

Cysts within Otherwise Probably Benign Solid Breast Masses and the Risk of Malignancy

Cistos no interior de nódulo mamários benignos: risco de malignidade

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Abstract

Objective The objective of this study is to assess whether the largest cyst diameter is useful for BI-RADS ultrasonography classification of predominantly solid breast masses with an oval shape, circumscribed margins, and largest axis parallel to the skin, which, except for the cystic component, would be likely classified as benign.

Methods This study received approval from the local institutional review board. From March 2009 to August 2014, we prospectively biopsied 170 breast masses from 164 women. We grouped the largest cyst and mass diameters according to histopathological diagnoses. We used Student's *t*-test, linear regression, and the area under the receiver operating characteristic curve (AUC) for statistical assessment.

Results Histopathological examination revealed 143 (84%) benign and 27 (16%) malignant masses. The mean largest mass diameter was larger among malignant (mean \pm standard deviation, 34.1 ± 16.6 mm) than benign masses (24.7 ± 16.7 mm) ($P < 0.008$). The mean largest cyst diameter was also larger among malignant (9.9 ± 7.1 mm) than benign masses (4.6 ± 3.6 mm) ($P < 0.001$). Agreement between measurements of the largest mass and cyst diameters was low ($R^2 = 0.26$). AUC for the largest cyst diameter (0.78) was similar to the AUC for the largest mass diameter (0.69) ($p = 0.2$). A largest cyst diameter < 3 , ≥ 3 to < 11 , and ≥ 11 mm had a positive predictive value of 0, 15, and 52%, respectively.

Conclusion A largest cystic component < 3 mm identified within breast masses that show favorable characteristics may be considered clinically inconsequential in ultrasonography characterization. Conversely, masses with a largest cystic component ≥ 3 mm should be classified as BI-RADS-US category 4.

Keywords

- ▶ breast cancer
- ▶ breast imaging reporting and data system
- ▶ breast sonography
- ▶ circumscribed masses
- ▶ complex masses

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Resumo

Objetivo Avaliar se o maior diâmetro do cisto é útil para a classificação ultrassonográfica BI-RADS de nódulos mamários predominantemente sólidos, com forma oval, margens circunscritas e maior eixo paralelo à pele que, exceto pela presença do componente cístico, seriam classificados como provavelmente benignos.

Métodos Este estudo foi aprovado pelo Comitê de Ética local. De março de 2009 a agosto de 2014, 170 nódulos mamários de 164 mulheres foram prospectivamente biópsiados. As medidas do maior diâmetro do maior cisto e do maior diâmetro do nódulo foram agrupados de acordo com os diagnósticos histopatológicos. O teste t de Student, a regressão linear e a área sob a curva ROC (AUC) foram utilizados para a avaliação estatística.

Resultados O exame histopatológico revelou 143 (84%) nódulos benignos e 27 (16%) nódulos malignos. A média da medida do maior diâmetro dos nódulos foi maior entre os nódulos malignos (média \pm desvio padrão, 34,1 \pm 16,6 mm) do que nos nódulos benignos (24,7 \pm 16,7 mm) ($p < 0,008$). A média do maior diâmetro do maior cisto também foi maior entre os nódulos malignos (9,9 \pm 7,1 mm) do que nos nódulos benignos (4,6 \pm 3,6 mm) ($p < 0,001$). A concordância entre as medidas dos maiores diâmetros dos nódulos e do maior diâmetro do maior cisto foi baixa ($R^2 = 0,26$). A AUC do maior diâmetro do maior cisto (0,78) foi semelhante à AUC do maior diâmetro do nódulo (0,69) ($p = 0,2$). Os maiores diâmetros dos maiores cistos medindo < 3 ; ≥ 3 e < 11 ; e ≥ 11 mm tiveram um valor preditivo positivo de 0, 15 e 52%, respectivamente.

Conclusão Componentes císticos < 3 mm identificados dentro de nódulos mamários que apresentam as demais características provavelmente benignas podem ser considerados clinicamente irrelevantes na caracterização ultrassonográfica. Por outro lado, nódulos que apresentam um componente cístico medindo ≥ 3 mm devem ser classificadas na categoria BI-RADS-US 4.

Palavras-chave

- ▶ câncer de mama
- ▶ BI-RADS
- ▶ ultrassonografia mamária
- ▶ nódulos circunscritos
- ▶ nódulos complexos

Introduction

Breast lesions may be sonographically characterized with the Breast Imaging Reporting and Data System (BI-RADS-US) according to the malignancy risk.¹⁻³ Breast masses with solid and cystic echo pattern should be described as complex solid and cystic and classified as BI-RADS-US category 4.³⁻⁹ In this category, the risk of malignancy is $> 2\%$ to $\leq 95\%$ and such lesions should be investigated by biopsy.³⁻⁹ In contrast, breast masses with an oval shape, circumscribed margins, orientation parallel to the skin, and hypoechoic echo pattern are coded as probably benign and classified as BI-RADS-US category 3.^{3,10} The risk of malignancy in this category is $< 2\%$, and biopsy may be avoided if the mass maintains the same morphology and stable dimensions during follow-up.^{3,10} Therefore, sonographic identification of a cyst or several cysts within a predominantly solid breast mass, in which the other morphologic features are consistent with BI-RADS-US category 3, still justifies a description of the mass as complex. Hence, a predominantly solid mass with an oval shape, circumscribed margins, and largest axis parallel to the skin should be classified as BI-RADS-US category 4.¹¹ However, recom-

mending biopsy may seem exaggerated in such cases, particularly if there is only one discrete cystic focus.¹¹

This issue led us to carry out a prospective study of predominantly solid breast masses with an oval shape, circumscribed margins, and largest axis parallel to the skin, which, except for the cystic component, would otherwise be classified as probably benign. A previous pilot study presented the results of a sample of 48 breast masses. These masses accounted for 3% of breast ultrasound studies in a breast imaging section located in a reference university hospital for breast cancer treatment.¹¹ The prevalence of malignancy in that sample was 25%, confirming that such masses should be described as BI-RADS-US category 4. Moreover, the largest cyst diameter of each mass was significantly related to the histopathological diagnosis of malignancy. All masses with a largest cyst diameter < 3 mm were benign, and all masses with a largest cyst diameter > 13 mm were malignant.¹¹

The purpose of the current study was to assess whether the largest cyst diameter is a useful ultrasonography variable for BI-RADS-US classification of predominantly solid breast masses with an oval shape, circumscribed margins, and largest axis parallel to the skin, which, except for the cystic

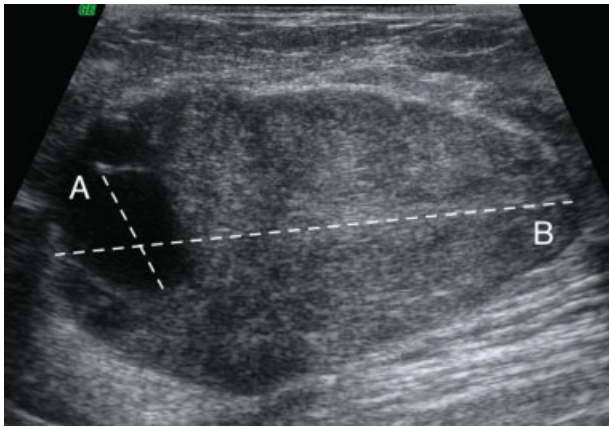


Fig. 1 First illustrative example of a mass in this study. There were two cystic foci that alone or combined did not occupy more than half of the mass. (A) The largest cystic diameter of the largest cyst measured 13 mm. (B) The largest mass diameter measured 49 mm. In our routine breast ultrasound practice, this mass would be described as complex solid and cystic, classified as BI-RADS-US category 4, and biopsied. This patient was 28 years old, and the mass was palpable. Pathological analysis confirmed pseudoangiomatous stromal hyperplasia.

component, would otherwise be classified as probably benign.

Methods

This cross-sectional study with prospective collection data was approved by our Institutional Review Board under number 031/2009. All participants signed an informed consent term. The research was performed according to the Declaration of Helsinki, which was reviewed in 2008.

In a previous pilot study published in 2012, we presented the results of 48 breast masses.¹¹ This prior article suggested that the largest cyst diameter of each mass was significantly related to the histopathological diagnoses of malignancy. In

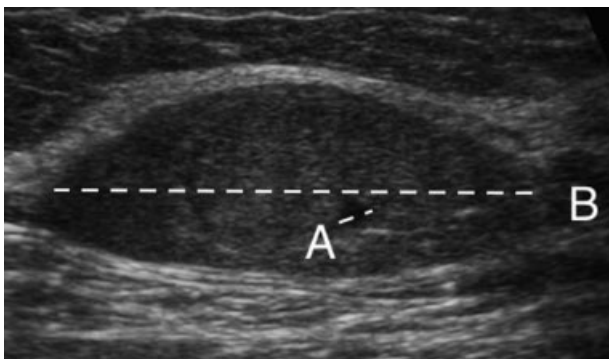


Fig. 2 Second illustrative example of a mass in this study. Only one discreet cystic focus was present. (A) The largest cystic diameter measured 2 mm. (B) The largest mass diameter measured 31 mm. In our routine breast ultrasound practice, this mass would be described as complex solid and cystic, classified as BI-RADS-US category 4, and biopsied. The patient was 47 years old, and the mass was not palpable. Pathological analysis confirmed a complex fibroadenoma. In this study, we demonstrated that a largest cystic component < 3 mm may be ignored in the description and characterization of breast masses.

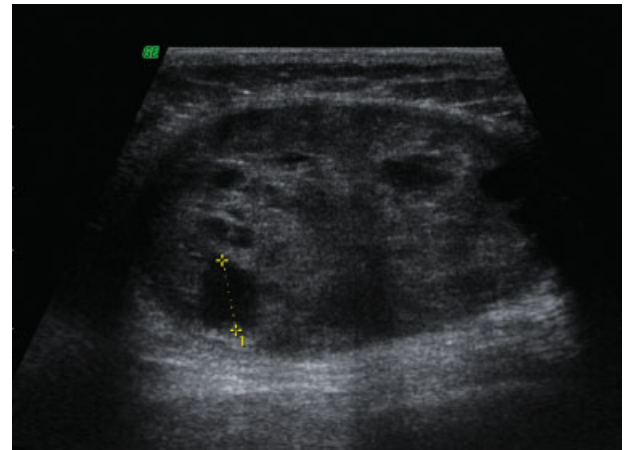


Fig. 3 Third illustrative example of a mass in this study. There were several cystic foci that alone or combined did not occupy more than half of the mass. The largest cyst diameter measured 9 mm. The largest mass diameter measured 49 mm. In our routine breast ultrasound practice, this mass would be described as complex solid and cystic, classified as BI-RADS-US category 4, and biopsied. The patient was 52 years old, and the mass was palpable. Pathological analysis confirmed a carcinosarcoma.

this article, we report this finding in a more representative sample of 170 masses and assess the association between largest cyst diameter and largest mass diameter.

Among all women who underwent breast ultrasound, we selected those with predominantly solid breast masses with an oval shape, circumscribed margins, and largest axis parallel to the skin, which, except for the cystic component, would otherwise be classified as probably benign. The medical indications for the examinations were sonographic evaluation of masses categorized as BI-RADS-MG category 0, sonographic follow-up of breast masses previously coded as BI-RADS-US category 3, sonographic screening in high-risk patients with mammographically dense breasts, and sonographic assessment of palpable breast masses.

In total, 170 masses from 164 women were included in this study. Prior mammograms were available for 95/170 (56%) of the breast masses. Most women undergoing mammography (70/95; 74%) were categorized as having BI-RADS category 0 masses because of circumscribed/obscured mass margins or focal asymmetry. In 20/95 (21%) women, the mammogram was negative (BI-RADS-MG category 1 or 2). Only 3/95 (3%) mammograms identified suspicious lesions (BI-RADS-US-MG category 4), including microlobulated margins (2 masses) or architectural distortion (1 mass).

All ultrasonographic examinations were performed from March 2009 to August 2014 by the same clinician (R.M.J.) with 12 years of experience in breast imaging. No patient that met the ultrasonographic criteria was excluded from the study. The Voluson 730 Expert (GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom) and Accuvix V10 (Medison Co., Ltd., Seoul, Korea) ultrasound machines were the diagnostic equipment used.

We assessed predominantly solid breast masses with an oval shape, circumscribed margins, and largest axis parallel to the skin, which except for the cystic component would

otherwise be classified as probably benign. We included in our sample only masses in which the largest cystic component measured ≥ 2 mm because cystic foci < 2 mm may not be properly characterized by ultrasound. The cystic focus or foci did not occupy more than half of the breast mass, and the masses were therefore characterized as predominantly solid. In breast masses with more than one cystic focus, only the largest focus was measured and considered for analysis. **► Figs. 1 to 3** show examples of these breast masses. In our routine breast ultrasound practice, these masses are described as complex solid and cystic, classified as BI-RADS-US category 4, and biopsied.¹¹

We performed histopathological assessment of the majority of the masses (157/170; 92% of lesions) by ultrasound-guided core needle biopsy using an automated biopsy gun with a 14-gauge needle (Magnum; Bard Biopsy Systems, Tempe, AZ). In 33/157 (21%) of the masses initially evaluated by core needle biopsy, analysis was supplemented by excisional biopsy. In 13/170 (8%) of the cases, we directly evaluated the lesions by excisional biopsy.

Statistical Analysis

We included age, menstrual status, and physical examination findings of the breasts as control variables. Ultrasound variables assessed in the masses were the largest mass diameter and the largest cyst diameter, both in millimeters (**► Fig. 1**). We used a two-sample Student's *t*-test or a chi-squared test to compare data according to the benign or malignant histopathological diagnosis.

The association between the largest cyst diameter and largest mass diameter was evaluated by linear regression, including measurement of correlation coefficient (R^2) and analysis of a scatterplot graph. The R^2 is a numerical measure of the strength of the relationship between two quantitative variables.

The performance of the largest cyst diameter and largest mass diameter in terms of malignancy prediction were calculated by the area under the receiver operating characteristic (ROC) curve. Through the coordinates of the ROC

curve, we selected ranges of the largest cyst diameter measures related to the positive predictive values (PPVs) suitable for BI-RADS categories. We also drew a pairwise comparison of the areas under the ROC curve (AUC) for these variables using Venkatraman's projection-permutation test, using the software R Environment for Statistical Computing (R Project).¹² We performed all other statistical calculations with SPSS software version 15 (SPSS Inc., Chicago, IL). A *P* value < 0.05 was considered as indicating a significant difference.

Results

In total, 170 breast masses from 164 women were available for analysis. Histopathological examination revealed 143/170 (84%) benign and 27/170 (16%) malignant pathological diagnoses. These masses had a high prevalence of complex fibroadenomas (36/143, 25%) and benign phyllodes tumors (7/143, 5%), but the major benign pathological diagnosis was simplex fibroadenoma (53/143, 37%). In contrast, the most frequent malignant pathological diagnoses were invasive ductal carcinoma (15/27, 55%) and mucinous carcinoma (4/27, 15%) (**► Table 1**).

Women presenting with malignant histopathological findings were older (mean \pm standard deviation, 55.1 ± 18.2 years; range, 32–77 years) than women with benign results (39.5 ± 11.6 years; range, 14–66 years) ($P < 0.001$). Malignancy rates were higher for postmenopausal women (15/39, 38%) than for premenopausal women (12/131, 9%) ($P < 0.001$). Palpable masses were more frequently malignant (22/112, 19.6%) than were nonpalpable masses (5/58, 8.6%) ($p = 0.046$) (**► Table 2**).

The largest mass diameter was larger in malignant masses (34.1 ± 16.6 mm; range, 11–66 mm) than in benign masses (24.7 ± 16.7 mm; range, 8–135 mm) ($p = 0.008$). The largest cyst diameter was also larger in malignant masses (9.9 ± 7.1 ; range, 3–31 mm) than in benign masses (4.6 ± 3.6 mm; range, 2–25 mm) ($P < 0.001$) (**► Table 3**).

The scattergraph calculated by linear regression indicated that there was a positive relationship between the largest

Table 1 Pathological diagnosis

Benign	N (%)	Malignant	N (%)
Fibroadenoma	94 (65.5)	Invasive ductal carcinoma	15 (55)
Simplex fibroadenoma	53 (37)	Mucinous carcinoma	4 (15)
Complex fibroadenoma	36 (25)	Papilliferous carcinoma	2 (7.5)
Hyalinized fibroadenoma	5 (3.5)	Malignant Phyllodes tumor	1 (3.7)
Benign Phyllodes tumor	7 (5)	In situ ductal carcinoma	1 (3.7)
PASH	7 (5)	Medullar carcinoma	1 (3.7)
Apocrine metaplasia	5 (3.5)	Carcinosarcoma	1 (3.7)
Lactating adenoma	4 (4)	Lymphoma	1 (3.7)
Other benign diagnosis	26 (17)	Metaplastic carcinoma	1 (3.7)
Total	143 (100)	Total	27 (100)

Abbreviation: PASH, pseudoangiomatous stromal hyperplasia.

Table 2 Distribution of control variables according to the final pathological diagnosis

Variables	Pathological diagnosis		Total	P
	Benign	Malignant		
	Mean/SD/Range	Mean/SD/Range		
Age	39.5 /11.6/14–66	55.1/18.2/32–77		< 0.001*
	N (%)	N (%)		
Menopause				< 0.001#
Yes	24 (16.8)	15 (55.6)	39	
No	119 (83.2)	12 (44.4)	131	
Total	143 (100)	27 (100)	170	
Palpable lesion				0.046#
Yes	90 (62.9)	22 (81.5)	112	
No	53 (34.1)	5 (18.5)	58	
Total	143 (100)	27 (100)	170	

Abbreviation: SD, standard deviation.

*Student's *t*-test. #chi-squared test.

cyst diameter and largest mass diameter. However, agreement between measurements of these variables was low ($R^2 = 0.26$) (→ Fig. 4).

The AUC for the largest cyst diameter was similar to that for the largest mass diameter (0.78 and 0.69, respectively; $p = 0.2$). The AUC for the largest cyst diameter was also similar (0.73) when only considering women < 40 years old, regardless of their clinical breast examination findings and women ≥ 40 years of age presenting with nonpalpable breast masses. Palpable breast masses in ≥ 40 -year-old women could be considered BI-RADS-US category 4, regardless of the cystic foci. Among all women, a largest cyst diameter < 3, ≥ 3 to < 11, and ≥ 11 mm had a PPV of 0%, 15%, and 52%, respectively (→ Fig. 5). These values are consistent with BI-RADS-US categories 3, 4b, and 4c, respectively.

Discussion

In this study, we demonstrated that the largest cyst diameter was useful for BI-RADS ultrasonography classification of predominantly solid breast masses with an oval shape, circumscribed margins, and largest axis parallel to the skin, which, except for the cystic component, would otherwise be classified as probably benign. The performance of the largest cyst diameter for malignancy prediction was maintained regardless of whether the clinical breast examination findings were considered.

Although the largest cyst diameter tended to be larger in larger breast masses, the majority of cases plotted in the graph did not demonstrate this trend ($R^2 = 0.26$). Measurement of the largest mass dimension is performed in routine practice during breast imaging studies.¹² The low

Table 3 Distribution of sonographic variables according to the final pathological diagnosis

Sonographic Variables	Pathological diagnosis		PPV (%)	P
	Benign	Malignant		
	Mean/SD/Range	Mean/SD/Range		
Largest mass diameter (mm)	24.7/16.7/8–135	34.1/16.6/11–66		0.008*
Largest cystic diameter (mm)	4.6/3.6/2–25	9.9/7.1/3–31		< 0.0001*
	N	N		
Largest cystic diameter < 3 mm	43	0	0/43 (0)	
Largest cystic diameter ≥ 3 mm and < 11 mm	90	16	16/106 (15)	
Largest cystic diameter ≥ 11 mm	10	11	11/21 (52)	
Total	143 (100)	27 (100)		

Abbreviations: PPV, positive predictive value; SD, standard deviation.

*Student's *t*-test.

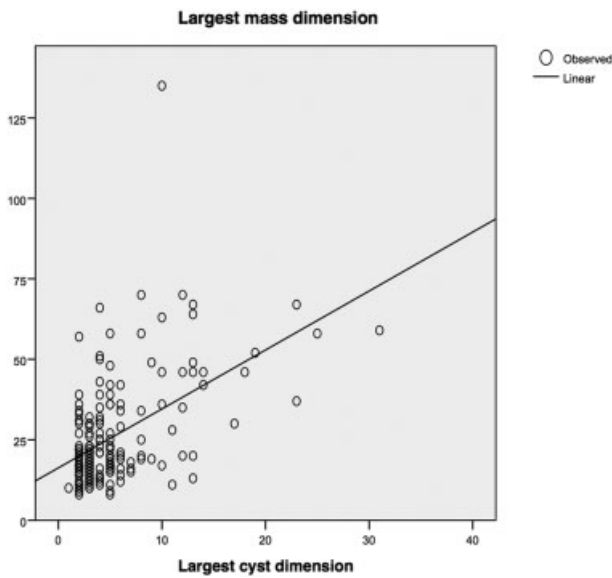


Fig. 4 Scatterplot graph calculated by linear regression. There was a positive relationship between the largest cyst diameter and largest mass diameter. However, agreement between measurements of these variables was low ($R^2 = 0.26$).

concordance rate between the largest mass dimension and the largest cyst dimension may justify including this measurement in the ultrasonography evaluation of complex solid and cystic masses, which, except for the presence of a cystic focus, would otherwise be classified as BI-RADS 3.

Another important contribution of our study was the determination of the prevalence of malignancy in predominantly solid breast masses with an oval shape, circumscribed margins, and largest axis parallel to the skin, which, except

for the cystic component, would otherwise be classified as probably benign. The prevalence of malignancy in the masses included in the current study (16%) was lower than that in a previous pilot study (25%).¹¹ This can be explained by the fact that the current sample had a higher rate of masses in which the cystic foci measured < 3 mm. Thus, the prevalence of 16% for the total sample is slightly lower than the rate described for complex masses (23–31%), but it is still relates to BI-RADS category 4.^{3,13}

With respect to the histopathological results of the breast masses studied, most masses had a histopathological result of fibroadenoma (94/170 masses). Many these fibroadenomas were classified as complex (36/94; 38% of benign masses). The expected prevalence rate of complex fibroadenomas is lower, ranging from 16% to 22% in proven fibroadenomas.^{14,15} The high prevalence of complex fibroadenomas in our sample was not surprising because the presence of simple cysts > 3 mm within fibroadenomas is one histopathological criterion that defines complex fibroadenoma. The remaining criteria include sclerosing adenosis, epithelial calcifications, and papillary apocrine changes.¹⁵

The significance of complex fibroadenoma is that women presenting with these lesions have a 3.1-fold higher relative risk of developing breast cancer compared with the general population.¹⁵ The findings of the current study suggest that the presence of small cysts within circumscribed masses may be related to complex fibroadenomas.

Another relevant factor in the analysis of the benign histologic results was the prevalence of benign phyllodes tumors. These tumors comprised 7/170 (4.0%) of the total sample and 7/105 (6.7%) of fibroepithelial neoplasms. These rates are higher than twice the expected rate of benign

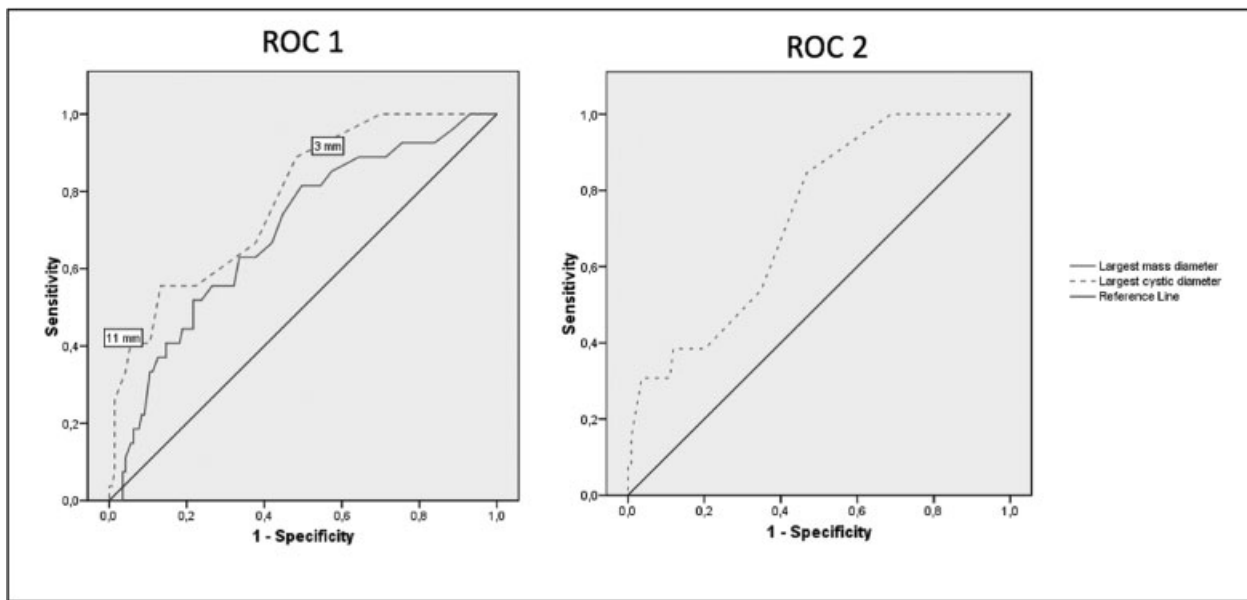


Fig. 5 Receiver operating characteristics curves. ROC 1: Complete sample, regardless of age and clinical breast examination findings (170 masses). Area under the curve (AUC) for largest cyst diameter = 0.78, and AUC for largest mass diameter = 0.69. ROC 2: Sample limited to < 40-year-old women regardless of clinical breast examination findings and ≥ 40-year-old women with nonpalpable breast masses (122 masses). AUC for largest cystic diameter = 0.73.

phyllodes tumors, which account for < 1% of all breast tumors and < 3% of fibroepithelial breast lesions.¹⁶ Phyllodes tumors are associated with a risk of recurrence and distant metastases.¹⁷ Preoperative identification of phyllodes tumors is crucial for appropriate surgical planning and prevention of surgical complications resulting from inadequate excision. Mammography and ultrasound examination cannot adequately distinguish between fibroadenomas and phyllodes tumors.¹⁸ The presence of a cystic foci has been described as important in the diagnosis of this type of tumor.^{19–22} Most of the masses in the present study had histopathological results consistent with fibroadenomas, not phyllodes tumors. Conversely, the size of the largest cystic component may prove useful in identifying malignant phyllodes tumors.

The strengths of our study are its large sample size, which required over four years of data gathering in a breast imaging reference center; the homogeneous sample of patients, all of whom were selected by a single experienced observer; and, most importantly, its conclusion is easily applicable in patient care.

A limitation of our study was our failure to clarify the precise histopathology of the cystic foci. Nevertheless, we can assume that the cystic foci in the four cases diagnosed as mucinous carcinoma represented mucin. Furthermore, in the remaining malignant histologic types included in our sample, the cystic foci seen on ultrasonography were likely to correspond to small areas of necrosis associated with inefficient vascularity related to rapid tumor growth. Our sample was restricted to circumscribed masses, which are usually related to rapidly growing lesions.^{23–25}

In conclusion, a largest cystic component < 3 mm identified within breast masses that show favorable characteristics may be considered clinically inconsequential. Conversely, masses with a largest cystic component \geq 3 mm should be classified as BI-RADS-US category 4 and biopsied.

Conflicts of Interests

The authors have no conflicts of interests to declare.

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