

Clinical Predictors and Long-term Outcomes of Non-benign Breast Phyllodes Tumors

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Abstract

Background/Aim: Phyllodes tumors of the breast are rare fibroepithelial neoplasms with heterogeneous biological behavior. Reliable preoperative predictors of non-Benign (borderline and malignant) tumors remain incompletely defined. This study aimed to identify clinical predictors of non-Benign phyllodes tumors and to evaluate long-term outcomes.

Patients and Methods: We retrospectively analyzed 106 patients who underwent surgical resection for breast phyllodes tumors at a single institution. Tumors were classified as benign, borderline, or malignant according to World Health Organization criteria. The presence of rapid tumor growth was determined based on clinical records. Univariate and multivariate logistic regression analyses were performed to identify predictors of non-Benign tumors. Local recurrence-free survival was assessed using long-term follow-up data.

Results: Of the 106 tumors, 54 were benign, 46 borderline, and 6 malignant. The median follow-up period was 109 months. In univariate analysis, age and the presence of rapid tumor growth were significantly associated with non-Benign tumors. Multivariate analysis demonstrated that both age and the presence of rapid tumor growth were independent predictors of non-Benign phyllodes tumors. Tumor size and preoperative diagnosis were not independently associated with non-Benign tumors. Only one case (0.9%) of local recurrence was observed, and no distant metastases occurred during follow-up.

Conclusion: Breast phyllodes tumors have an excellent long-term prognosis with a very low risk of recurrence. Age and the presence of rapid tumor growth are useful clinical indicators for predicting non-Benign phyllodes tumors and may aid in preoperative assessment and clinical decision-making.

Keywords: Phyllodes tumor, breast, non-benign, rapid tumor growth, prognosis, long-term follow-up.



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Introduction

Phyllodes tumors are rare biphasic fibroepithelial neoplasms, accounting for approximately 0.3-0.9% of all breast tumors (1). Clinically, they exhibit a wide spectrum of biological behavior ranging from benign to malignant and are often difficult to distinguish from fibroadenomas.

According to the World Health Organization (WHO) classification (2), phyllodes tumors are categorized into benign, borderline, and malignant subtypes based on histopathological features of the stromal component, including cellular atypia, mitotic activity, stromal cellularity, stromal overgrowth, and tumor margins with respect to surrounding tissue invasion. However, it has been reported that these histological criteria alone do not always fully reflect clinical behavior, and substantial variability in recurrence and metastatic risk has been observed even within the same pathological category (3).

Therefore, comprehensive prognostic assessment of phyllodes tumors incorporating clinical factors in addition to histological classification is considered important.

Surgical resection remains the standard treatment for phyllodes tumors, and excision with surrounding normal tissue is generally recommended. The National Comprehensive Cancer Network (NCCN) guidelines (4) recommend achieving a surgical margin of at least 1 cm; however, the optimal margin width remains a subject of ongoing debate.

Reported postoperative local recurrence rates of phyllodes tumors range from 8% to 17% (5). In contrast, a systematic review by Yu *et al.* (6) reported recurrence rates of 7.1%, 16.7%, and 25.1% for benign, borderline, and malignant tumors, respectively. These findings suggest that particularly in benign phyllodes tumors with favorable prognosis, excessively wide surgical excision may constitute overtreatment.

The present study aimed to identify clinical predictors of non-Benign (borderline and malignant) phyllodes tumors among 106 patients treated at our institution and to reassess recurrence and long-term outcomes based on extended follow-up data.

Patients and Methods

A retrospective analysis was conducted of 106 patients who underwent surgical resection for phyllodes tumors at our institution between February 1999 and December 2022. Patients who underwent surgery for recurrent tumors at our institution but had their initial resection performed at another hospital were excluded. The median follow-up period was 109 months (range=0–333 months).

Pathological classification. Tumors were classified as benign, borderline, or malignant according to WHO criteria.

Definition of rapid tumor growth. The presence of rapid tumor growth was determined based on documentation in the medical records indicating obvious enlargement over a short period, supported by imaging findings or physical examination.

Definition of recurrence. Local recurrence was defined as a lesion occurring in the same breast and same quadrant after initial surgery that was diagnosed as a phyllodes tumor by needle biopsy or postoperative pathological examination.

Evaluation of gross margin. Gross margin was evaluated in 95 cases for which cross-sectional photographs of surgical specimens were available. The shortest distance between the tumor edge and the resection margin was measured macroscopically by the author using a standardized method. This assessment was based on gross inspection and therefore included a degree of subjectivity.

Statistical analysis. Univariate and multivariate logistic regression analyses were performed with benign versus non-Benign (borderline and malignant) tumors as the outcome. Statistical significance was defined as $p < 0.05$. All analyses were conducted using JMP® 18 (JMP Statistical Discovery LLC, Cary, NC, USA).

Table I. Patient and tumor characteristics and postoperative outcomes. Patient demographics, tumor characteristics, surgical procedures, and postoperative clinical outcomes in the study cohort (n=106).

Patient characteristics	n=106	Pathological findings	n=106
Age, median (range)	44 (13-80)	Tumor size(mm), median (range)	60 (10-210)
Female/Male	106/0	0-20 mm, n (%)	12 (11.3)
Biopsy method		20-50 mm, n (%)	67 (63.2)
CNB, n (%)	86 (81.1)	50-100 mm, n (%)	23 (21.7)
FNA, n (%)	7 (6.6)	100 mm, n (%)	4 (3.8)
Not performed, n (%)	13 (12.3)	Tumor subtype	
Preoperative diagnosis		Benign, n (%)	54 (50.9)
Fibroadenoma, n (%)	26 (24.5)	Borderline, n (%)	46 (43.4)
Fibroadenoma or phyllodes, n (%)	15 (14.1)	Malignant, n (%)	6 (5.7)
Phyllodes, n (%)	42 (39.6)	Recurrence, n (%)	1(0.9)
Others, n (%)	10 (9.4)	Local recurrence, n (%)	1(0.9)
Not performed	13 (12.3)	Distant metastasis, n (%)	0(0)
Rapid tumor growth, n (%)	14 (13.2)	Death/alive, n	1/105
Surgical procedure			
Wide local excision, n (%)	101 (95.3)		
Mastectomy, n (%)	5 (4.7)		
Gross margin (mean)	2.0 mm		

Table II. Clinicopathological characteristics according to histological subtype. Clinicopathological characteristics according to histological subtype of phyllodes tumors (benign, borderline, and malignant). Values are presented as median (range) or number (%), as appropriate. The number of patients in each subgroup is shown in the column headers. In this table, cases diagnosed preoperatively as "fibroadenoma or phyllodes tumor" were classified as phyllodes tumor.

	Benign (n=54)	Borderline (n=46)	Malignant (n=6)
Age at diagnosis, median (range)	39 (13-78)	50 (20-80)	51.5 (41-56)
Tumor size at presentation, median (mm)	30 (10-70)	27.5 (10-160)	67.5 (40-190)
0-20 mm, n (%)	5 (9.3)	5 (10.9)	0 (0)
20-50 mm, n (%)	40 (74.1)	31 (67.4)	1 (16.7)
50-100 mm, n (%)	7 (13.0)	5 (10.9)	3 (50.0)
≥100 mm, n (%)	0 (0)	3 (6.5)	2 (33.3)
Rapid tumor growth, n (%)	2 (3.7)	11 (23.9)	1 (16.7)
Preoperative diagnosis, n (%)			
Fibroadenoma	18 (33.3)	11 (23.9)	0 (0)
Phyllodes	29 (53.7)	25 (54.3)	4 (66.7)
Others	0 (0)	4 (3.8)	0 (0)
Not performed	7 (13.0)	6 (13.0)	2 (33.3)
Surgical procedure, n (%)			
Wide local excision	54 (100)	43 (93.5)	4 (66.7)
Mastectomy	0 (0)	3 (6.5)	2 (33.3)

Results

Patient characteristics and tumor features. A total of 106 patients who underwent surgical resection for breast phyllodes tumors were included in the analysis. Patient demographics, tumor characteristics,

surgical procedures, and postoperative outcomes are summarized in Table I. According to pathological classification, 54 tumors were benign, 46 were borderline, and 6 were malignant.

Clinicopathological characteristics according to histological subtype are shown in Table II, including age,

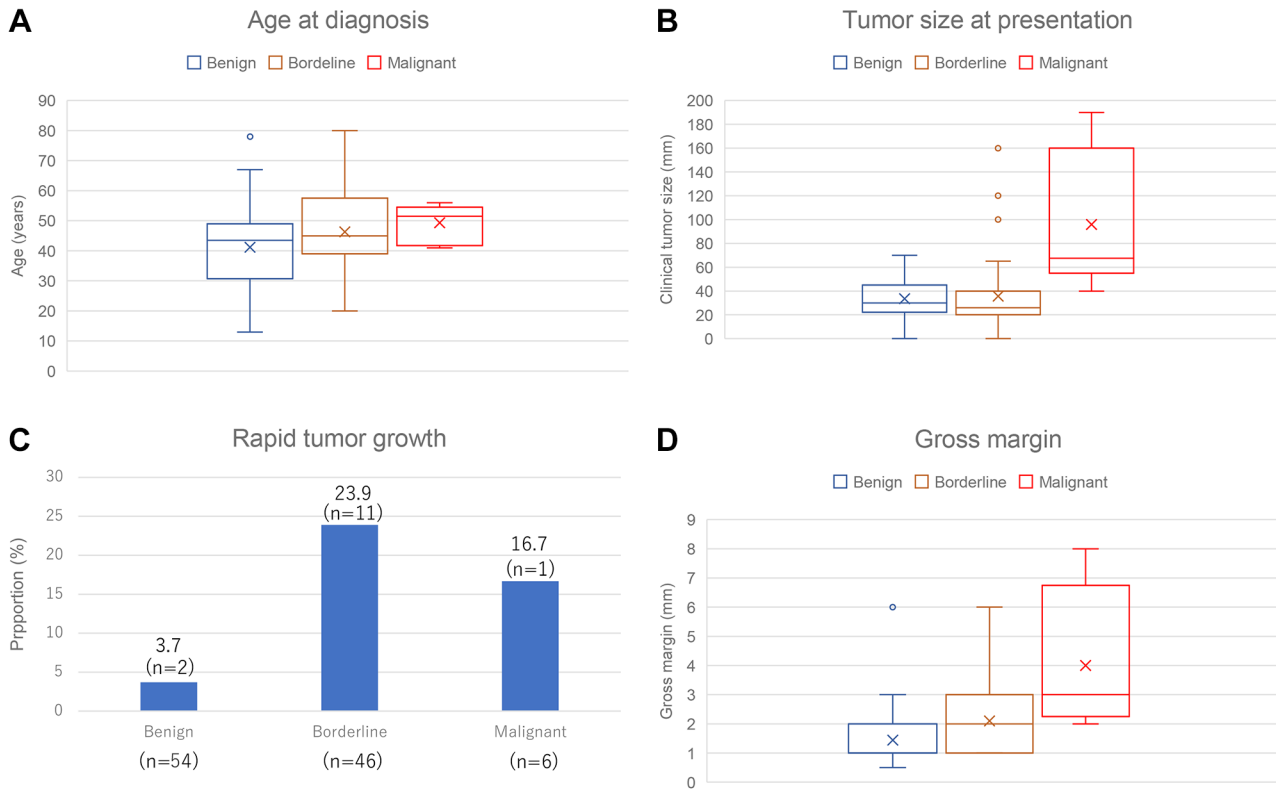


Figure 1. Clinicopathological characteristics according to histological subtype of phyllodes tumors (benign, borderline, and malignant). (A) Age at diagnosis, (B) tumor size at presentation, (C) presence of rapid tumor growth, and (D) gross margin are shown. Statistical comparisons among the three groups were performed using the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. *p*-Values for comparisons among the three groups were as follows: (A) Age at diagnosis, $p=0.0942$; (B) tumor size at presentation, $p=0.0081$; (C) presence of rapid tumor growth, $p=0.0116$; (D) gross margin, $p=0.0001$.

tumor size, presence of rapid tumor growth, preoperative diagnosis, gross margin, and surgical procedure.

Comparison of clinicopathological factors among histological subtypes. When clinicopathological factors were compared among histological subtypes, no significant difference in age was observed among benign, borderline, and malignant tumors (Figure 1A). In contrast, tumor size, the presence of rapid tumor growth, and gross margin differed among the three groups (Figure 1B-D).

Among these factors, the presence of rapid tumor growth (yes/no), a categorical variable, showed a statistically significant difference among the three groups (chi-square test, $p=0.0116$) (Figure 1C).

Predictors of non-Benign phyllodes tumors. Univariate and multivariate logistic regression analyses were performed with benign versus non-Benign (borderline and malignant) tumors as the outcome (Table III). In univariate analysis, age and rapid tumor growth were significantly associated with non-Benign tumors.

Multivariate analysis incorporating these factors, along with tumor size considered clinically relevant, demonstrated that age and rapid tumor growth were independently associated with non-Benign phyllodes tumors. Tumor size was not independently associated with non-Benign tumors in multivariate analysis.

Postoperative outcomes and long-term prognosis. The median follow-up period was 109 months. Only one

Table III. Univariate and multivariate logistic regression analyses identifying predictors of non-benign phyllodes tumors. Univariate and multivariate logistic regression analyses identifying clinical predictors of non-Benign phyllodes tumors (borderline and malignant). Odds ratios (ORs) with 95% confidence intervals (CIs) are shown. Because of the limited number of non-benign cases, confidence intervals for some variables are wide.

Characteristics	Univariate analysis OR (95%CI)	p-Value	Multivariate analysis OR (95% CI)	p-Value
Age (per year increase)	1.035 (1.004-1.070)	0.028*	1.042 (1.001-1.089)	0.043*
Tumor size at presentation (per 1 mm increase)	1.014 (0.999-1.034)	0.123	1.015 (0.996-1.040)	0.122
Rapid tumor growth (yes vs. no)	7.800 (1.982-52.00)	0.002*	14.301 (1.978-303.076)	0.006*
Biopsy method (CNB vs. FNA)	1.706 (0.394-8.740)	0.483	-	-
Preoperative diagnosis (Phyllodes vs. FA)	1.381 (0.557-3.486)	0.486	-	-

*Statistically significant at p-value <0.05.

case (0.9%) of local recurrence was observed, and no distant metastases occurred. One patient died of thyroid cancer, which was unrelated to phyllodes tumor. Local recurrence-free survival (LRFS) is shown in Figure 2. The single case of local recurrence occurred 33 months after surgery.

Discussion

In this retrospective study of 106 patients with breast phyllodes tumors, multivariate analysis identified age and rapid tumor growth as clinical factors independently associated with non-Benign (borderline and malignant) tumors. In addition, during a long-term follow-up with a median duration of 109 months, only one local recurrence was observed, indicating that phyllodes tumors overall have an excellent prognosis.

The WHO classification is based on histopathological features of the stromal component, such as cellular atypia and mitotic activity; however, it has been suggested that this classification may not fully reflect clinical behavior. Our findings demonstrate that clinical factors such as age and rapid tumor growth are associated with non-Benign phyllodes tumors, supporting the importance of integrating clinical features in addition to pathological classification. Furthermore, preoperative distinction between phyllodes tumors and fibroadenomas remains challenging in clinical practice (7), reinforcing the need for reliable clinical indicators to guide surgical decision-making.

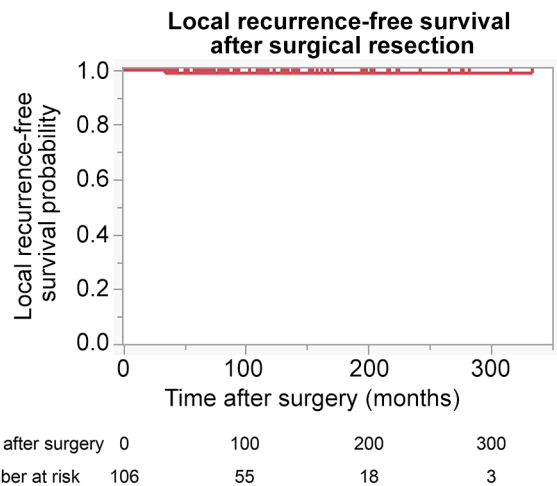


Figure 2. Local recurrence-free survival after surgical resection. Local recurrence-free survival after surgical resection of phyllodes tumors. The Kaplan-Meier curve shows local recurrence-free survival (LRFS) for the entire cohort (n=106). Only one local recurrence occurred at 33 months after surgery. The median follow-up period was 109 months. Numbers at risk are shown below the plot, and tick marks indicate censored observations.

In recent years, the AMOS (Atypia-Mitosis-Overgrowth-Surgical margin) criteria proposed by Tan *et al.* (8) have been reported to demonstrate superior predictive ability for recurrence compared to the conventional WHO classification. This observation suggests that pathological classification alone may be insufficient to predict the clinical behavior of phyllodes tumors and is consistent with the need for multifaceted evaluation incorporating clinical factors, as demonstrated in the present study. In recent years, several studies have focused on risk stratification of phyllodes tumors based on histological or procedural

factors. Mimoun *et al.* (9) demonstrated that histological tumor size ≥ 45 mm and dense stromal cellularity were independent risk factors for local recurrence of phyllodes tumors, whereas tumor grade and surgical margin width were not significantly associated with recurrence. In addition, Park *et al.* (10) reported recurrence rates and clinicopathological characteristics of phyllodes tumors diagnosed by ultrasound-guided vacuum-assisted breast biopsy, highlighting the challenges in preoperative diagnosis and risk stratification.

With respect to postoperative outcomes, only one case of local recurrence (0.94%) was observed in this cohort. Previous retrospective studies (11-13) have typically reported median follow-up periods of approximately 4-7 years, whereas reports evaluating recurrence risk based on follow-up exceeding 10 years remain limited. The extended follow-up period of 109 months in this study therefore provides reliable insight into the long-term clinical course of phyllodes tumors.

Local recurrence of phyllodes tumors is known to occur predominantly in the early postoperative period, with most recurrences reported within 2–3 years after surgery (8, 14). The single recurrent case in this study occurred 33 months after surgery, which is consistent with previously reported recurrence timing.

Despite a relatively narrow mean gross margin of 2.0 mm, the local recurrence rate in this cohort was extremely low. Although NCCN guidelines recommend a surgical margin of at least 1 cm, the optimal margin width remains controversial. Our findings suggest that when negative margins are achieved, extensive resection may not be uniformly required, and that the biological characteristics of the tumor may play a more important role in recurrence risk.

In the single recurrent case, the primary tumor was classified as benign, but histological upgrading to borderline malignancy was observed at recurrence. A tendency toward pathological progression with recurrence has been described in previous studies (14, 15), supporting the possibility of biological evolution in phyllodes tumors over time. These findings underscore the importance of

careful and prolonged follow-up even in patients initially diagnosed with benign phyllodes tumors.

Overall, this study supports that phyllodes tumors are associated with a low risk of recurrence and a favorable long-term prognosis based on real-world clinical data with extended follow-up. The long median follow-up period of 109 months represents a key strength of this study and provides valuable insight into the natural history of phyllodes tumors.

Study limitations. First, it is a single-institution retrospective analysis with a limited sample size. However, the single-institution design allowed for relatively consistent diagnostic criteria, surgical strategies, and follow-up protocols, contributing to data homogeneity.

Second, assessment of rapid tumor growth and gross margin measurements was based on medical records and surgical specimen photographs and therefore may include a degree of subjectivity. Nevertheless, all evaluations were performed using standardized criteria across cases, supporting the validity of relative comparisons. Third, detailed histological factors such as stromal atypia and overgrowth, as well as molecular biological markers, were not included in the analysis.

Conclusion

This study demonstrates that breast phyllodes tumors have an extremely low risk of recurrence and an overall favorable prognosis with long-term follow-up. Age and rapid tumor growth are useful clinical indicators for predicting non-Benign (borderline and malignant) phyllodes tumors and may play an important role in preoperative assessment. Furthermore, in cases with negative margins, excessively wide surgical excision may not be uniformly necessary.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Emi Tsukiyama designed the study, analyzed the data, and drafted the manuscript. Akira Matsui supervised the study and critically revised the manuscript. All Authors approved the final manuscript.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (ChatGPT, OpenAI) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning-based image enhancement tools.

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