categories and the pathologic prognostic factors, including tumor diameter, axillary lymph node status, histologic grade, ER, PR status, and C-erb-B2, Ki-67 and p53 expression is shown in Table 1.

The association between the 3D ultrasonographic characteristics of breast tumors, namely convergence sign, appearance of tumor margins and echotexture of tumor boundary, and pathologic prognostic factors is shown in Table 2.

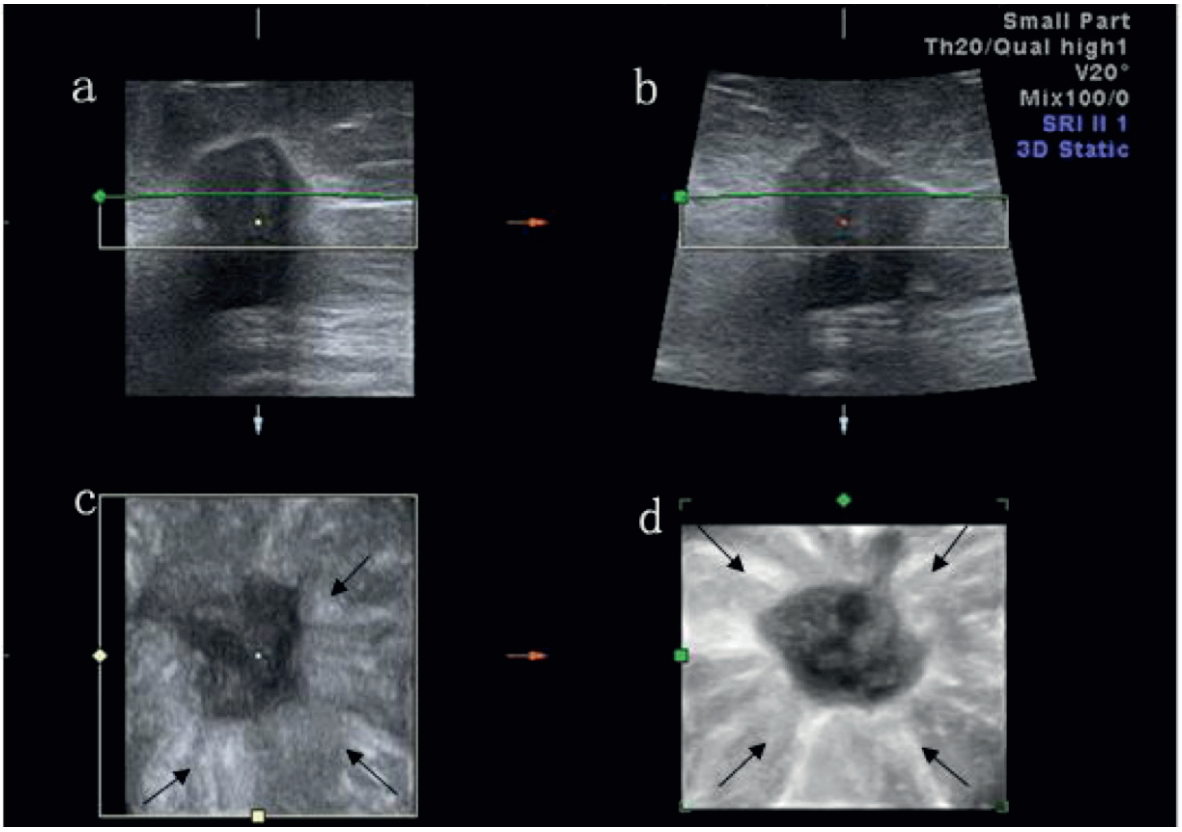

Figure 1. Three-dimensional (3D) ultrasonographic scan of a malignant breast lesion. (**a**) cross-sectional plane of the lesion, (**b**) longitudinal plane of the lesion, (**c**) coronal plane of the lesion and (**d**) volume imaging of coronal plane. A prominent retraction phenomenon (convergence sign) is visible in the coronal plane (↑), the echotexture of tumor boundary is heterogeneous and the tumor margins are irregular. The histopathological diagnosis was infiltrating ductal carcinoma.

Table 1. Relationship between pathological tumor type and pathologic prognostic factors

	Patients, N (%)	*Positive axillary lymph nodes N (%)*	*ER positive N (%)*	*PR positive N (%)*	*C-erb-B2 positive N (%)*	*Ki-67 positive N (%)*	*p53 positive* N (%)*
Tumor pathology	221 (100)	75 (33.9)	150 (67.9)	122 (55.2)	135 (61.1)	207 (93.7)	83/155 (53.5)
ID Ca	7 (3.2)	0 (0)	6 (2.7)	6 (2.7)	5 (2.3)	7 (3.2)	4/155 (2.6)
D Ca *in situ*	7 (3.2)	1 (0.5)	4 (1.8)	2 (0.9)	5 (2.3)	7 (3.2)	3/155 (1.9)
IL Ca	8 (3.6)	3 (1.4)	6 (2.7)	5 (2.3)	4 (0.9)	8 (3.6)	2/155 (1.3)
IND Ca	185 (83.7)	69 (37.3)	125 (56.6)	101 (45.7)	118 (53.4)	176 (79.6)	71/155 (32.1)
Mucinous Ca	11 (5.0)	0 (0)	9 (4.1)	8 (3.6)	2 (0.9)	6 (2.7)	1/155 (0.6)
Medullary Ca	3 (1.4)	2 (0.9)	0 (0)	0 (0)	1 (0.5)	3 (1.4)	2/155 (1.3)
Grade I	17 (7.7)	8 (3.6)	12 (5.4)	14 (6.3)	10 (4.5)	15 (6.8)	4/155 (2.6)
Grade II	120 (54.3)	43 (19.5)	90 (40.7)	74 (33.5)	79 (35.7)	115 (52.0)	48/155 (31.0)
Grade III	48 (21.7)	18 (8.1)	23 (10.4)	13 (5.9)	29 (13.1)	46 (20.8)	19/155 (12.3)

* assessed only in 155 breast tumors in which p53 expression was identified by immunohistochemistry
ID: intraductal Ca, D: ductal Ca, IL:invasive lobular Ca, IND: infiltrating ductal Ca, Ca: cancer

The convergence sign was correlated to the tumor diameter, axillary lymph node status, histologic grade, and ER and PR status (Figure 2). The convergence sign was found significantly more frequently in the small tumor group (diameter ≤2 cm; p=0.001), in breast tumors associated with axillary lymph node metastases (p=0.034), in lower histologic grade (grade I and II; p=0.011) and in the positive ER and PR expression group (p=0.049; p=0.023) (Table 2).

The appearance of the tumor margins was correlated to axillary lymph node status and C-erb-B2

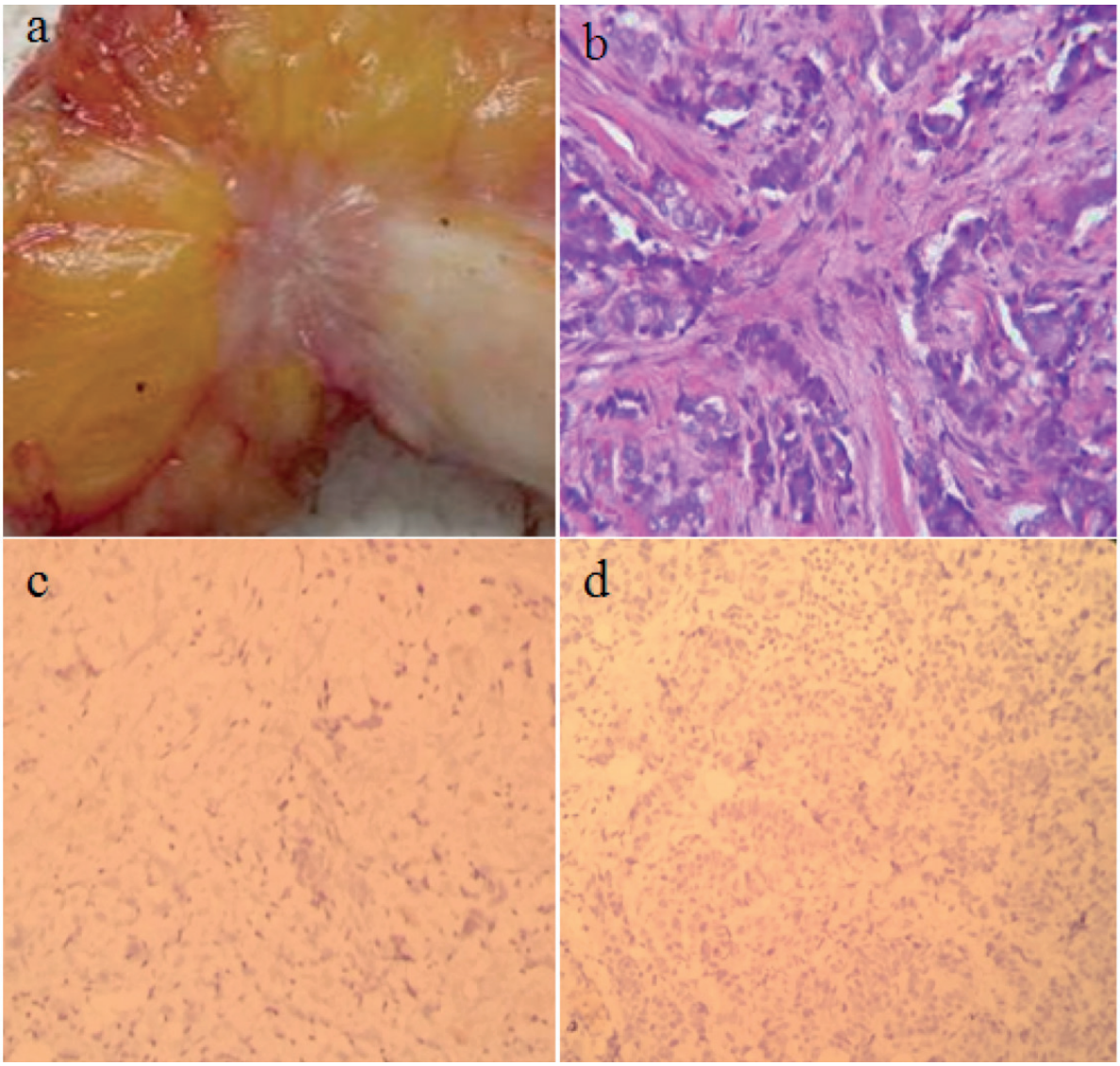

Figure 2. (**a**) Pathological specimen from a 54-year-old woman with a palpable right breast mass. (**b**) Pathological examination (x200) showed invasive ductal carcinoma. Immunohistochemical analysis revealed grade I 18-mm-diameter invasive ductal carcinoma with ER (**c**) and PR (**d**) positive expression (original magnification, x100).

expression, with most breast tumors associated with axillary lymph node metastases and negative C-erb-B2 expression exhibiting irregular margins on 3D ultrasonography (p=0.000; p=0.039, respectively). The homogeneity of tumor boundary was detected significantly more frequently in breast tumors without axillary lymph node metastases (p=0.037) (Table 2).

Discussion

The 5-year survival rate of early breast cancer can be as high as 98%, while that of advanced breast cancer is only 23% [14]. Therefore, early diagnosis of breast cancer is crucial. However, on 2D ultrasonography, early-stage breast cancer may appear as a benign lesion, with distinct borders and uniform internal echo. 3D ultrasonography not only retains all the advantages of 2D ultrasonography but also enables imaging in three planes (A, B, C) and along three different axes (X, Y, Z) of each plane. Moreover, it can show the coronal plane, which cannot be visualized using 2D ultrasonography. Thus, 3D ultrasonography can shed new light on the diagnosis of breast cancer.

The convergence sign on 3D ultrasonography seems to be closely related with malignant tumors [15], exhibiting a high specificity of 94.6% [8]. This sign may be caused by the infiltrating growth of malignant tumors, tumor invasion and compression of blood vessels and carcinomatous involvement of the surrounding glands and fat tissue. Studies have shown that tumor blood flow, as assessed using color Doppler ultrasonography,

Table 2. Association between the 3D ultrasonographic characteristics of breast tumors and pathologic prognostic factors

	Convergence sign			*Tumor margins*			*Echotexture of tumor*		
	Positive	*Negative*	*p-value*	*Smooth*	*Irregular*	*p-value*	*Homoge-neous*	*Heteroge-neous*	*p-value*
	Patients, N			*Patients, N*			*Patients, N*		
Tumor diameter (cm)									
≤2	70	60	0.001	34	96	0.366	59	71	0.064
2–5	29	62		19	72		30	61	
Axillary lymph nodes									
Positive	41	34	0.034	6	69	0.000	23	52	0.037
Negative	58	88		27	99		66	80	
Histologic grade*									
I and II	75	62	0.011	26	111	0.494	52	85	0.405
III	16	32		7	41		15	33	
ER									
Positive	74	76	0.049	35	115	0.743	62	88	0.640
Negative	25	46		18	53		47	44	
PR									
Positive	63	59	0.023	30	92	0.814	49	73	0.971
Negative	36	63		23	76		40	59	
C-erb-B2									
Positive	65	70	0.209	26	109	0.039	58	77	0.307
Negative	34	52		27	59		31	55	
Ki-67									
Positive	94	113	0.480	48	159	0.288	83	124	0.838
Negative	5	9		5	9		6	8	
**p53									
Positive	38	45	0.725	18	65	0.284	30	53	0.162
Negative	35	37		21	51		34	38	

*analysed was only infiltrating ductal carcinoma because it provided histologic grade
**analysed were only 155 breast tumors in which p53 expression was immunohistochemically identified

correlated well with the histological tumor grade and Nottingham Prognostic Index [16]. However, no relationship between the convergence sign and the prognosis of breast cancer has yet been established.

Tumor size, histologic grade and axillary lymph node status are particularly important prognostic indicator of breast cancer [17,18]. In our study, the convergence sign was correlated to the tumor diameter, axillary lymph node status, and histologic grade. Tumors < 5cm in diameter were divided into two groups: those with small (≤2 cm) and those with large (2-5 cm) diameter. We found that the convergence sign was significantly more common in the small tumors group, in the group of breast tumors associated with axillary lymph node metastasis, and in the lower histologic grade (grade I and II) group. Folkman [19] theorized that tumor growth depended on angiogenesis and that the rate of microvessel formation was considerably lower than the rate of tumor growth, thus the rate of microangiogenesis is relatively low in large tumor masses, and tumor growth and invasion of the surrounding tissue occurs more slowly in such tumors. This may explain why the convergence sign was less frequent in the larger masses than in the smaller masses in our study. Liotta and Strache [20] reported that tumor microangiogenesis has been shown to indirectly promote lymph node metastasis. Cancers with convergence sign are thought to grow faster and more aggressively, and according to Folkman's theory [19] their rate of microangiogenesis is relatively high, which facilitates axillary lymph

node metastasis. A tumor with lower histologic grade has a better prognosis than a tumor with higher histologic grade. We found that the convergence sign was significantly more common in a lower (grade I and II) than in a higher histologic grade (grade III). The convergence sign was less common in higher histologic grade tumors, maybe due to faster growth and high aggressiveness, leaving less time for stromal fibrous proliferation or destroying the original proliferation structure [21].

A breast tumor that lacks ER and PR expression usually indicates poor prognosis [22]. The expression of ER and PR helps physicians determine if the patient with breast cancer should receive antihormonal therapy. Ki-67, C-erb-B2, and p53 are the biomarkers that are related with invasiveness and the metastatic capacity of the breast cancer [23-25]. In this study, the convergence sign was found significantly more frequently in the positive ER and PR expression group. In a breast tumor with convergence sign antihormonal therapy will be more effective, and the prognosis will be better.

Irregular margins were found in 76.0% (168/221) of the tumors, while homogeneity of the tumor boundary was observed in only 40.3% (89/221) of the cases. Tumor margins and echotexture were associated, but not significantly, with the prognostic factors. In this study, most breast tumors associated with axillary lymph node metastases and negative C-erb-B2 expression exhibited irregular margins on 3D ultrasonography. Homogeneity of the tumor boundary was detected significantly more frequently in breast tumors without axillary lymph node metastases.

This study has certain limitations. First, it is a retrospective study, and we could not provide details of immunohistochemical staining. Second, some benign neoplasms can exhibit the convergence sign; therefore, differentiation between benign and malignant masses requires the use of a combination of imaging methods.

In summary, the 3D ultrasonographic characteristics of breast tumors, especially the convergence sign, may be used to predict breast cancer prognosis and provide a basis for making more accurate therapeutic decisions.

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