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ORIGINAL ARTICLE

Phyllodes Tumour of the Breast: Differentiation of Histological Grade by Ultrasonography

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ABSTRACT

Objectives: *To retrospectively evaluate whether benign and aggressive phyllodes tumours have distinguishing ultrasonographic features.*

Methods: *We searched the breast imaging database for patients with diagnoses of phyllodes tumours between 2003 and 2014. The imaging studies of eligible patients were retrospectively reviewed.*

Results: *A total of 46 patients (all women; mean age, 41.1 years; range, 20-69 years) were enrolled in the study. The histological grades were benign in 67.4% (n = 31), borderline in 23.9% (n = 11), and malignant in 8.7% (n = 4) of patients. The mean long-axis diameter of the tumour was 3.1 cm (range, 0.7-6.9 cm) in benign tumours and 5.8 cm (range, 3.0-13.0 cm) in aggressive tumours. As compared with benign phyllodes tumours, aggressive tumours showed larger long-axis diameter (p = 0.01), more frequently irregular shape (60% vs. 3.2%), indistinct or microlobulated margins (66.7% vs. 25.8%), and complex cystic and solid echogenicity (46.7% vs. 0%). Benign phyllodes tumours more commonly showed heterogeneous echogenicity with small anechoic clefts (54.8% vs. 20.0%).*

Conclusion: *Several sonographic findings including long-axis diameter, shape, margin, and echogenicity were helpful to differentiate benign and aggressive phyllodes tumours. Irregular shape was a strong, independent predictor of aggressive phyllodes tumours.*

Key Words: *Breast; Phyllodes tumor; Ultrasonography*

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Ethics Approval: This study was approved by the Institutional Ethical Review Board of Inje University College of Medicine (Ref 14-0150). Informed consent was obtained from all patients to be included in the study.

中文摘要

乳腺葉狀腫瘤：超聲波檢查對組織學分級的影響

GW Shin、YM Park、JH Park、HJ Kim、HJ Choo、HJ Baek、DW Kim、SJ Lee、JH Ryu

目的：回顧性評估良性和侵襲性乳腺葉狀腫瘤是否有可以區分兩者的超聲波特徵。

方法：我們從乳腺成像數據庫中檢索在2003年至2014年期間診斷葉狀腫瘤患者，對符合條件患者的影像學檢查進行回顧分析。

結果：共46名患者被納入研究（全部為女性；平均41.1歲，年齡介乎20至69歲）。組織學分級為良性佔67.4%（n = 31）、臨界佔23.9%（n = 11）、惡性佔8.7%（n = 4）。良性葉狀腫瘤的平均長軸直徑為3.1 cm，侵襲性葉狀腫瘤則為5.8 cm。與良性腫瘤相比，侵襲性腫瘤有較大長軸直徑（p = 0.01）；並較為常見不規則形狀（60%比3.2%）、不清楚或微小分頁狀邊緣（66.7%比25.8%）和複雜的囊性和實質性迴聲（46.7%比0%）。良性腫瘤較常見微小的不均勻迴聲中伴無回聲裂（54.8%比20.0%）。

結論：超聲波檢查中的長軸直徑、形狀、邊緣和迴聲有助區分良性和侵襲性葉狀腫瘤。不規則形狀是侵襲性葉狀腫瘤的强獨立預測因子。

INTRODUCTION

Phyllodes tumours are uncommon breast neoplasms that account for less than 1.0% of all breast tumours.[1] An incidence rate of about 2.1 per million has been reported, and the peak age of occurrence in women is 45 to 49 years.[2,3] Phyllodes tumours usually present as large tumours without pain.[4] The tumours are composed of both epithelial and connective tissue stromal components.[5] Histologically, phyllodes tumours are classified into three grades: benign, borderline, and malignant.[4] Yabuuchi et al[6] reported that some magnetic resonance imaging findings of phyllodes tumours such as cystic changes with an irregular wall, low T2-weighted image signal intensity, and low apparent diffusion coefficient value correlated significantly with malignancy. However, according to several previous studies, it is difficult to differentiate benign phyllodes tumours from borderline or malignant ones on imaging.[7,8]

The purpose of the study was to retrospectively evaluate whether benign and aggressive phyllodes tumours have distinguishing ultrasonographic features.

METHODS

Patient Selection

This study was approved by the Institutional Ethical Review Board of Inje University College of Medicine. Following approval by our Institutional Review Board, our ultrasound database was searched to identify all patients with diagnoses of phyllodes tumours between June 2003 and October 2014. We found 46 patients with phyllodes tumour of the breast who had undergone whole-breast ultrasound. All patients were female, and the cases were confirmed histopathologically by ultrasound-guided 14-gauge core needle biopsy using a semi-automated gun (Stericut; TSK Laboratory, Tochigi, Japan) and thereafter either ultrasound-guided 8-gauge vacuum-assisted biopsy (Mammotome; Ethicon Endo-Surgery, Cincinnati [OH], US) [n = 4] or surgery (n = 42). Patients' age at diagnosis and clinical signs / symptoms were recorded.

Mammography

Standard craniocaudal and mediolateral oblique mammograms were routinely obtained with dedicated equipment (DMR+ before January 2007, Senographe DS [GE Healthcare, Buc, France] beginning in January 2007). Additional mammographic images were obtained as needed.

Mammographic features of the tumours were recorded per the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) Atlas 5th edition[9]: mass (shape, margin, and density), calcifications

(shape and distribution), and other associated findings such as architectural distortion. The patient's breast density on mammogram was graded as entirely fat, scattered fibroglandular tissue, heterogeneously dense, or extremely dense fibroglandular tissue.

Ultrasonography

Breast ultrasonography was performed by one of three dedicated breast radiologists using a 10 to 14 MHz (HDI 5000; Advanced Technology Laboratories, Bothell [WA], US) or 7 to 15 MHz (iU22 Ultrasound System, Philips Ultrasound, Bothell [WA], US) linear array transducer. Before the ultrasound examination, the radiologist interpreted the patient's mammograms, if they were available.

The ultrasonograms of lesions were assessed according BI-RADS: long-axis diameter, shape (round, oval, irregular), margin (circumscribed, non-circumscribed including indistinct, microlobulated, angular, spiculated), internal echogenicity (isoechoic, hypoechoic, hyperechoic, complex cystic and solid, heterogeneous), orientation (parallel, non-parallel), posterior echo features (no posterior acoustic features, enhancement, shadowing, combined pattern), presence of calcifications, surrounding tissue changes such as duct ectasia or architectural distortion, and location of vascularity on Doppler ultrasonography (absent, internal vascularity, vessels in rim). The ultrasonographic findings of the remaining breasts were also evaluated. The final BI-RADS assessment category relied on a comprehensive review of both mammographic and ultrasonographic features.

Data Analysis

The 46 patients' imaging findings were analysed by two radiologists by consensus without knowing the histological grades. Then, we correlated these findings with the histopathological results. For statistical analysis, we classified the cases into benign and aggressive phyllodes tumours (ie, borderline and malignant).

Median differences in terms of age and longest tumour diameter were compared between benign and aggressive phyllodes tumours using the Mann-Whitney *U* test. Group comparisons of categorical variables representing all ultrasonographic features were performed using the Pearson χ^2 test. Multiple logistic regression analysis was conducted to investigate the associations between histopathological type of phyllodes tumour and each ultrasonographic feature. The results of the analysis were presented as odds ratio estimates with corresponding 95% confidence intervals and p values from the Wald test. A receiver operating characteristic curve was constructed to differentiate aggressive from benign phyllodes tumours, and the optimal cut-off values were defined as the value at which the sum of the sensitivity and specificity was maximised. The area under the receiver operating characteristic curve (A_z value) was compared using the method by DeLong et al.[10] All statistical analyses were performed with SPSS (Windows version 19.0; IBM Corp, Armonk [NY], US), and p values < 0.05 were considered statistically significant.

RESULTS

The 46 patients with phyllodes tumours were aged 20 to 69 years (mean, 41.1 years), and the histopathological findings were benign in 67.4% (n = 31; mean age, 38.9 years), borderline in 23.9% (n = 11; mean age, 44.4

Table 1. Correlation between sonographic findings and pathological grade of phyllodes tumours.*

Ultrasonography findings	No. (%) of findings		p Value
	Benign (n = 31)	Aggressive (n = 15)	
Mean long-axis diameter (cm)	3.1 (range, = 0.7-6.9)	5.8 (range, 3.0-13.0)	0.01
Shape			0.001
Oval or round	30 (96.8%)	6 (40.0%)	
Irregular	1 (3.2%)	9 (60.0%)	
Margin			0.019
Circumscribed	23 (74.2%)	5 (33.3%)	
Indistinct or microlobulated	8 (25.8%)	10 (66.7%)	
Echogenicity			0.001
Isoechoic	7 (22.6%)	4 (26.7%)	
Hypoechoic	7 (22.6%)	1 (6.7%)	
Complex	0	7 (46.7%)	
Heterogeneous	17 (54.8%)	3 (20.0%)	
Posterior acoustic features			0.608
Posterior enhancement	12 (38.7%)	9 (69.2%)	
None	19 (61.3%)	4 (30.8%)	
Unknown	0	2	
Location of vascularity			0.346
None	4 (13.8%)	0	
Vessels in rim	11 (37.9%)	5 (33.3%)	
Internal	14 (48.3%)	10 (66.7%)	
Unknown	2	0	
Breast Imaging Reporting and Data System category			0.001
3	22 (71.0%)	2 (13.3%)	
4a	8 (25.8%)	6 (40.0%)	
4b	1 (3.2%)	5 (33.3%)	
4c	0	2 (13.3%)	
Multiplicity†	19 (61.3%)	3 (20.0%)	

* Data are shown as No. (%), unless otherwise specified.
† Multiplicity is defined as >5 benign lesions in each of the contralateral and the remaining ipsilateral breast.

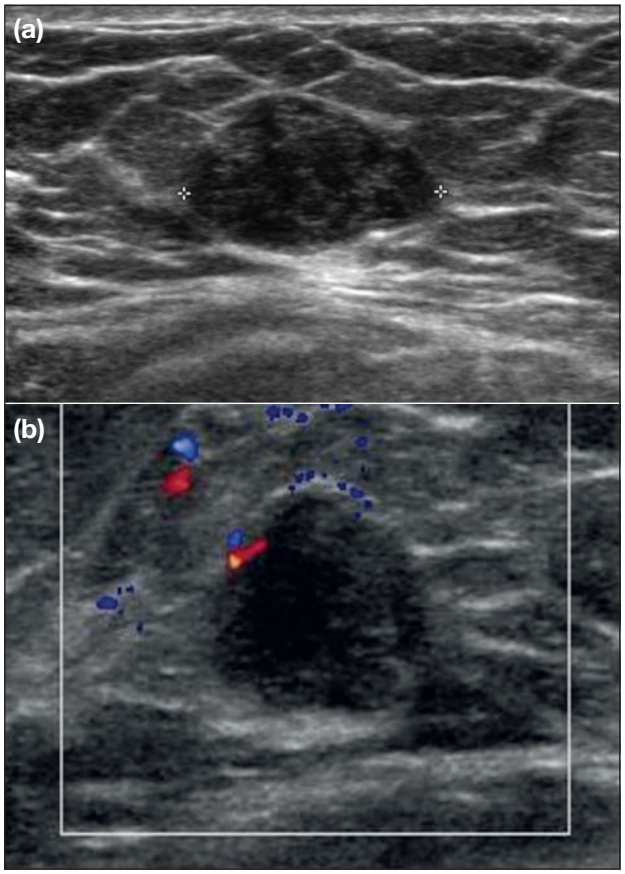

Figure 1. Benign phyllodes tumour of right breast in a 42-year-old woman. (a) Axial ultrasonogram showing a 2.0-cm well-defined oval mass with heterogeneous echogenicity and multiple small anechoic clefts. (b) Colour Doppler ultrasonogram of longitudinal view showing focal increased peripheral vascularity.

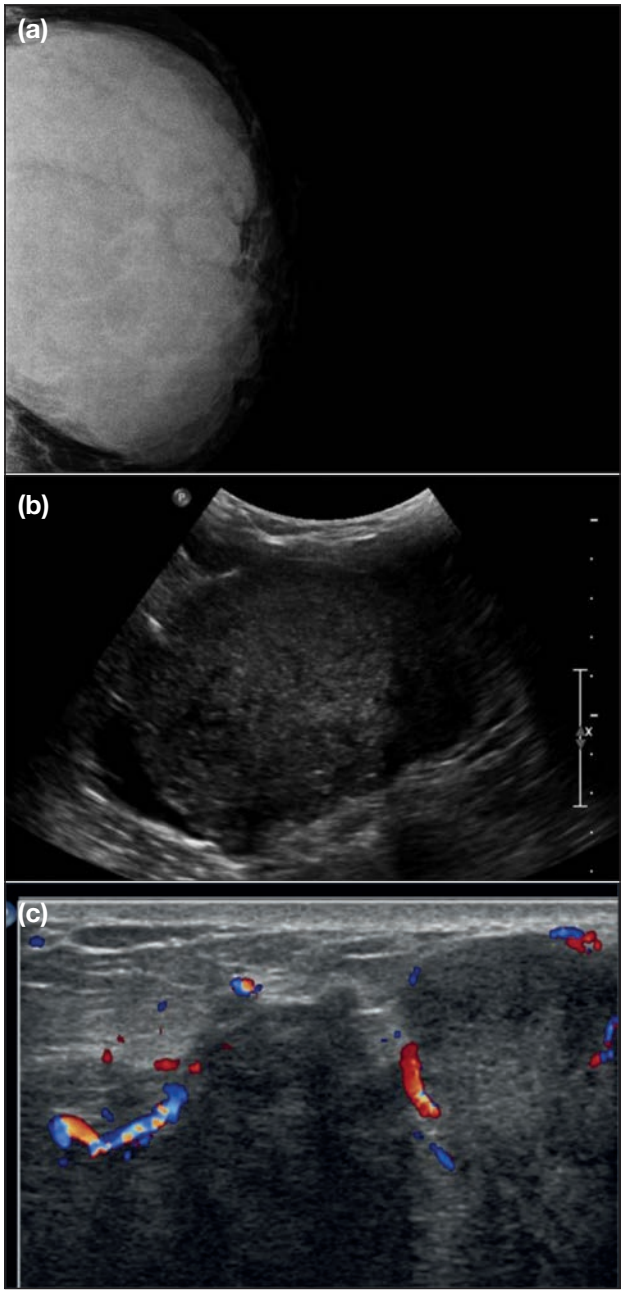

Figure 2. Borderline phyllodes tumour of left breast in a 63-year-old woman with a palpable lump. (a) Left mammogram showing an oval circumscribed hyperdense mass. (b, c) Ultrasonograms showing an oval circumscribed complex echoic mass with increased internal vascularity.

years), and malignant in 8.7% (n = 4; mean age, 51.5 years) of the cases. There was no statistically significant age difference between the patients with different histological grades of phyllodes tumours (p = 0.109). A relationship between palpability and tumour was more common in aggressive phyllodes tumours (15/15, 100%) than in benign ones (26/31, 83.9%).

The correlation between sonographic findings and pathological grade of phyllodes tumours is listed in Table 1. The mean long-axis diameter of the tumour was 3.1 cm in benign tumours (range, 0.7 cm-6.9 cm) and 5.8 cm in aggressive tumours (range, 3 cm-13.0 cm) [p = 0.01].

On sonography, all 46 patients' tumours were demonstrated as a mass. The most common sonographic findings of benign phyllodes tumours were oval or round shape (30/31, 96.8%), circumscribed margin (23/31, 74.2%), heterogeneous echogenicity (17/31, 54.8%), absence of posterior acoustic features (19/31, 61.3%), and increased vascularity (25/29, 86.2%) [Figure 1]. In aggressive phyllodes tumours, the most common sonographic findings were irregular shape (9/15, 60%), indistinct or microlobulated margin (10/15, 66.7%), complex cystic and solid echogenicity (7/15, 46.7%), posterior acoustic enhancement (9/15, 69.2%), and increased vascularity (15/15, 100%) [Figures 2 and 3].

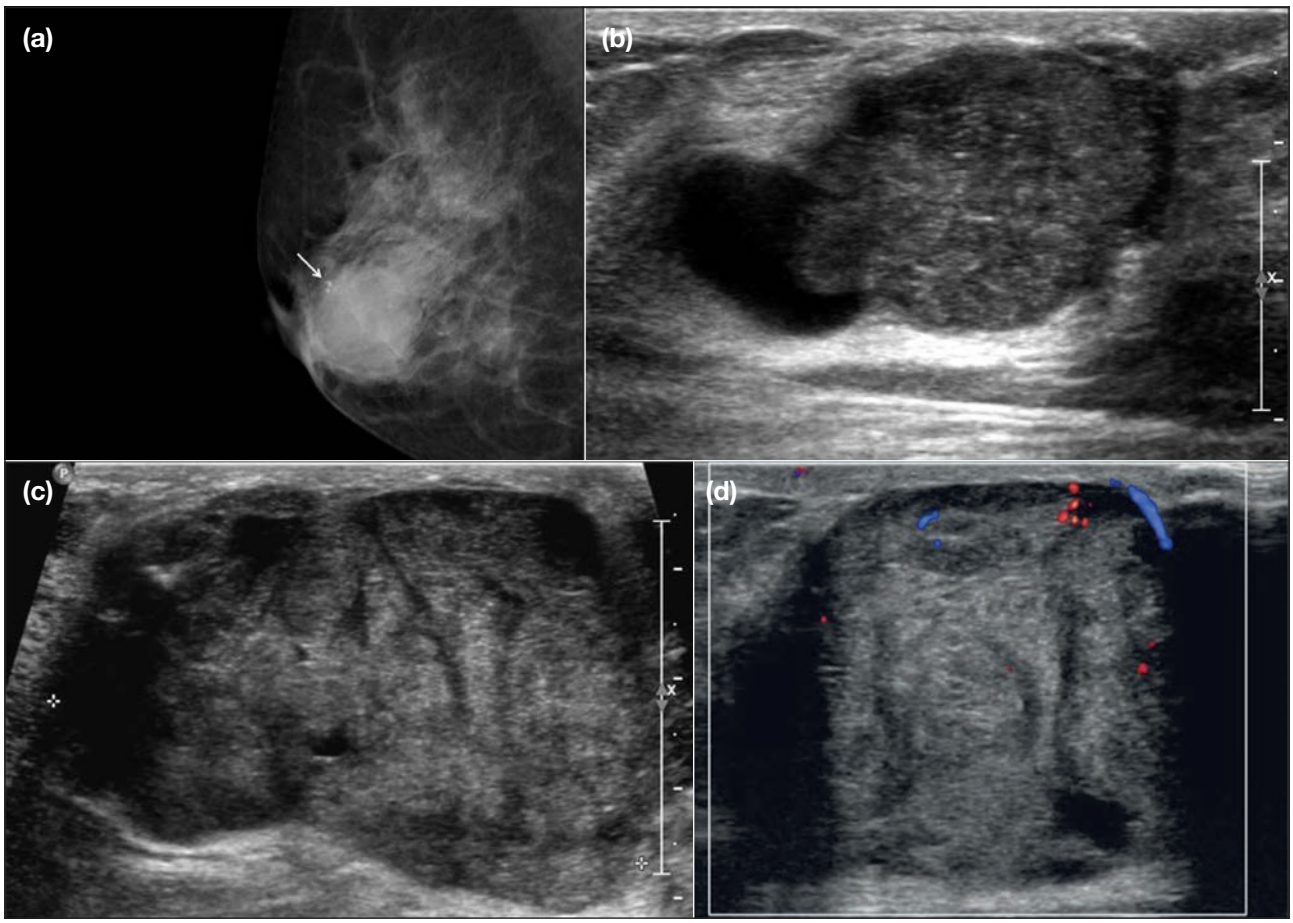

Figure 3. Malignant phyllodes tumour of right breast in a 39-year-old woman with a palpable lump. (a) Right mammogram showing a hyperdense mass with indistinct margin and marginal clustered coarse heterogeneous calcifications (arrow). (b) Ultrasonograms showing an irregular complex echoic mass with indistinct margin, posterior acoustic enhancement. Ultrasound-guided core needle biopsy specimen proved to be a fibroadenoma. (c, d) After 17 months, the mass shows enlargement from 4.1 cm to 5.8 cm and increased internal vascularity on repeat ultrasonogram. The lesion was finally diagnosed as a malignant phyllodes tumour by surgery.

As compared with benign phyllodes tumours, aggressive tumours more frequently showed irregular shape ($p = 0.001$), indistinct or microlobulated margin ($p = 0.019$), and complex cystic and solid echogenicity ($p = 0.001$). In addition, benign phyllodes tumours characteristically showed heterogeneous echogenicity with numerous small anechoic clefts in 17 out of 31 cases (54.8%), whereas aggressive tumours showed this characteristic in three out of 15 cases (20.0%, $p = 0.001$). The posterior acoustic features and location of vascularity did not differ significantly between benign and aggressive phyllodes tumours.

Benign phyllodes tumours were most commonly assessed as BI-RADS final assessment category 3 (22/31, 71.0%), whereas aggressive phyllodes tumours were most commonly assessed as category 4 (13/15, 86.7%, $p = 0.001$) [Table 1].

Interestingly, 19 (61.3%) out of 31 patients with benign phyllodes tumours had multiple (≥5) probably benign lesions in the contralateral breast and remaining ipsilateral breast on ultrasonography, whereas only three (20%) out of 15 patients with aggressive tumours had these features.

Mammography was available in 21 patients. All of those 21 patients' mammograms revealed a mass with ($n = 2$) or without ($n = 19$) calcifications. Regardless of histological grade, mammographic findings were usually a mass with oval shape ($n = 19$), circumscribed or obscured margin ($n = 17$), and high density ($n = 14$). There were no significant differentiating findings on mammogram between benign and aggressive phyllodes tumours.

According to univariate analysis, the following variables

had statistically significant power to differentiate between benign and aggressive phyllodes tumours on sonography: long-axis diameter (p = 0.01), shape (p = 0.001), margin (p = 0.019), echogenicity (p = 0.001), and BI-RADS final assessment category (p = 0.001) [Table 1]. Multiple logistic regression analysis showed that the irregular shape was independently and strongly associated with aggressive phyllodes tumours (odds ratio = 26.51; 95% confidence interval = 1.82-385.35; p = 0.016) [Table 2]. The diagnostic indices of individual ultrasonographic features for differentiating aggressive phyllodes tumours from benign phyllodes tumours are summarised in Table 3. Shape showed the highest A_z value (0.804), with specificity of 96.4% and positive predictive value of 90.0%.

DISCUSSION

Phyllodes tumours were described as a type of giant fibroadenomas in 1774.[11] These tumours were first named as cystosarcoma phyllodes by Johannes Müller in 1838.[12] Then, the World Health Organization renamed this tumour "phyllodes tumour" in 1981.[13] Rosen subclassified this tumour histologically as benign, borderline, or malignant according to several features such as margin, stromal overgrowth, tumour necrosis, cellular atypia, and number of mitoses per high-power field.[14]

Table 2. Multiple logistic regression analysis of ultrasonography features for differentiation of aggressive phyllodes tumours from benign phyllodes tumours.

Ultrasonography features	Odds ratio (95% confidence interval)	p Value
Shape	26.51 (1.82-385.35)	0.016
Margin	3.09 (0.23-42.43)	0.398
Echogenicity	0.50 (0.19-1.30)	0.154
Posterior acoustic features	1.31 (0.15-11.50)	0.806
Location of vascularity	1.40 (0.39-5.11)	0.607

In our study, the following findings were more common in aggressive phyllodes tumours than benign ones, with statistical significance: larger diameter, irregular shape, indistinct or microlobulated margin, complex cystic and solid echogenicity, and higher final BI-RADS assessment category. These results are thought to reflect the histologically greater proliferative activity of aggressive phyllodes tumours.

Several previous studies have reported the relationship between size or imaging findings and histological grade of phyllodes tumours. Tan et al[5] reported that the malignancy rate increased significantly with increasing tumour size. However, Yabuuchi et al[6] reported that there was no significant correlation between size and histological grade. Liberman et al[8] reported that the observation of cystic areas by sonography was more common in malignant than benign phyllodes tumours, although the difference was statistically insignificant. Tan et al[5] reported that irregular shape was significantly correlated with borderline and malignant phyllodes tumours; however, there were no significant differences on the basis of margin, echogenicity, or vascularity. Whereas Tan et al[5] reported that there was no significant difference between histological grade and BI-RADS final assessment category, our study revealed that most aggressive phyllodes tumours were assigned to category 4, and benign tumours were most commonly assigned to category 3 (86.7% vs. 71.0%, p = 0.001). Therefore, BI-RADS assessment categorisation based on sonographic findings may be helpful to predict the histological grade of phyllodes tumours.

According to Stavros,[15] the small anechoic clefts in benign phyllodes tumours reflect the slit-like cystic space between leaf-like stromal proliferations. In the previous study by Chao et al,[16] the heterogeneous echogenicity associated with small anechoic clefts was a characteristic sonographic feature of benign phyllodes tumours. In our

Table 3. Diagnostic performance of ultrasonography features for differentiation of aggressive phyllodes tumours from benign phyllodes tumours.

Ultrasonography features	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	A_z value	p Value
Shape	64.3	96.4	90.0	84.4	0.804	<0.0001
Margin	71.4	71.4	55.6	83.3	0.714	0.005
Echogenicity	85.7	53.6	48	88.2	0.608	0.219
Posterior acoustic features	28.6	78.6	40	68.7	0.536	0.630
Location of vascularity	100	17.9	37.8	100	0.622	0.147

Abbreviations: A_z = largest area under the receiver operating characteristic curve; NPV = negative predictive value; PPV = positive predictive value.

study, benign phyllodes tumours also most commonly revealed heterogeneous echogenicity with multiple small anechoic clefts on sonography, whereas aggressive tumours were most commonly complex cystic and had solid echoic properties.

Interestingly, in 19 out of 31 patients (61.3%) with benign phyllodes tumours, multiple (≥5) various sized circumscribed oval masses suggesting benignity were found in the contralateral breast and the remaining ipsilateral breast. In aggressive phyllodes tumours, only three patients had these findings. In the ACRIN (American College of Radiology Imaging Network) 6666 study, circumscribed masses with similar appearance that were seen at ultrasound screening were almost always benign, with no malignancies found among such lesions.[17] Patients with benign tumours might have a tendency to have a multiplicity of them.

Recently, Jung et al[18] reported that some growing masses on follow-up sonography, which had first been diagnosed as benign tumours by ultrasound-guided core biopsy, were confirmed as benign or malignant phyllodes tumours by subsequent excisional biopsy. In our series, 10 cases had been initially diagnosed as fibroadenoma by ultrasound-guided core biopsy and were finally confirmed as phyllodes tumours by complete removal (benign phyllodes tumour: 7/31, aggressive phyllodes tumour: 3/15). Therefore, repeat ultrasonography should be still performed to exclude possibility of phyllodes tumours in patients with biopsy-proven fibroadenomas, especially in patients aged ≥40 years.

This study has several limitations. First, this is a retrospective study. Second, some patients with diagnoses of phyllodes tumours were excluded from the study population because their ultrasonograms were not available. The exclusion might have caused selection bias. Third, there is a relatively small number of enrolled patients. Particularly, the group of malignant phyllodes tumours was too small to compare with borderline malignancies. However, as the malignancy rate of phyllodes tumours is about 5% to 25%,[2] four cases of malignant phyllodes tumour among a total of 46 cases (8.6%) is an acceptable proportion.

CONCLUSION

In conclusion, several sonographic findings such as long-axis diameter, shape, margin, and echogenicity were helpful to differentiate between benign and aggressive phyllodes tumours. Irregular shape was independently and strongly associated with aggressive status of phyllodes tumours.

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