



Original Article

Clinical Features, Prognostic Factors, and Treatment Outcomes in 611 Patients with Phyllodes Tumors of the Breast: The Experience of a Single Institution in Taiwan

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Abstract

Background: Phyllodes tumors are uncommon biphasic breast tumors for which clinical findings remain insufficient to determine the optimal management strategy. The aim of this study was to report our experience of the clinicopathological features, prognostic factors, surgical treatment, and outcomes of patients presenting with phyllodes tumors in two different periods. **Materials and Methods:** We retrospectively reviewed the clinical and pathological data of 611 patients with histologically proven phyllodes tumors. The patients were separated into two groups: Period A, those who were treated from January 2006 to August 2013, and period B, those who were treated from September 2013 to September 2019. Clinical characteristics, histopathologic parameters, and outcomes were collected from patient records, and parameters were compared between the two periods. **Results:** The median follow-up was 7 months (range 0.5–84) in treatment period A and 14 months (range 0.5–118) in treatment period B. The median age was 38 years (range 12–75) in treatment period A and 40 years (range 12–79) in treatment period B. Analysis of the two treatment periods revealed an increase in tumor size at the diagnosis from 3.6 cm during period A to 4.5 cm during period B ($P = 0.001$). Most tumors were found in the upper outer quadrant, with an equal propensity to occur in either breast (34.6% vs. 42.2%). The pathologic diagnoses included 419 benign, 97 borderline, and 40 malignant lesions. Sixty cases (20 in period A and 40 in period B) experienced recurrence after surgery, including 35 benign phyllodes tumors (43% vs. 57%), 16 borderline tumors (38% vs. 63%), and 9 malignant tumors (44% vs. 56%) in either period ($P = 0.003$). Three cases (0.5%) (1 in period A and 2 in period B) had pulmonary metastases (0.3% vs. 0.7%). Multivariable linear regression analysis revealed that tumor size and a positive or undetermined surgical margin were the independent predictors of recurrence ($P = 0.006$, 0.020, and 0.004, respectively). **Conclusion:** Breast-conserving surgery with clear margins is technically feasible and a safe treatment for phyllodes tumors, but this strategy does not effectively further reduce local recurrence. Our findings demonstrated that clinical characteristics, tumor size, surgical margin, and pathologic features are the important predictors for tumor recurrence in patients with phyllodes tumors.

Keywords: Breast, phyllodes tumor, surgical margin

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INTRODUCTION

Phyllodes tumors are characterized by a double-layered epithelial component surrounded by a hypercellular mesenchymal component, typically presenting in leaf-like processes that have the potential for recurrence.^[1] Phyllodes tumor is an extremely rare tumor of the breast with an incidence between 0.3% and 0.9% of all breast tumors and 2.5% of all fibroepithelial tumors of the breast.^[2] Most (up to 60%) phyllodes tumors are benign,^[1] and they are most commonly found in women aged between 40 and 50 years.^[3]

The World Health Organization (WHO) has published guidelines classifying this tumor as being benign, borderline or malignant according to histological features such as stromal cellularity, stromal overgrowth, stromal atypia, mitoses per high power field, and tumor margin. Borderline and malignant phyllodes tumors, if not adequately treated, have a propensity for rapid growth, recurrence, and metastatic spread. In comparison, benign phyllodes tumors are often indistinguishable from fibroadenomas clinically, radiologically and cytologically, and they can be cured by local surgery alone, which remains the most common approach.^[4,5]

Wide surgical excision, defined as negative surgical margins greater than or equal to 1 cm, without axillary lymph node dissection, is considered to be the standard of care to reduce the risk of local recurrence. The use of adjuvant radiotherapy (RT) and adjuvant chemotherapy for completely resected phyllodes tumors is controversial. The survival rate for malignant phyllodes tumors has been reported to be approximately 60%–80% at 5 years.^[6–8] Distant metastases have been reported in up to 22% of malignant phyllodes tumors with expansion to nearly all internal organs, in particular the lungs and skeleton.^[9] Axillary lymph node metastases are rare, and metastasis most frequently involves the lungs. After the development of metastasis, the mean overall survival is 30 months.^[10]

The optimal management strategy for these lesions has yet to be determined and may consist of close clinical and radiological follow-up in selected patients to avoid the costs and morbidity associated with a surgical procedure. Previous research results have been published by Chen *et al.* 2005, Cheng *et al.* 2006, and Huang *et al.* 2014.^[11–13] Tumor histologic profile still serves as an important prognostic indicator, because borderline and malignant subtypes metastasize hematogenously.^[11] Positive surgical margins have only been significantly correlated with recurrence.^[12,13] New treatment results and concepts have been reported in the past few years. We have tracked the status of this disease at Mackay Memorial Hospital since the 1990s. As more cases have been treated at our institution since our last report, the aim of this retrospective study was to present updated results of the clinicopathological features, prognostic factors, and treatment outcomes of patients with phyllodes tumors.

SUBJECTS AND METHODS

Study patients and procedures

Patients who were diagnosed with a phyllodes tumor and underwent surgical management at Mackay Memorial Hospital between January 2006 and December 2019 were enrolled in this study. The patients were divided into two periods: (1) From January 1, 2006, to August 31, 2013 (period A), and from September 1, 2013, to September 30, 2019 (period B). We compared the patients treated during these periods to determine if there were changes in either the tumor characteristics or the rates of local recurrence. The medical records of the patients were retrospectively reviewed and clinical characteristics were collected including age, presenting symptoms and signs, location of the tumor and tumor size from physical examinations, and pathology records. Male patients, patients who refused to operate, patients lacking follow-up data (surgical pathology report or the outer courtyard had been operated but the information was incomplete), the concurrent presence of invasive ductal carcinoma, and those in whom the final pathological diagnosis was not a phyllodes tumor such as juvenile type fibroadenoma, fibromatosis, leiomyosarcoma, myofibroblastoma, angiomyofibroblastoma, malignant stromal cell tumor, and fibroadenolipoma were excluded from this study.

An accurate preoperative diagnosis of a phyllodes tumor was based on clinical, mammographic, sonographic, and histologic assessments, allowing for appropriate surgical planning. Three basic surgical procedures for surgical management were used including local excision, wide excision followed by mastectomy if the margin was inadequate and total mastectomy. For recurrent benign tumors, the choice of operation depended on the surgeon's preference. Some performed a mastectomy, and others performed local or wide excision to achieve a negative margin.

The final pathological diagnoses following surgery were divided into benign, borderline and malignant phyllodes tumors in accordance with the WHO criteria. Stromal overgrowth was defined as exclusion of the ductal component in at least one $\times 40$ low-power field.^[14] The presence of heterologous sarcomatous elements or necrosis was recorded. Follow-up data were obtained from the hospital's database and through interviews. The Mackay Memorial Hospital Institutional Review Board (Taipei, Taiwan) approved this study (approval number: 21MMHISO84e). The patient consent was waived by the IRB.

Statistical analysis

Clinical features, histologic parameters, and the type of primary surgical intervention were correlated with local recurrence and compared between the two periods using the Student's *t*-test, Fisher's exact test, or Chi-square test, as appropriate. Kaplan – Meier analysis for local recurrence was calculated from the time of diagnosis until the first local recurrence. The significance of clinical and pathologic factors was compared using the log-rank test. Cox proportional-hazards modeling

was used to investigate major prognostic factors. The joint effect of the independent variables that showed significance in univariate analysis was assessed with hierarchical regression analysis. Running line curve smoothers were used to relate the probability of having borderline or malignant tumors to age and the longest lesion diameter on ultrasound. $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed with SPSS for Windows, version 21.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

A total of 611 female patients including one patient with synchronous bilateral tumors were enrolled in this study, including 332 and 279 patients in treatment period A and period B, respectively.

Table 1 shows the clinical characteristics of these patients. The median ages were 37.7 years old (range: 12–75 years) and 39.7 years old (range: 12–79 years) in period A and period B, respectively ($P = 0.053$). The number of patients

younger than or equal to 40 years old were 189 (57.4%) and 141 (50.5%) in period A and period B, respectively. Laterality was equally distributed between the left and right breasts. A higher incidence of tumors in the upper outer quadrant was observed in both groups (34.6% and 42.2%, respectively). None of the patients had lymph node or distant metastasis at the time of presentation.

During treatment period A, a mastectomy was usually performed when a frozen section reported a malignant tumor or when an excisional biopsy revealed a borderline or malignant tumor. At times, the breast lump was so large that a mastectomy was performed under the clinical suspicion of carcinoma. Mastectomy was generally performed in a skin-sparing fashion so that skin grafts were unnecessary. For recurrent benign tumors, the choice of surgery depended on the surgeon's preference. Some surgeons performed a mastectomy, and others performed local or wide excision to achieve a negative margin. During this period, all patients underwent a mastectomy without axillary lymph node dissection.

Table 1: Clinical characteristics of the 611 patients with a phyllodes tumor during the two treatment periods

Parameters	Total (n=611)		P
	Period A (2006-2013) (n=332)	Period B (2013-2019) (n=279)	
Age			
Median (SD)	37.7 (12.345)	39.7 (12.335)	0.053
Minimum-maximum	12-75	12-79	
Age (years), n (%)			
≤40	189 (57.4)	141 (50.5)	0.088
>40	140 (42.6)	138 (49.5)	
Tumor size (cm), n (%)			
≤5	277 (83.4)	212 (77.1)	0.049
>5	55 (16.6)	63 (22.9)	
Laterality*, n (%)			
Right	169 (51.1)	152 (54.5)	0.537
Left	161 (48.6)	127 (45.5)	
Bilateral	1 (0.3)	0 (0.0)	
Quadrant, n (%)			
Upper outer	115 (34.6)	116 (42.2)	<0.001
Lower outer	65 (19.6)	19 (6.9)	
Upper inner	67 (20.2)	30 (10.9)	
Lower inner	25 (7.5)	14 (5.1)	
Central	60 (18.1)	96 (34.9)	
Treatment, n (%)			
Local excision	235 (70.8)	128 (45.9)	<0.001
Partial mastectomy (i.e., WE)	83 (25.0)	87 (31.2)	0.089
Total mastectomy	14 (4.2)	13 (4.7)	0.791
MRM	2 (0.6)	1 (0.4)	>0.999
PM + SLND	0 (0.0)	1 (0.4)	0.457
TM + SLND	1 (0.3)	4 (1.4)	0.184
Margin status, n (%)			
Negative	193 (58.1)	127 (55.0)	0.677
Positive	123 (37.0)	94 (40.7)	
Undetermined	16 (4.8)	10 (4.3)	

WE: Wide excision, MRM: Modified radical mastectomy, PM: Partial mastectomy, TM: Total mastectomy, SLND: Sentinel lymph node dissection, SD: Standard deviation

During treatment period B, most operations were performed after a core needle biopsy (either ultrasound or mammography guided) to rule out malignant disease. A mastectomy was performed only when a malignant tumor was diagnosed after tissue proof. A general benign lesion rarely required an excision to attain a clear margin. Sentinel lymph node dissection was performed for huge benign lesions >10 cm or when ultrasound or a physical examination detected abnormal lymph nodes. If a phyllodes tumor >4 cm was suspected pre- or perioperatively, a wide excision was performed with a margin of healthy tissue (≥ 1.0 cm). When the margin of the excised benign or borderline tumor was ≤ 0.1 cm, reoperation was performed if the patient agreed.

Of the 48 patients with malignant tumors, 29 (60.4%) underwent a mastectomy. Of 516 patients with a nonmalignant histology, 145 (28.1%) were treated by breast-conserving surgery ($P < 0.001$). During period A, 12 (57.1%) of 21 patients with a malignant tumor underwent a mastectomy. During period B, 18 (66.7%) of 27 patients with malignant disease underwent breast-conserving surgery; however, one patient developed distant failure. All pathology reports of the mastectomy specimens indicated clear margins, with normal breast tissue surrounding the tumor. In the 48 malignant cases, only four axillary lymph node dissections were performed at the time of mastectomy, but no nodal metastasis was found in either group. For the patients treated by breast-conserving surgery, nine in period A and eight in period B had margin involvement, and they were either not offered further treatment or refused it.

The median longest dimensions for benign versus borderline or malignant phyllodes tumors were 2.3 cm (range, 1.0–21.0 cm) versus 6.7 cm (range, 1.0–26.5 cm) ($P < 0.001$) in both groups. The median age of the patients was 37 years (range, 12–79 years) for those with benign phyllodes tumors versus 44 years (range, 17–76 years) for those with borderline and malignant phyllodes tumors ($P < 0.001$) in both groups. The average tumor size was 3.62 cm (range: 1.0–20 cm) during treatment period A and 4.53 cm (range: 1.0–26.5 cm) during period B. The tumor size was significantly larger in period B ($P = 0.001$). Benign, borderline, and malignant tumors had mean diameters of 3.5, 5.7, and 7.6 cm, respectively ($P < 0.001$, one-way analysis of variance f -test). For the 25 patients (benign: 7, borderline: 14, malignant: 4) treated by total mastectomy in both groups, the tumor size ranged from 1.0–26.5 cm (mean 4.2 cm) ($P < 0.001$). For the 170 patients treated by partial mastectomy, the mean tumor size was 4.6 cm for 145 nonmalignant lesions (benign: 106 and borderline: 39).

Tumor classification showed that 419 (75.4%) phyllodes tumors were benign, 97 (17.4%) were borderline malignant, and 40 (7.2%) were malignant. Six (1.8%) and 15 (6.6%) patients had tumor necrosis in period A and period B, respectively ($P = 0.003$). Twenty-five tumors had an infiltrating margin, five (20%) of which recurred. No other differences

in pathologic characteristics were found between the two periods [Table 2].

The median times to recurrence were 14.5 months (22 patients) and 14 months (41 patients) in treatment period A and period B, respectively ($P < 0.001$). Four of 26 patients (15.4%) with malignant tumors in period A and 15 of 27 patients (55.6%) with malignant tumors in period B developed local recurrence after a median follow-up of 34 months (range, 0.5–84 months); among these patients, only seven (2 in period A vs. 5 in period B) had recurrence within the 1st year of follow-up. Most patients received local excision followed by mastectomy.

Figure 1 shows the overall actuarial freedom from local recurrence of the patients following treatment of their phyllodes tumor during the two periods, and there was a significant difference (log-rank test, $P < 0.001$). Figure 2 shows the actuarial freedom from local recurrence of the patients following treatment of their phyllodes tumor stratified by tumor size. The patients with a tumor size >5 cm had a significantly increased likelihood of recurrence (log-rank test, $P < 0.001$). Figure 3 shows the local outcome stratified by margin status for the overall series. The median time to recurrence was 12 months (25 patients) in those with a positive surgical margin ($P = 0.017$) and 15.5 months (six patients) in those with an undetermined surgical margin ($P < 0.001$).

Table 3 shows the relationships between potential risk factors and delivery latency in univariable and multivariable linear regression analyses. Among the parameters studied, period B, tumor size >5 cm, and positive surgical margin showed a significant association with recurrence (adjusted hazard ratios: 2.41, 2.42, and 1.99, respectively), whereas none of the other prognostic factors were statistically significant.

Of the 611 cases, 60 experienced recurrence after surgery: 35 with benign phyllodes tumors (8.4% local recurrence), 16 (16.5%) borderline (1 case developed pulmonary metastasis), and 9 (23.1%) malignant (2 cases developed pulmonary metastasis) ($P = 0.003$). We found that older age (>40 years), malignant phyllodes tumor, and size of the tumor (>5 cm) were the strongest risk factors for the formation of a malignant phyllodes tumor ($P < 0.001$) [Table 4].

Imaging characteristics

Mammography and ultrasonography were used to evaluate the phyllodes tumors before surgery during treatment period B. In general, regular mammograms were not recommended for women under 40 years of age, some suggested under 45, unless they had an immediate family member with a history of breast cancer. Ultrasonography alone was used in 225 cases and 54 cases did not receive an imaging study [Table 5]. Tumor shapes were irregular in 112 cases [Figure 4], oval in 340 cases, and round in 14 cases. The groupings of the margin borders of the tumor were circumscribed in 370 cases and noncircumscribed in 96 cases.

All 279 patients received gray scale and power Doppler sonography during treatment period B. Most patients did not

Table 2: The pathologic parameters of the 611 patients with a phyllodes tumor during the two treatment periods

Parameters	Period A (2006-2013) (n=332)	Period B (2013-2019) (n=279)	P
Histology type, n (%)			
Benign	253 (76.4)	166 (73.8)	0.441
Borderline	58 (17.5)	39 (17.3)	
Malignant	21 (6.3)	27 (9.7)	
Tumor borders, n (%)			
Pushing	321 (96.7)	212 (93.8)	0.106
Infiltrative	11 (3.3)	14 (6.2)	
Stromal cellularity, n (%)			
Mild to moderate	316 (95.2)	214 (94.7)	0.794
Marked	16 (4.8)	12 (5.3)	
Nuclear atypia, n (%)			
Mild to moderate	320 (97.3)	214 (94.7)	0.118
Marked	9 (2.7)	12 (5.3)	
Mitoses (per 10 HPF), n (%)			
0-4	252 (75.9)	179 (79.2)	0.637
5-9	36 (10.8)	20 (8.8)	
≥10	44 (13.3)	27 (11.9)	
Stromal overgrowth, n (%)			
Absent	313 (94.3)	204 (90.3)	0.075
Present	19 (5.7)	22 (9.7)	
Heterologous elements, n (%)			
Absent	331 (99.7)	224 (99.6)	>0.999
Present	1 (0.3)	1 (0.4)	
Tumor necrosis, n (%)			
Absent	326 (98.2)	211 (93.4)	0.003
Present	6 (1.8)	15 (6.6)	

HPF: High power field

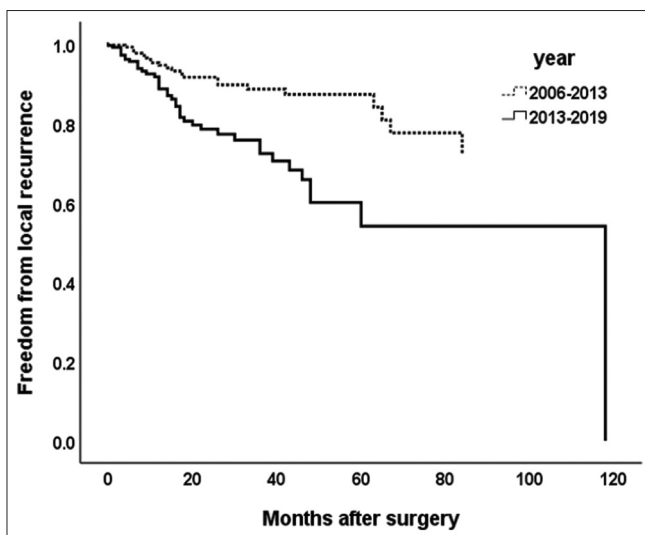


Figure 1: Overall actuarial freedom from local recurrence for patients following treatment of their phyllodes tumor during the two periods. Curves were plotted based on the Kaplan-Meier method. Significant difference was seen by log-rank test ($P < 0.001$)

have ultrasound records during treatment period A. Thirty-two percent (240/279) of the women underwent ultrasound-guided biopsy before surgery. Twelve patients were referred from an outside institution for ultrasound-guided biopsy, and the outside preoperative images were reviewed. Thirty-three

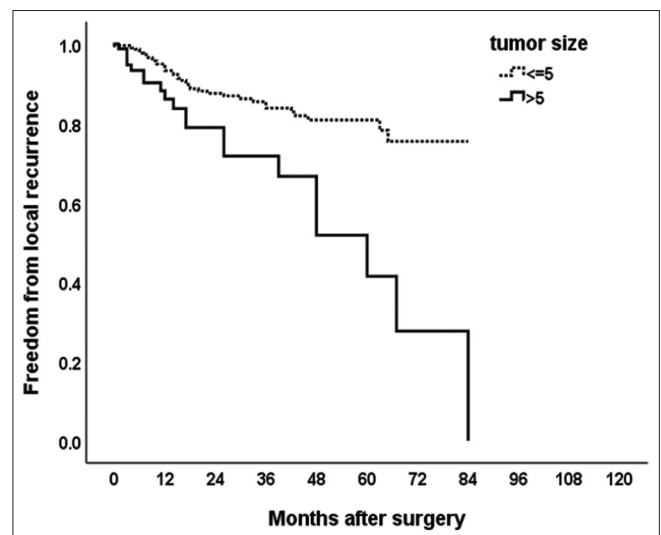


Figure 2: Actuarial freedom from local recurrence for patients following treatment of their phyllodes tumor stratified by tumor size. Patients with tumor size more than 5cm had a significantly increased likelihood of recurrence. Curves were plotted based on the Kaplan-Meier method. Significant difference was seen by log-rank test ($P < 0.001$)

percent (20/61) of irregularly shaped tumors in sonography had borderline or malignant histologic profiles ($P = 0.012$). Thirty-six percent (15/42) of tumors with a nonparallel

Table 3: Prognostic factors of disease local recurrence analyzed by simple and multiple Cox proportional hazard models

Characteristics	Unadjusted HR	95% CI	P	Adjusted HR	95% CI	P
Treatment period						
Period A	1.0			1.0		
Period B	2.744	1.608-4.681	<0.001	2.410	1.340-4.335	0.003
Age (years)						
≤40	1.0			1.0		
>40	1.714	1.029-2.853	0.038	1.503	0.855-2.643	0.157
Tumor size (cm)						
≤5	1.0			1.0		
>5	2.816	1.640-4.834	<0.001	2.421	1.291-4.540	0.006
Surgical margin						
Negative	1.0			1.0		
Positive	1.970	1.127-3.442	0.017	1.996	1.115-3.573	0.020
Undetermined	4.630	1.874-11.437	0.001	4.481	1.613-12.448	0.004
Tumor borders						
Pushing	1.0					
Infiltrative	1.456	0.454-4.670	0.528			
Nuclear atypia						
Absent	1.0					
Present	1.934	0.601-6.221	0.268			
Mitosis (per 10 HPF)						
0-4	1.0			1.0		
5-9	1.963	0.913-4.221	0.084	1.166	0.478-2.842	0.736
≥10	2.001	1.019-3.928	0.044	1.368	0.669-2.794	0.390
Stromal cellularity						
Mild to moderate	1.0					
Marked	1.806	0.720-4.532	0.208			
Tumor necrosis						
Absent	1.0					
Present	3.034	0.937-9.820	0.064			

CI: Confidence interval, HPF: High power field, HR: Hazard ratio

Table 4: Patient and tumor characteristics of 611 patients stratified by types of phyllodes tumor during the two treatment periods

Parameters	Types of phyllodes tumors			P
	Benign (n=419)	Borderline (n=97)	Malignant (n=40)	
Treatment period, n (%)				
Period A	253 (60.4)	58 (59.8)	21 (52.5)	0.441
Period B	166 (39.6)	39 (40.2)	27 (67.5)	
Age (years), n (%)				
≤40	245 (58.9)	36 (37.1)	17 (42.5)	<0.001
>40	171 (41.1)	61 (62.9)	23 (57.5)	
Tumor size (cm), n (%)				
≤5	362 (86.6)	59 (61.5)	18 (46.2)	<0.001
>5	56 (13.4)	37 (38.5)	21 (53.8)	
Surgical margin, n (%)				
Negative	235 (56.1)	53 (54.6)	26 (65.0)	0.188
Positive	168 (40.1)	35 (36.1)	13 (32.5)	
Undetermined	16 (3.8)	9 (9.3)	1 (2.5)	
Recurrence, n (%)				
Yes	35 (8.4)	16 (16.5)	9 (23.1)	0.003
No	384 (91.6)	81 (83.5)	30 (76.9)	

Undetermined surgical margin, the resection margin could not be properly evaluated due to the fragmentation of specimen or the adequacy of the surgical margin could not be determined

Table 5: The sonographic features of 279 patients with a phyllodes tumor during period B

Feature	Total number of tumors (<i>n</i> =279), <i>n</i> (%)	Number of benign tumors (<i>n</i> =166), <i>n</i> (%)	Number of borderline or malignant tumors (<i>n</i> =59), <i>n</i> (%)	<i>P</i>
Shape				
Irregular	61 (21.9)	31 (19.7)	20 (40.8)	0.012
Oval	191 (68.5)	121 (77.1)	28 (57.1)	
Round	8 (2.9)	5 (3.2)	1 (2.0)	
Orientation				
Nonparallel	42 (15.1)	23 (14.7)	15 (30.6)	0.013
Parallel	217 (77.8)	133 (85.3)	34 (69.4)	
Margins				
Circumscribed	208 (74.6)	129 (82.2)	33 (67.3)	0.027
Other (noncircumscribed)	52 (18.6)	28 (17.8)	16 (32.7)	
Echo patterns				
Heterogeneous	19 (6.8)	9 (5.7)	7 (14.3)	0.102
Hypoechoic	240 (86.0)	147 (93.6)	42 (85.7)	
Hyperechoic	1 (0.4)	1 (0.6)	0 (0.0)	
Posterior acoustic features				
Enhancement	12 (4.3)	8 (5.1)	1 (2.0)	0.631
Shadowing	3 (1.1)	2 (1.3)	1 (2.0)	
No change	244 (87.5)	146 (93.6)	47 (95.9)	
Calcification	3 (1.1)	1 (0.6)	2 (3.4)	0.169

Most patients in period A have no ultrasound records

Table 6: Changes in the histologic grade of phyllodes tumors in women with locally recurrent disease

Change in diagnosis	Recurrence				Total	Percentage	<i>P</i>
	First	Second	Third	Fourth			
Benign to benign	13	26	10	1	50	45.0	<0.001
Benign to borderline	2	9	0	1	12	10.8	<0.001
Benign to malignant	0	1	0	0	1	0.9	0.143
Borderline to benign	0	2	0	0	2	1.8	0.023
Borderline to borderline	3	12	4	5	24	21.6	<0.001
Borderline to malignant	1	2	1	1	5	4.5	<0.001
Malignant to benign	0	1	0	0	1	0.9	0.143
Malignant to borderline	0	1	0	0	1	0.9	0.143
Malignant to malignant	2	9	4	0	15	13.5	<0.001
Total	21	63	19	8	111		

orientation in sonography had borderline or malignant histologic profiles ($P = 0.013$). Thirty-one percent (16/52) of the phyllodes tumors with noncircumscribed margins were classified as being borderline or malignant in histologic analysis ($P = 0.027$). No significant differences were observed in lesion boundary, posterior acoustic features, calcification, or echo pattern between benign and borderline or malignant phyllodes tumors in sonography. Table 5 shows a summary of the demographic and sonographic features of these tumors [Table 6].

Most (80.1%) cases of recurrence were of the same grade. Upgrading to the next category was observed in 16.2% of cases of recurrence. Only one originally benign phyllodes tumor recurred locally as a histologically malignant tumor; it was treated by mastectomy and did not recur. Twelve originally benign phyllodes tumors recurred locally as

histologically borderline tumors. The second recurrent episode was eventually controlled by mastectomy. Distant metastasis was found in three patients undergoing mastectomy, two of whom originally had malignant phyllodes tumors and one a borderline tumor. The time to distant metastasis was <1 year in all cases (mean 5.3 months). Three patients died of metastasis to the lungs without local recurrence, with a mean survival of 5 months (range 1–13 months). In addition, nine patients subsequently developed invasive ductal carcinoma of the breast (four ipsilateral and five contralateral).

DISCUSSION

Phyllodes tumors are rare fibroepithelial tumors, with an incidence of about 0.5% of all breast neoplasms.^[14] The most common age at the diagnosis is 45–49 years, which is older than for the highest risk group of fibroadenoma by

20 years;^[2] however, in our patients, the average age was 40 years in period B. In this study, the malignant phyllodes tumors occurred more frequently in patients >40 years [Table 4].

Clinical presentation is usually a painless rapidly growing mass. Images from mammography and ultrasonography should raise suspicion of a phyllodes tumor if the tumor is a well-circumscribed oval or lobulated mass with rounded borders.^[15] All phyllodes tumors were readily visualized in ultrasound as masses in this study, and borderline and malignant phyllodes tumors were disproportionately represented as irregular masses with noncircumscribed margins. With most of the imaging characteristics, it is difficult to distinguish fibroadenoma from phyllodes tumors.^[16,17] In cases with a giant phyllodes tumor ≥ 10 cm, the use of preoperative computed tomography could be helpful in distinguishing between a benign and malignant phyllodes tumor, and it is also a useful modality for the diagnosis of axillary lymph node metastasis.

Phyllodes tumors were most commonly found in the upper outer quadrant (46.0%) with an equal propensity to occur

in either breast (34.6% vs. 42.2%) in our study, similar to the results in other series.^[18,19] In our series, one patient was found to have a phyllodes tumor in the arm and two in axilla area. This unique case shows that an unusual presentation of phyllodes tumor can occur, and this should be kept in mind.

In the present study, the histopathological parameters during the two periods were similar, and Cox regression analysis showed that a tumor size >5 cm and a positive or undetermined surgical margin were prognostic of local recurrence [Table 3]. In addition, the limitation of the current study is its retrospective nature. The inability to demonstrate correlations between the tumor characteristic and surgical procedure may be due to selection bias for the type of surgery (i.e., radical surgery was more likely for more malignant disease), and therefore, it is difficult to make specific treatment recommendations based on our study.

Tumor size has generally been considered to be of prognostic significance;^[20,21] however, this has not been reliably produced.^[22,23] The size of the tumor should be considered. The average size of fibroadenoma is 2 cm compared to 4–7 cm for phyllodes tumors.^[14,15,24,25] In our series, the average size of a phyllodes tumor was 4.1 cm, and increase in tumor size was observed with the type of phyllodes (3.5 cm in benign, 5.7 cm in borderline, and 7.6 cm in malignant). The size of the phyllodes tumor also increased with increasing degree of malignancy. However, an increased tumor size at diagnosis makes it difficult to achieve a negative surgical margin with breast-conserving surgery. In the present study, recurrence was significantly correlated with tumor size. This may be explained by the fact that our surgeons tended to perform local or wide excision for lesions ≤ 5 cm or that were benign, whereas more aggressive surgery was performed for larger or malignant phyllodes tumors.

Surgical management to remove the tumor is the mainstay of treatment for all classes of phyllodes tumors, with the aim of achieving a negative margin of at least 1 cm to reduce local recurrence.^[8,14,26,27] If the surgical margin did not reach 1 cm, further management is different in each classification of phyllodes. Benign phyllodes tumors should be watched

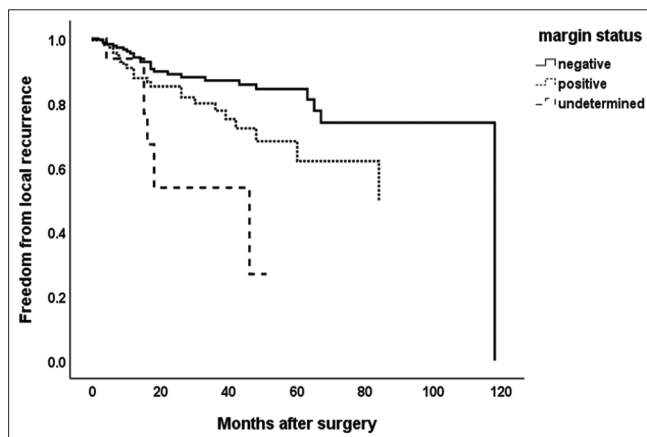


Figure 3: The graph shows the actuarial freedom from local recurrence for patients following treatment of their phyllodes tumor during the two periods. The surgical margin is expressed as a categorical variable. The presence of the positive and undetermined margin indicate a significantly increased likelihood of recurrence. Curves were plotted based on the Kaplan-Meier method. Reference group is negative surgical margin

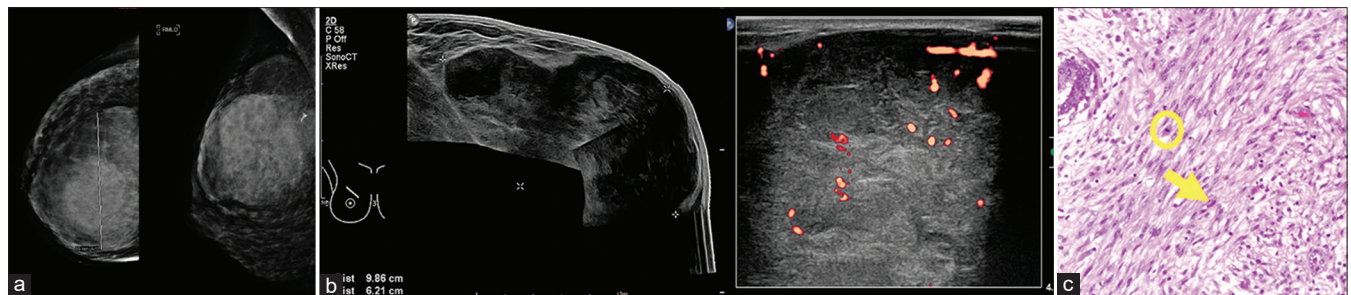


Figure 4: A 53-year-old woman with palpable finding in right breast that was determined to be malignant phyllodes tumor. (a) Craniocaudal (right) and mediolateral oblique (right) mammograms showed a huge well demarcated mass with high attenuation about 9 cm in diameter in upper half of right breast suspicious of phyllodes tumor. (Corresponding to BI-RADS category 5). (b) Transverse ultrasound showed noncircumscribed irregular hypoechoic oval mass with hypervascularity. (c) Photomicrograph (H and E, stain, $\times 200$): Malignant phyllodes tumor showed hypercellularity, composed of dense spindle cells and with marker cellular pleomorphism (arrow) and brisk mitosis (circle)

carefully because a positive margin with a benign tumor has not been related to local recurrence.^[28] However, in cases of borderline and malignant phyllodes tumors, a re-excision or mastectomy to achieve an adequate margin should be carried out.^[15,29] In our study, we found that phyllodes tumors differed significantly in recurrence rate between a negative and positive margin ($P = 0.02$), while the borderline and malignant phyllodes tumors recurred significantly more frequently in cases of an inadequate margin ($P = 0.003$) [Table 4].

In our study, 133 patients had a positive surgical margin in period B, four of whom (two underwent local excision and two had wide excision) decided to subsequently undergo re-excision (two wide excision and two total mastectomy, respectively), after which all margins were free of tumor involvement, and none of them recurred. All of the other patients chose close observation. A problem we encountered was that it was difficult to persuade patients to undergo additional radical surgery, even in those with margin involvement. Many patients declined when they realized that further surgery did not guarantee no further recurrence in future. However, 22 patients (12 first underwent local excision and 10 wide excision) with positive margins experienced recurrence. The management of recurrence in these 22 patients was 6 local excision, 14 wide excision and 1 total mastectomy, and one patient refused surgery. None had a second recurrence. In the present series, 69 patients who underwent wide excision had negative surgical margins, and 11 had recurrence. The local control rate was 84.1%, which is lower than in previous reports. In comparison, 73 patients had local excision with negative margins and 10 had recurrence, resulting in a local control rate of 86.3%. Eight patients had a total mastectomy with negative surgical margins, and only one had recurrence (87.5% local control rate).

On the basis of our experience, in patients with benign phyllodes tumors with positive surgical margins, close monitoring for local recurrence for 3–6 weeks is suggested. However, in patients with borderline or malignant phyllodes tumors with positive surgical margins, we recommended further radical surgery to avoid local recurrence.

In addition, in patients with a phyllodes tumor >4 cm at presentation, we recommend wide excision rather than local excision to reduce local recurrence. Axillary lymph node dissection is generally not recommended, because malignant phyllodes tumors usually spread by a hematogenous route rather than a lymphatic route. The reported incidence of axillary lymph node metastases is approximately 10%, and routine axillary exploration is usually not recommended.^[30] In our series, two cases with total mastectomy for malignant tumors in period A and one in period B had concurrent axillary dissection. However, none of these patients had axillary node metastases. Several earlier studies have reported similar results.^[7,31,32]

Contemporary studies of malignant and borderline phyllodes tumors have reported local recurrence rates ranging from 9% to

24% within 2 years of surgery,^[33,34] of which 2%–24% develop distant metastasis.^[33,35,36] The median time to recurrence in the present study was 14 months. Three cases experienced distant metastasis during the study period: 1 borderline and 3 malignant (3 cases developed pulmonary metastasis and 1 case was a simultaneous bone metastases). Although phyllodes tumors have a good prognosis with a 5-year cancer-specific survival rate reaching 80%–92%, patients developing distant metastasis suffer from rapid progression and have a high mortality rate.^[37–39]

The National Comprehensive Cancer Network guidelines and the other studies suggest the use of RT in recurrent cases of malignant phyllodes tumors.^[40] Some authors suggest adjuvant RT to decrease the possibility of local recurrence in both borderline and malignant phyllodes tumor patients who are treated with breast-conserving surgery.^[41] Other studies have suggested that additional RT does not improve the prognosis and is unnecessary,^[42] whereas others have suggested that adjuvant radiation therapy may be appropriate for high-risk patients with margins <0.5 cm, tumors >10 cm in diameter, or following resection of recurrent disease.^[43] However, RT has not been reported to affect overall survival or disease-free survival.^[39,41] At our institution, we consider the use of adjuvant RT in patients with malignant phyllodes tumors undergoing surgical management with wide excision. With regards to adjuvant therapy, one case with a borderline tumor due to positive surgical margins and two cases with malignant tumors due to positive surgical margins and two time relapses in our series received postoperative RT. One of the patients with a malignant lesion received adjuvant chemotherapy (regimen: Dacarbazine plus liposomal doxorubicin for 4 cycles) due to positive surgical margins after total mastectomy. However, the extent of resection and the role of adjuvant RT or chemotherapy are still controversial.^[30,44,45]

CONCLUSION

Phyllodes tumors are extremely rare tumors that occur in relatively young women; however, older women have an increased risk of malignant phyllodes formation. It is difficult to distinguish between fibroadenoma and phyllodes tumors clinically. However, aggressive treatment should be considered in patients who exhibit rapid tumor growth within 6 months. On the basis of our experience, we believe that wide excision with an adequate margin is the preferred initial therapy in patients with concerns of malignancy or continued growth. In order to minimize the risk of local recurrence and achieve a better outcome in phyllodes tumors, we recommend wide excision with a margin of at least 1 cm, rather than excision with narrower margins or enucleation alone. Nevertheless, clinicians face a major challenge to technically obtain a clear margin and also a satisfactory cosmetic outcome for patients. Therefore, a narrower but clear margin can be acceptable for benign, but not borderline or malignant phyllodes tumors. Furthermore, phyllodes tumors can often be treated with breast-conserving surgery (partial mastectomy), and mastectomy but not modified

radical mastectomy is only required if adequate margins cannot be achieved with breast-conserving surgery. With the use of active surveillance, many women may potentially be spared from the unnecessary risk, anxiety, and economic cost associated with surgery.

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Conflicts of interest

There are no conflicts of interest.

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