

## Original Article

# Diagnostic and prognostic value of retraction phenomenon observed in 3D ultrasonography of breast masses

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**Abstract:** This study aimed to investigate the clinical value of the retraction phenomenon observed in 3D ultrasonography (RP-3DU) in diagnosing breast masses and evaluating their prognosis. Preoperative 3D ultrasonography was performed on 165 patients with breast masses. The observed RP of the masses was then compared with the tumor size, histological grade, lymph node status, and clinical biomarkers such as the estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (CerbB-2), and Ki-67 to analyze the correlation between RP-3DU and the above indexes. The sensitivity and specificity of RP-3DU in diagnosing malignant breast masses were 67.7% and 93.1%, respectively. The observed rate of RP in 3DU was significantly different ( $P < 0.001$ ) between the invasive and non-invasive cancers. Compared to the non-RP-3DU group, the tumor size in the RP-3DU group was  $\leq 20$  mm ( $P < 0.05$ ), and the histological grade was mostly grade II ( $P < 0.05$ ). Furthermore, the RP-3DU group showed significantly higher numbers of ER and PR positive masses ( $P < 0.05$ ), while there was no significant difference between the two groups with respect to lymph node status, CerbB-2, and Ki-67 expression ( $P > 0.05$ ). The occurrence of RP in 3DU could therefore contribute to the prognostic evaluation of breast cancer.

**Keywords:** 3D ultrasonography, breast mass, retraction phenomenon, prognosis

## Introduction

Breast cancer (BC) is a common and frequently occurring disease in women with a continued decrease in the onset age. In 2012, 229,060 cases of BC were reported in the USA, of which 39,220 cases were fatal [1]. In some cities of China, the incidence of BC exceeded that of cervical cancer and showed the highest incidence among female malignant cancers [2]. Mammography is an effective diagnostic modality recognized internationally for the diagnosis of BC, but its diagnostic accuracy might be influenced by the densities of the mammary glands. Therefore, the mammography images of dense breast glandular lesions are not very satisfactory [3]. As one of the preferred methods in the screening of breast diseases, the sonographic features and color blood flow distributions of 2D ultrasonography provide preliminary information that can identify benign and malignant breast masses. 3D ultrasonography inherits the merits of 2D ultrasonogra-

phy, such as simplicity, low cost of use, no pain for the patient, no-radioactivity, and excellent repeatability. Furthermore, it has exhibited significant advantages in the imaging of dense breast masses and small breast cancers [4, 5]. The unique retraction phenomenon (RP) observed in the coronal plane is considered an important indicator in the diagnosis of BC [6].

The biological factors of BC determine its biological behavior and histopathological changes, thus determining the imaging features. The mass size, histological grade, and lymph node status are the three most important indicators for the clinical prognostic evaluation of BC. Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (CerbB-2), and Ki-67 are the biological factors that could effectively assess the prognosis of BC. Certain studies have shown that the lesions with a mass diameter of  $\leq 20$  mm, low histological grade, and non-lymph node metastasis have relatively good prognosis [7]. ER and PR

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positivity usually indicates high survival rate and low invasion, while the CerbB-2 and Ki-67 positivity indicates the opposite [8]. Currently, 3D ultrasonography is widely used to identify benign and malignant breast masses, while investigations focusing on the relationship between RP in 3D ultrasonography (RP-3DU) and the above prognostic factors are rare [9, 10]. As it is an imaging manifestation of histopathological factors, RP is not uniquely expressed in all malignant breast masses. Some benign lesions may also exhibit certain types of RP. Therefore, our focus is to gain a better understanding of the pathological basis of RP-3DU, as well as to effectively connect them with the prognostic evaluation of BC. The present study investigated the diagnostic value of RP-3DU in benign and malignant breast masses and their relationship with the expression patterns and prognostic indicators in different pathological types of BC. The study aimed to improve the diagnostic efficiency and prognostic evaluation capability of 3D ultrasonography of breast masses and to avoid unnecessary biopsy.

### Materials and methods

#### *General information*

A total of 165 female patients with breast masses, who had no prior history of radiotherapy or chemotherapy, and underwent 3D ultrasonography in our hospital from Apr 2013 to Mar 2014, were included in this study. All the lesions were confirmed by surgical pathologies, among which 72 cases (aged 19-64 years;  $39.0 \pm 11.6$  years) were benign lesions with maximum diameters ranging from 5 to 40 mm ( $20.4 \pm 8.5$  mm); 93 cases (aged 35-86 years;  $51.8 \pm 11.2$  years) involved malignant lesions with maximum diameters ranging from 8 to 44 mm ( $22.5 \pm 9.25$  mm). The malignant masses included 72 cases of non-specific invasive carcinoma, two cases of invasive lobular carcinoma, one case of invasive cribriform carcinoma, one case of mucinous carcinoma, two cases of lobular carcinoma *in situ*, eight cases of ductal carcinoma *in situ*, and seven cases of intraductal papillary carcinoma. The benign masses included 32 cases of fibroadenoma, 17 cases of adenosis-like hyperplasia, 10 cases of breast hyperplasia, five cases of benign phyllodes tumor, three cases of inflammatory lesion, four cases of catheter dilatation, and one case of papilloma. Due to the limited scanning range of

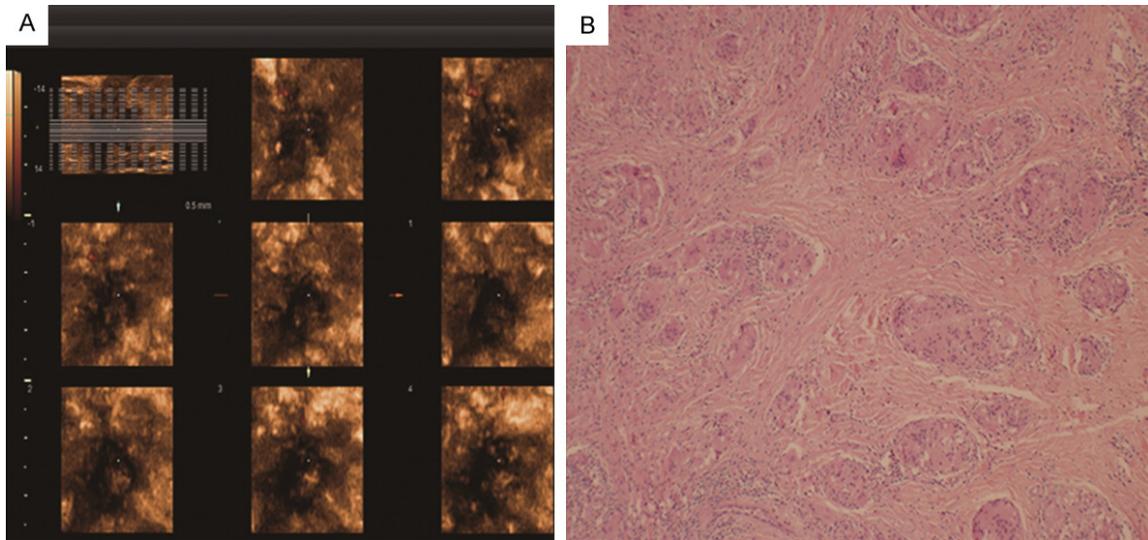
the probes, masses with long diameters  $\geq 50$  mm were excluded. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Guangxi People's Hospital. Written informed consent was obtained from all participants.

#### *Instruments and methods*

GE Voluson E8 Expert 3D ultrasonography imaging system (GE Healthcare, GmbH & Co OG Austria) together with 6-16D RSP 3D volume high-frequency probe (linear array broadband probe, frequency 6-12 MHz) was used for the inspection. The patient was placed in the supine position, maintaining calm breathing and fully exposing the breasts and armpits. First, 2D ultrasonography was performed on both breasts to record the mass location, number, size, shape, border, and internal echo, etc. Secondly, both armpits were scanned to verify the existence of lymphadenectasis. The same settings were then applied for all the patients (pulse repetition frequency of 0.9 kHz, wall filtering set at "low 1", image quality at "high 2", scanning angle of  $25^\circ$ ), and the regions of interest were selected. The sampling frame was then adjusted for real-time 3D imaging and the 3D tissue tomographic technology was used for the offline analysis. The coronal section of mass was selected, using a layer distance of 0.5 mm, to observe RP on each layer. The image analysis was independently performed by two experienced ultrasonographers (without knowledge of the pathological results), and the disagreements over the results were resolved after consultations. RP was defined by the presence of funicular starlight-shaped signs, with medium or high echo, radially extending around the lesions.

#### *Pathological inspection*

All the specimens were sampled within 24 h after the surgery: Ki-67, ER, PR, and CerbB-2 expression was determined by immunohistochemical analysis, using the two-step MaxVision assay following the manufacturers' instructions (Fuzhou Maxim Bioengineering Co. Ltd.). The expression levels of Ki-67, ER, PR, and CerbB-2 were analyzed by pathologists without prior knowledge of the sample conditions. A positive Ki-67 sample was defined as a sample with  $\geq 20\%$  positive cells. ER and PR positivity was defined as the presence of  $\geq 10\%$  positive cells.



**Figure 1.** 3D ultrasonographic and pathological findings of granulomatous mastitis. A: The coronal image showed irregular tumor border and no envelope, appearing the manifestations of RP; B: Fibrous tissues proliferated around, mutually intertwined and dragged, appearing the radial shape (HE×10).

**Table 1.** Comparison of RP-3DU and pathologic findings [n (%)]

RP-3DU	Pathologic findings		Sum
	Malignant	Benign	
Malignant	63 (67.7%)	5 (6.9%)	68
Benign	30 (32.3%)	67 (93.1%)	97
Sum	93	72	165

**Table 2.** Relationships between the BC histologic types and manifestations of RP

Group	Cases	Pathological type	
		Non-invasive cancer	invasive cancer
RP group	63	2 (3.2%)	61 (96.8%)
Non-RP group	30	15 (50%)	15 (50%)
$\chi^2$		29.829	
<i>P</i>		0.000	

A positive result for CerbB-2 was defined based on the presence of brown particles inside the tumor cells and graded as follows: 0 point, no stained cell or stained cells < 10%; 1+, stained cells  $\geq$  10% together with the appearance of an incomplete weak brown membrane; 2+, stained cells  $\geq$  10% and complete positive membrane; 3+, stained cells > 30% and a complete strong positive membrane. “0~1+” was defined as negative expression, and “2+ to 3+” were defined as positive. The pathological and histological grading of the masses was performed

according to the BC histological classification and diagnostic criteria of WHO [11].

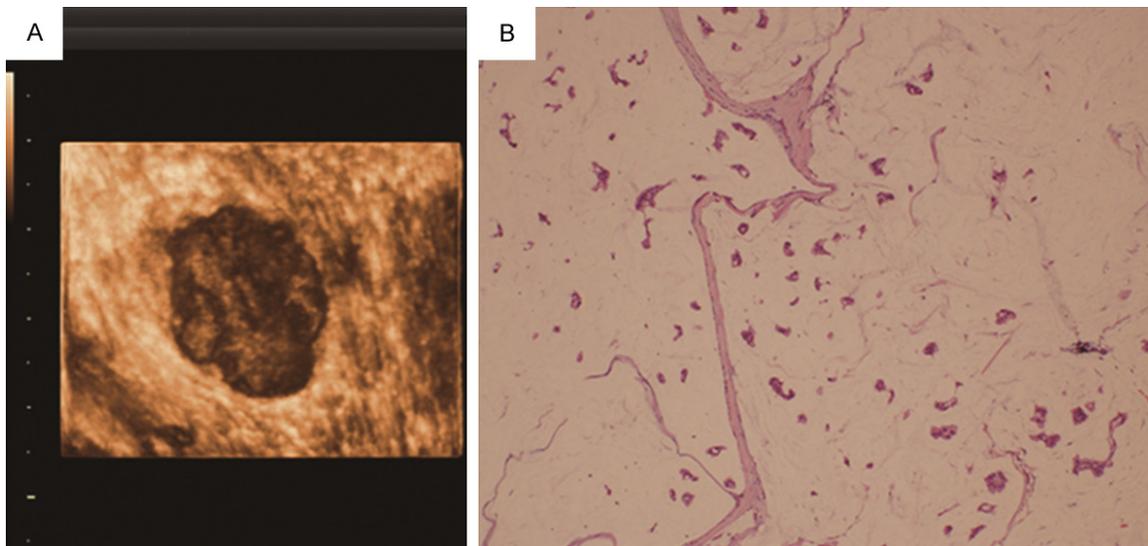
#### Statistical methods

All the data in our study were presented as counting data. Comparison of the features between RP group and non-RP group were performed using the  $\chi^2$  test. The sensitivity and specificity of the RP-3DU in diagnosing malignant breast masses were obtained using the method with the best diagnostic performance. Then the receiver operator characteristic (ROC) curve was used to analyze the diagnostic performance of RP-3DU in diagnosing malignant breast masses. A *p* value of < 0.05 was regarded as statistically significant. These analyses were performed with SPSS1 software for windows (Version 16.0, SPSS Inc).

#### Results

##### Diagnostic value of RP-3DU in the evaluation of benign and malignant breast masses

Sixty-three cases of malignant masses (67.7%), and five cases of benign masses (6.9%) displayed RP. The RP-3DU and pathological findings of granulomatous mastitis are shown in **Figure 1**. The sensitivity and specificity of RP-3DU in diagnosing malignant breast masses were 67.7% and 93.1%, respectively. The receiver operating characteristic (ROC) curve analysis showed that AUC of the RP-3DU diag-



**Figure 2.** 3D ultrasonographic and pathological results of mucinous carcinoma. A: The coronal image showed clear and smooth tumor border while no RP; B: The cancer cells floated in the mucus, exhibiting low inductive effects towards the surrounding interstitial tissues (HE×10).

**Table 3.** Relationships between the manifestations of RP and clinical prognostic indicators of BC [n (%)]

Group	Cases	Mass size		Histologic grade			Axillary lymph node metastasis	
		0 < d ≤ 20 mm	20 < d ≤ 50 mm	Grade I	Grade II	Grade III	Yes	No
RP group	63	36 (57.1%)	27 (42.9%)	7 (11.9%)	48 (81.3%)	4 (6.8%)	28 (44.4%)	35 (55.6%)
Non-RP group	30	8 (26.7%)	22 (73.3%)	4 (15.4%)	8 (30.8%)	14 (53.8%)	18 (60%)	12 (40%)
$\chi^2$		7.527		26.062			1.967	
<i>P</i>		0.006		0.000			0.161	

nostic curve was 0.196 (95% CI = 0.126-0.265,  $k = 0.585$ ), indicating that the diagnostic efficiency of RP-3DU for BC was low (**Table 1**).

#### *Expressions of RP in different pathological types of BC*

Among the 93 cases of breast masses, the RP was observed in 80.3% (61 out of 76) of the invasive cancers and 11.8% of non-invasive cancers (2 out of 17); the difference was statistically significant ( $P < 0.001$ , **Table 2**). The 3D image and pathological findings of mucinous carcinoma are shown in **Figure 2**.

#### *Relationship between the manifestation of RP and clinical prognostic indicators of BC*

The manifestation of the RP in malignant breast masses showed statistically significant differences with the tumor size and histologic grading ( $P < 0.05$ ). The RP was prevalent in the invasive masses with diameters  $\leq 20$  mm (81.8% to

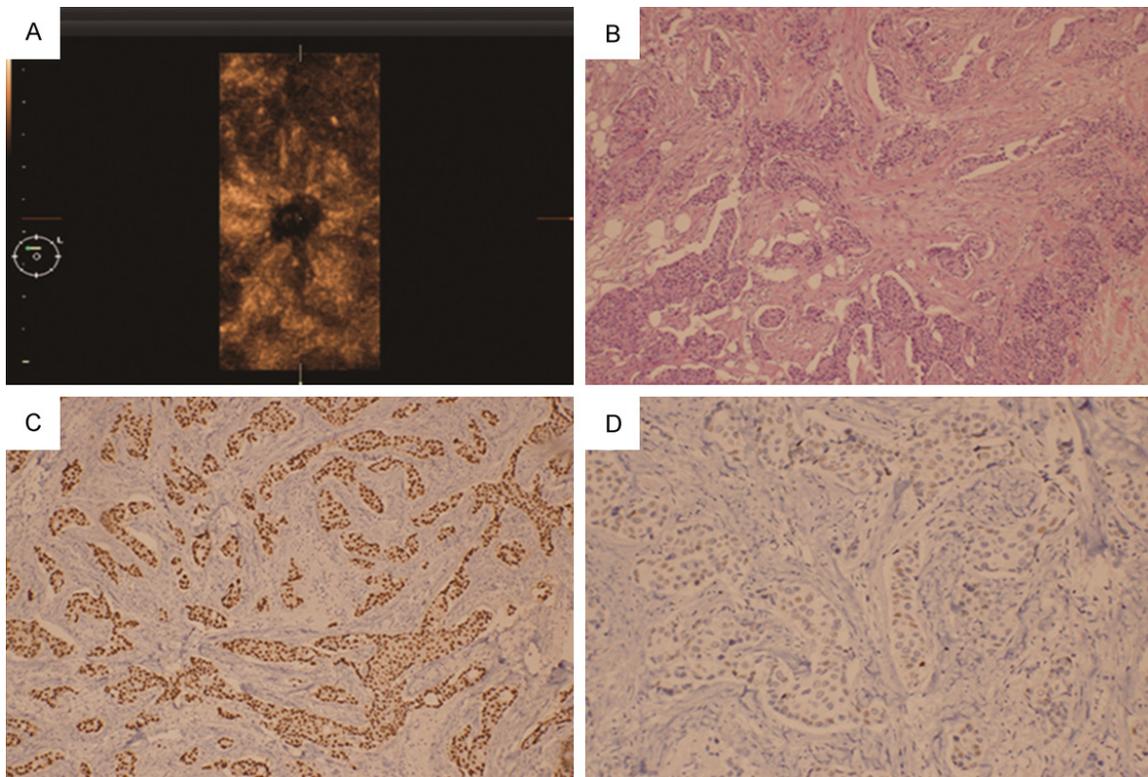
18.2%,  $P < 0.05$ ) and histological grade II (81.3% to 14.3%,  $P < 0.05$ ). However, the lymph node status showed no significant difference between the RP and non-RP groups ( $P > 0.05$ , **Table 3**). The 3D images with and without typical RP, as well as the corresponding pathological findings of the invasive breast cancer, are shown in **Figures 3 and 4**.

#### *Relationships between the RP and immunohistochemical prognostic indicators of BC*

Among the 93 cases, the positive expression rates of ER and PR in the RP group were higher than the non-RP group ( $P < 0.05$ ) while no statistically significant differences were observed in *CerbB-2* and *Ki-67* expression between the two groups ( $P > 0.05$ , **Table 4**).

#### **Discussion**

Observing the tissue around the breast masses is one of the methods used to identify benign



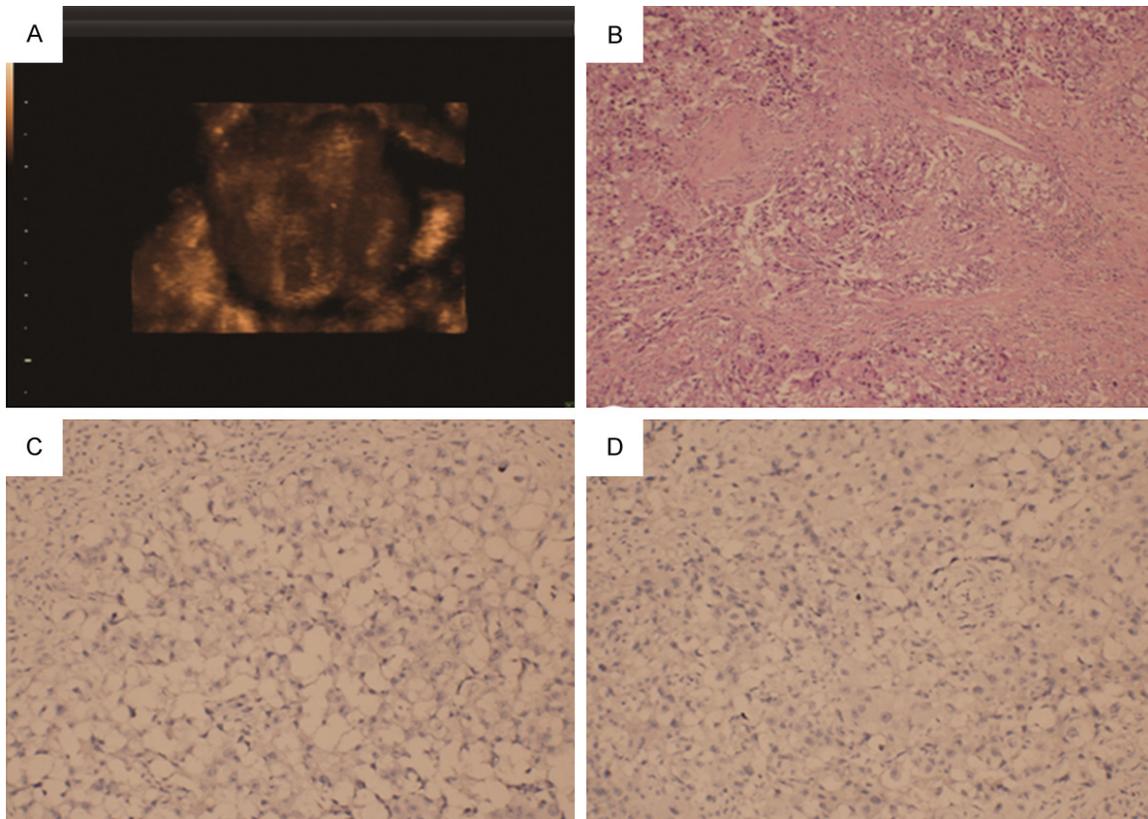
**Figure 3.** 3D ultrasonographic and pathological findings of non-specific invasive carcinoma (mass size 8×9×9 mm). A: The coronal image exhibited the typical RP; B: Histological grade II, the fibrous tissues proliferated around, mutually intertwined and dragged, appearing the radial shape (HE×10); C: ER-positive (×10); D: PR-positive (×20).

and malignant breast masses. 3D ultrasonographic reconstruction technique can identify the infiltration between the masses and surrounding tissues [12]. Previous studies have shown that the RP has significant value in differentiating and diagnosing benign and malignant breast masses [13]. Other investigators have also pointed out that the sensitivity and specificity of RP towards the diagnosis of BC was in the range of 55%-89% and 93%-100%, respectively [6, 13-15]. Therefore, investigating the pathological basis of the observed high specificity and low sensitivity of RP towards the diagnosis of BC as well as the relationship between their expression and prognostic factors in BC were the main objectives of this study.

The results of this study showed that the observed rates of RP between the invasive and non-invasive cancers are significantly different (80.3% vs. 11.8%,  $P > 0.05$ ). RP typically manifested in most non-specific invasive cancers (mass diameter  $\leq 20$  mm, histological grade II), while it was less prevalent in partial non-inva-

sive cancers and some specific invasive cancers. This is in agreement with the observations of Chen *et al.* [16]. The reason for this observation might be that the pathological basis of the RP is based on the various degrees of inductive effects between the cancer cells and interstitial substances. When the cancer cells infiltrate the surrounding tissues, they stimulate the proliferation of the fibrous connective tissues around the lesions, thus generating the radial high echo caused by the mutual traction among the above proliferating tissues [17]. However, due to the different growth patterns of invasive and non-invasive cancers, the extent of these kinds of inductive effects towards the surrounding interstitial substances is also different. Since the cells of the non-invasive cancers are only limited to the inside of their ducts or lobe, and cannot break through the peripheral breast duct or acinar basement, they will have low inductive effects on the surrounding tissues and therefore demonstrate insignificant signs of infiltration. However, in partial specific invasive cancers, such as mucinous carcinoma, the cancer cells float around

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**Figure 4.** 3D ultrasonographic and pathological findings of non-specific invasive carcinoma (mass size 35×32×26 mm). A: The coronal image showed that the mass shape was irregular, the envelope was not obvious, and no obvious RP; B: Histological grade III, the fibrous tissues proliferated around, with irregular arrangement while no obvious radial shape (HE×10); C: ER-negative (×20); D: PR-negative (×20).

**Table 4.** Relationships between the RP and immunohistochemical prognostic indicators of BC [n (%)]

Group	Cased	Ki-67		ER		PR		CerbB-2	
		Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
RP group	63	44 (69.8%)	19 (30.2%)	50 (79.4%)	13 (20.6%)	49 (77.8%)	14 (22.2%)	48 (76.2%)	15 (23.8%)
Non-RP group	30	26 (86.7%)	4 (13.3%)	17 (56.7%)	13 (43.3%)	16 (53.3%)	14 (46.7%)	20 (66.7%)	10 (33.3%)
$\chi^2$		3.091		5.199		5.771		0.938	
<i>P</i>		0.079		0.023		0.016		0.333	

in a lot of mucus, whose border is separated by fibrous tissues, thus preventing significant diffusion and infiltration of the cancer cells towards the surrounding tissues. Therefore, ultrasonography might display the mass with a relatively clear and smooth border. The reason that such benign lesions, such as granulomatous mastitis, exhibited the RP was because the inflammatory cells could also chronically infiltrate the surrounding fibrous connective tissues, thus inducing their proliferation. However, because the degree and nature of this kind of induction was different from the cancer cells, the RP was mostly atypical.

The mass size, armpit lymph node status, and histological grade are important prognostic factors in the clinical diagnosis of BS [18]. In this study, the RP exhibited typical manifestations in lesions with a diameter  $\leq 20$  mm, but less in lesions with a diameter of  $> 30$  mm and higher histological grades. Evans *et al.* [19] and Irshad *et al.* [20] observed that the cases with apparent glitches around the lesions by mammography and ultrasonography, respectively, had lower histological grade and invasiveness, consistent with our findings. Lamb *et al.* [21] pointed out that there was no significant correlation between the peri-lesion glitch signs and mass

size in mammography. In contrast, Jiang *et al.* [10] opined that the RP was more sensitive in the masses with a maximum diameter of < 20 mm, and the diagnostic sensitivity would decrease with increasing mass size, similar to the results of this study. The possible reason might be that those small masses had a low histological grade, slow growth, and low invasive ability. Therefore, the surrounding fibrous connective tissues would have enough proliferation time, resulting in a significant RP. It might also be due to the fact that highly invasive cancer cells grow rapidly, and break through the original proliferated tissues and continued to spread peripherally, thus resulting in the interweaving of the proliferated fibrous tissues and attracted mutually, and structures were deficient accordingly [20]. It is also possibly caused by the limits of the probe's scanning range, which prevents masses with large diameters from completely displaying their surrounding tissue. This affects the observation of the RP to some extent, thus making it difficult to make accurate judgments. In addition, this study shows that there was no significant difference in auxiliary lymph node status between the two groups ( $P > 0.05$ ). Contrary to our study, Xu *et al.* [22] reported that the RP had high prevalence rate in a patient group with lymph node metastasis, and they inferred that the masses with obvious RP usually grew faster and had stronger invasion strength. The reason for this difference between the two studies might be due to the fact that the auxiliary lymph node metastasis might be related not only to the tumor invasion strength but also to the location, pathologic type, size, and blood supply branch of the primary lesion. Therefore, it should be considered as the result of the combined influence of multiple factors.

ER, PR, and CerbB-2 are important factors for the prognostic evaluation of BC and in the selection of a clinical treatment protocol [23]. Previous studies have shown that the positive results of ER and PR in the mammary glandular epithelial cell carcinoma indicate that the growth and reproduction of the masses were still under the endocrine regulation. Therefore, the endocrine treatment would be effective and results in high survival rate [24]. The results of this study showed the positive rates of ER and PR in the positive RP group were higher than those in the non-positive RP group ( $P < 0.05$ ).

This might imply that the RP were the manifestation of low invasiveness, namely the proliferated fibrous connective tissues around the tumor, limiting the spread of the cancer cells to some extent and play a kind of self-protection role. In addition, during this study, we observed a lower incidence rate of the RP in BC with high histological grade, which also verified the conjecture that the RP were the manifestation of low invasiveness. CerbB-2 participates in regulating the growth, proliferation and differentiation of cells, and its over-expression suggested early recurrence, a tendency for distant metastasis, as well as poor prognosis of BC [25]. The Ki-67 antigen is currently accepted as the confirmatory nuclear proliferation marker, and better reflects the proliferation activity of tumor cells. Its positive expression exhibits a great significance for the development, metastasis, and prognosis of BC [26]. Previous studies have shown that the expression of CerbB-2 was associated with ultrasonographic characteristic as glitches [22], and of course, there were other studies proposing the opposite view [27]. In this study, the expression levels of CerbB-2 and Ki-67 were not significantly different between the two groups ( $P > 0.05$ ). The possible reason might be that the expression of the RP was not only related to the invasiveness and proliferation of BC, but also affected by tumor size, or histological grade. In addition, as important prognostic factors of BC, CerbB-2 and Ki-67 have not yet been thoroughly studied, and requires an expanded sample size for further studies.

Our study was limited by the small sample size. Since it was a retrospective study, its diagnostic value towards non-invasive cancers, such as intraductal carcinoma and mucinous carcinoma, as well as other special types of invasive cancers could only be ascertained after further studies involving a larger cohort of cases. Our study was also limited by the probe size and adjustable angles, which limited the observation in the coronal plane of some large masses (> 30 mm). This prevented an effective judgment of the RP due to the truncated collection of signal from the surrounding normal tissue. Further studies using a larger sample size, with minimum human errors, and long-term prospective experiments designed to evaluate effectively the relationship between the 3D ultrasonographic performance and the prognos-

sis of BC, are needed. This can further enrich and validate our presumptions and the results obtained in this study.

In summary, the RP observed in the coronal plane of 3D ultrasonography was the result of low invasiveness of BC to some extent. BC with obvious RP was usually less than 20 mm, with lower histological grade, and was ER- and PR-positive. Therefore, RP had some predictive ability for the biological behavior of breast masses, thus exhibiting significant factors for the prognostic evaluation and in the development of a treatment plan for BC.

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### Disclosure of conflict of interest

None.

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