

# Is wide excision really needed? Correlation between resection margin and recurrence in benign phyllodes tumors of the breast

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**Purpose:** Phyllodes tumors are similar to fibroadenomas in imaging and in pathological characteristics and are difficult to identify preoperatively. The purpose of this study was to analyze the recurrence rate after excision stratified by the surgical margin width and to propose and emphasize the “wait and watch” treatment strategy for benign phyllodes tumors.

**Methods:** We performed a retrospective cohort study of patients diagnosed with benign phyllodes tumors by surgical excision between January 2000 and December 2022 at our institution. The medical and histopathological records were reviewed.

**Results:** The results were obtained using the Cox proportional hazard regression and logistic regression. Resection margin status and recurrence were the independent variables. In each variable selection model, the resection margin was positive or less than 1 cm, and the recurrence rate was 3.7 and 1.04 times higher than the control group, but the difference was not statistically significant in 2 analyses.

**Conclusion:** The surgical resection margin status of benign phyllodes tumors did not significantly affect locoregional recurrence. Therefore, follow-up imaging at short intervals without additional surgery is a feasible clinical option when the surgical resection margin is positive or less than 1 cm.

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**Key Words:** Breast neoplasms, Phyllodes tumor, Recurrence, Reoperation, Resection margin

## INTRODUCTION

Phyllodes tumors are rare fibroepithelial neoplasms that occur in the stromal tissues of the breast. Although the clinical and pathological characteristics of phyllodes tumors are similar to those of fibroadenomas that originate from the breast stromal tissue, breast surgeons cannot consider important clinical features of phyllodes tumors to be identical to those of fibroadenomas when treating them.

Phyllodes tumors are classified into 3 categories—benign,

borderline, and malignant—according to their pathological characteristics, such as stromal cellularity, atypia, and overgrowth, the tumor border, and mitotic count. These pathological factors have already been reported to be associated with recurrence in previous studies [1].

The National Comprehensive Cancer Network (NCCN) guidelines and many studies recommend that phyllodes tumors, regardless of the grade, should be totally resected, and the resection margin width should be at least 1 cm wide to minimize the recurrence rate.

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However, identifying phyllodes tumors, especially benign phyllodes tumors, is difficult in preoperative studies using ultrasound or biopsy because phyllodes tumors are similar to fibroadenomas on imaging and in pathological characteristics. Therefore, surgeons may not be able to obtain the surgical margin recommended by the NCCN guidelines. If a patient is diagnosed with phyllodes tumors postoperatively, most surgeons will plan a wide excision to obtain a surgical margin that is more than 1 cm wide [2,3].

However, some previous studies and the recently updated NCCN guidelines suggest the "wait and watch" strategy for benign phyllodes tumors with a narrow resection margin because the recurrence rate of benign phyllodes tumors is lower than that of the other grades. Nevertheless, many surgeons face a dilemma regarding the need for reoperation in patients with benign phyllodes tumors with narrow surgical margins.

The purpose of this study was to analyze the recurrence rate after excision of phyllodes tumors stratified by the surgical margin width and to propose and emphasize the "wait and watch" treatment strategy for benign phyllodes tumors.

## METHODS

This study was conducted in strict accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Soonchunhyang University Cheonan Hospital (No. SCHCA 2023-02-040) prior to data collection. Written informed consent was obtained from all patients.

### Patients

In this study, we performed a retrospective cohort study of patients diagnosed with benign phyllodes tumors by surgical excision between January 2000 and December 2022 at our institution. Medical and histopathological records were reviewed by authors, and insufficient histopathological slides were reviewed by a single pathologist. According to the World Health Organization classification, benign phyllodes tumors were diagnosed by pathologists on the basis of histopathologic features such as degree of stromal hypercellularity, atypia, and overgrowth, mitotic counts, and the tumor border. Benign phyllodes tumors were defined as a breast mass diagnosed pathologically with the following benign features: mild stromal atypia, mildly increased stromal cellularity, absent stromal overgrowth, less than 5 of 10 high power field of mitotic count, well-defined tumor border, and absent malignant heterologous elements.

Because the recurrences of phyllodes tumor that we want to evaluate have to be related to previous surgery, only recurrences of ipsilateral breast were included. However, it was defined as recurrence even if the recurrence site occurred in any quadrants and locations of the ipsilateral breast, not the operation site.

In addition, the recurrence was defined as the recurrence of phyllodes tumor only, excluding other breast tumors such as fibroadenoma. The recurrences and reoperation were also reviewed for medical records.

The type of surgery was reviewed for the operation notes in the medical records. The resection margins were divided into 2 groups on the basis of data from the pathological reports: (1) more than 1 cm wide and (2) positive or less than 1 cm wide.

When the mass is excised by vacuum-assisted breast biopsy (VABB), the range of excision differs depending on the operator's decisions and the clinical and radiologic features of the mass. Therefore, if the mass was not found on ultrasound after VABB and the evaluation of the resection margin was not mentioned in the pathological report, the width of the resection margin was assumed to be less than 1 cm. Positive margin state was defined as a case in which a residual lesion was found on ultrasound after VABB or was reported as positive margin in a pathological report.

For patients who did not revisit the hospital for follow-up, individual contact was made to check the recurrence.

We excluded patients diagnosed with other malignant diseases or who received other nonsurgical treatment strategies, such as chemotherapy or radiotherapy. Patients whose clinicopathological information had not previously been evaluated and could not be reevaluated were excluded. In addition, Patients who could not be contacted for confirmation of recurrence were excluded.

### Statistics

All statistical analyses were performed using R software ver. 3.6.3 (R Foundation for Statistical Computing).

The chi-square and Fisher exact tests were used to compare categorical variables in a contingency analysis. Cox proportional regression and binomial logistic regression models were used to analyze the correlation between the resection margin status, histopathologic variables, and recurrence, and a P-value of <0.05 was considered statistically significant.

## RESULTS

### Clinical characteristics of patients

A total of 87 patients diagnosed with benign phyllodes tumors were reviewed in this study. The clinical characteristics of the patients were analyzed. The median follow-up duration was 31 months (mean  $\pm$  standard deviation [SD], 42.16  $\pm$  40.31).

Eighty-five patients (97.7%) underwent a wide excision or VABB (13 patients [15.0%]), but 2 underwent mastectomy because of the large tumor size and multiple masses. Thirty-seven patients (42.5%) underwent resection with an adequate resection margin width, as recommended by the previous

**Table 1.** Clinicopathological characteristics of 87 patients diagnosed with benign phyllodes tumors

Characteristic	All patients (n = 87)
No. of patients	87
Female sex	87 (100)
Age (yr)	41 (38.22 ± 11.15)
Size (cm)	2.4 (3.25 ± 2.69)
Follow-up period (mo)	31 (42.16 ± 40.31)
Time to recurrence (mo)	15 (19.14 ± 13.84)
Site	
Right	45 (51.7)
Left	41 (47.1)
Both	1 (1.2)
Surgery type	
Wide excision	72 (81.8)
Mastectomy	2 (2.3)
VABB	13 (15.0)
Margin status	
≥1 cm	37 (42.5)
<1 cm or positive	50 (57.5)
Recurrence	
No	80 (92.0)
Yes	7 (8.0)
Margin status, ≥1 cm	4 (4.6)
Margin status, <1 cm or positive	3 (3.5)
Stromal hypercellularity	
Mild	4 (4.6)
Moderate	81 (93.1)
Marked	2 (2.3)
Cellular atypism	
Little	82 (94.3)
Moderate or marked	5 (5.7)
Stromal overgrowth	
Absent	77 (88.5)
Present	10 (11.5)
Tumor border	
Pushing	71 (81.6)
Intermediate or infiltrate	16 (18.4)

VABB, vacuum-assisted breast biopsy.

NCCN guidelines. However, 50 patients (57.5%) underwent resection with a resection margin that was positive or less than 1 cm wide. There was a total of 8 patients (8.1%) with recurrence of benign phyllodes tumor, all of which recurred on the ipsilateral side. Of these patients, 4 (4.6%) had a resection margin more than 1 cm wide, and the other 3 (3.5%) had a resection margin that was positive or less than 1 cm wide. The median time to recurrence was 15 months (mean ± SD, 19.14 ± 13.84 months), and all patients diagnosed with recurrence underwent reoperation (Table 1).

### Age, tumor size, operation type as a predictive factor for recurrence

We evaluated the relationship between patient age, tumor

size, type of surgery, and recurrence rate of phyllodes tumor through Cox proportional hazard regression. In univariate, multivariate, and variable selection models, patient age and tumor size did not have a statistically significant correlation with the recurrence rate of phyllodes tumor.

In addition, to compare the recurrence rate according to the operation type, we evaluated the recurrence rate of phyllodes tumor in patients who underwent mastectomy or VABB compared to wide excision.

In multivariate analysis, the recurrence rate was about 0.94 times higher in the mastectomy group. The recurrence rate was expected to be low in the mastectomy group in which the entire ipsilateral breast was resected, and a similar result was confirmed, but there was no statistical significance (odds ratio [OR], 0.9414; 95% confidence interval [CI], -0.734 to 2.957; P = 0.238).

We assumed that patients who received VABB for which resection margins could not be evaluated would have a higher recurrence rate than excisions with wide resection margins. However, in all analyses, the recurrence rate was not high compared to the wide excision, but there was no statistical significance (univariate analysis and variable selection model: OR, 0.915; 95% CI, -0.741 to 2.845; P = 0.250/multivariate analysis: OR, 0.238; 95% CI, -0.230 to 0.703; P = 0.321) (Table 2).

### Resection margin as a predictive factor for recurrence

The association between the resection margin status and recurrence was analyzed using the Fisher exact test and the chi-square test as a recurrence-predictive factor.

In the chi-square test, the P-value was 0.638. Therefore, the resection margin state and recurrence were considered as independent variables. In the Fisher exact test, the OR was 1.8858, and the P-value was 0.452. This result can be interpreted as recurrence being 1.885 times higher in the group having a resection margin that is positive or less than 1 cm margin width group; however, the difference was not statistically significant.

### Univariate and multivariate survival analyses (Cox proportional hazard regression model)

Univariate analysis in the Cox proportional hazard regression showed that the recurrence rate of phyllodes tumor was 1.470 times higher in the positive or less than 1 cm margin width group, but the difference was not statistically significant (OR, 1.470; 95% CI, 0.245–8.831; P = 0.674). The intermediate tumor border group had about 3 times higher recurrence rate, but the difference was not statistically significant (OR, 3.018; 95% CI, 0.503–18.100; P = 0.227).

Similarly, in multivariate analysis, the recurrence rate was about 8.9 times higher in the positive or less than 1 cm margin width group, and the intermediate tumor border group also had

**Table 2.** Analysis of phyllodes tumor recurrence according to patient age, tumor size, and operation type

Variable	Univariate analysis		Multivariate analysis		Variable selection model	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	0.043 (-0.045 to 0.125)	0.353	0.051 (-0.073 to 0.125)	0.604	NA	NA
Tumor size	0.212 (-0.411 to 0.419)	0.986	155,673.813 (-30,532.921 to 30,491.786)	0.999	NA	NA
Operation type, mastectomy	16,158.212 (-31,689.169 to 31,649.857)	0.999	0.941 (-0.734 to 2.957)	0.238	16,158.212 (-31,689.169 to 31,649.857)	0.999
Operation type, VABB	0.915 (-0.741 to 2.845)	0.250	0.238 (-0.230 to 0.703)	0.321	0.915 (-0.741 to 2.845)	0.250

OR, odds ratio; CI, confidence interval; NA, not available; VABB, vacuum-assisted breast biopsy.

a recurrence rate about 6.8 times higher. However, both results were not statistically significant (OR, 8.920; 95% CI, 0.444–179.054;  $P = 0.157$ /OR, 6.842; 95% CI, 0.308–152.209;  $P = 0.224$ ).

In the variable selection model, the recurrence rate was about 3.7 times higher in the positive or less than 1 cm margin width group. However, the difference was not statistically significant (OR, 3.707; 95% CI, 0.385–35.661;  $P = 0.257$ ).

As a result, in all analysis models, we could not confirm the statistical significance between margin status, histopathological variables, and tumor recurrence (Table 3).

### Univariate and multivariate survival analyses (logistic regression model)

Because we could not find a statistically associated variable that affects the recurrence of benign phyllodes tumor through Cox proportional hazard regression, a binomial logistic regression model was used to determine whether the surgical margin status affected recurrence.

Contrary to the previous result, univariate analysis revealed that the risk of recurrence in the patients with a positive margin or less than 1 cm wide was lower than that in the control group, but the difference was not statistically significant (OR, 0.527; 95% CI, 0.111–2.510;  $P = 0.421$ ).

Regarding the histopathological variables, phyllodes tumors with intermediate tumor borders had a lower recurrence rate than those with pushing or infiltrative tumor borders (OR, 7.556; 95% CI, 1.498–38.097;  $P = 0.014$ ). The other histopathological variables were not significantly associated with recurrence.

In the multivariate analysis, compared with the univariate analysis, the association between the resection margin status and recurrence showed the opposite result. However, this difference was not statistically significant (OR, 1.969; 95% CI, 0.241–16.083;  $P = 0.527$ ). The tumor border also had a similar OR in the multivariate analysis to that in the univariate analysis, but the difference was not statistically significant (OR, 7.861; 95% CI, 0.951–64.983;  $P = 0.056$ ). Similar to the univariate analysis, in the multivariate analysis, the other histopathological variables were not statistically significant.

In the variable selection method, in which the margin state was set as a fixed variable, a resection margin that was positive or less than 1 cm wide was associated with a lower recurrence rate. However, the difference was not statistically significant (OR, 1.047; 95% CI, 0.177–6.195;  $P = 0.959$ ). In contrast, phyllodes tumors with an intermediate tumor border showed a 7.697 times higher recurrence rate (OR, 7.697; 95% CI, 1.312–45.165;  $P = 0.024$ ) (Table 4).

## DISCUSSION

Previous studies and NCCN guidelines recommend that the resection margin width should be at least 1 cm, regardless

**Table 3.** Coefficient estimates from univariate, multivariate, and variable selection models in Cox proportional hazard regression

Variable	Univariate analysis		Multivariate analysis		Variable selection model	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Margin <1 cm or positive	1.470 (0.245–8.831)	0.674	8.920 (0.445–179.054)	0.157	3.707 (0.385–35.661)	0.257
Stromal hypercellularity, modest	63,870,471 (NA)	0.999	270,323,783 (NA)	>0.999	121,002,001 (NA)	0.999
Stromal hypercellularity, marked	NA	NA	NA	NA	-	-
Cellular atypism, moderate or marked	3,931,435,797,721 (NA)	>0.999	NA	NA	-	-
Stromal overgrowth	$1.202 \times 10^{-8}$ (NA)	0.999	$7.319 \times 10^{-10}$ (NA)	0.999	-	-
Tumor border, intermediate	3.018 (0.503–18.100)	0.227	6.842 (0.308–152.209)	0.224	-	-

OR, odds ratio; CI, confidence interval; NA, not available.

**Table 4.** Coefficient estimates from univariate, multivariate, and variable selection models in logistic regression

Variable	Univariate analysis		Multivariate analysis		Variable selection model	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Margin <1 cm or positive	0.527 (0.111–2.510)	0.421	1.969 (0.241–16.0834)	0.527	1.047 (0.177–6.195)	0.959
Stromal hypercellularity, modest	3,403,584 (NA)	0.994	31,010,517 (NA)	0.998	-	-
Stromal hypercellularity, marked	42,544,809 (NA)	0.993	$7.327 \times 10^{23}$ (NA)	0.997	-	-
Cellular atypism, moderate or marked	3.167 (0.304–32.994)	0.335	$8.123 \times 10^{-9}$ (NA)	0.998	-	-
Stromal overgrowth	$8.647 \times 10^{-8}$ (NA)	0.994	$1.530 \times 10^{-15}$ (NA)	0.996	-	-
Tumor border, intermediate	7.556 (1.498–38.097)	0.014	7.861 (0.951–64.9829)	0.056	7.697 (1.312–45.165)	0.024

OR, odds ratio; CI, confidence interval; NA, not available.

of the phyllodes tumor grade. In particular, in the case of borderline and malignant phyllodes tumors with aggressive histopathological features, such as high mitotic counts, stromal overgrowth and hypercellularity, and infiltrative tumor borders, many studies have suggested that following the recommendations results in a lower recurrence rate. Therefore, the recommendation regarding the width of the resection margins is more appropriate for the treatment of borderline and malignant phyllodes tumors with high recurrence rates than for benign phyllodes tumors [4,5].

However, several recent studies have suggested that the widths of the resection margins of benign phyllodes tumors are not related to local recurrence. The common conclusion of these studies is that benign phyllodes tumors, unlike other types, have a lower recurrence rate because the histopathological factors known to affect the recurrence rate are less aggressive [6-8]. As a result of these studies, the NCCN guidelines were revised in 2022, and the recommendation was changed: benign phyllodes tumors incidentally diagnosed by excisional biopsy should be observed after 3 months [9].

Jang et al. [1], in a 2012 study at Samsung Medical Center, reported on the correlation between the resection margins and local recurrence of phyllodes tumors, indicating that positivity

of the resection margins affects the local recurrence of any grade of phyllodes tumors; however, there was no correlation between the resection margin width and local recurrence.

The purpose of this study was to confirm the conformance of the results of previous clinical studies in the Korean population at our institution. For this reason, we reviewed the surgical margin state and recurrence history of benign phyllodes tumors to identify the risk factors that may predict recurrence and optimize the postoperative management and follow-up for the patients.

In this study, we suggested that the surgical resection margins were not associated with the recurrence of benign phyllodes tumors, although the difference was not statistically significant. The main reason for these results was the differences from a previous study by Jang et al. [1] that assessed the resection margin status of the control group. In previous studies, patients with a margin that was positive or less than 1 cm wide were classified into different control groups. However, in our study, all patients with margins that were either positive or less than 1 cm wide were grouped together, and we had several reasons for this approach.

First, it is difficult to make a differential diagnosis from fibroadenoma based on the preoperative stage because the

clinical features of benign phyllodes tumors, such as a low recurrence rate, histopathological similarity, and imaging findings, are similar to those of fibroadenomas [10,11].

Second, it is difficult to specify the resection margin of a mass resected using VABB. Ultrasound-guided VABB is a common method used for the removal of and taking biopsies from breast masses. In some cases, phyllodes tumors were diagnosed after VABB for preoperatively presumed fibroadenomas. However, the sample obtained using VABB has the disadvantage of being inappropriate for evaluating the resection margins.

Inexperienced breast surgeons may not perform a wide excision with a resection margin of more than 1 cm wide during the first operation or VABB. However, there is no clear guideline for benign phyllodes tumors with respect to outpatient follow-up, including radiological studies with short intervals, or performing reoperation for wide margin when the pathological information of the resection margin is insufficient or the resection margin is positive.

Compared with the study reported by Barth et al. [12], the recurrence rate of patients with a margin positive or less than 1 cm in our hospital was lower than the recurrence rate of patients with benign phyllodes tumors who underwent local excision without wide excision in other studies. In addition, in a study reported by Spitaleri et al. [13], including more than 5,000 patients, the average recurrence rate of benign phyllodes tumor was reported to be about 15%. However, in our study, 7 out of 87 total patients, and only less than 1% (3 of 50) of patients with a margin of less than 1 cm or positive, had recurred.

The median time to recurrence was 15 months (mean  $\pm$  SD, 19.14  $\pm$  13.84 months). The shortest time to recurrence was 6 months and the longest time was 44 months. We suggest that the appropriate follow-up period to check the recurrence of benign phyllodes tumor after surgery is a 6 to 12-month interval in consultation with the patient.

Therefore, we suggest close observation without additional surgery as a viable option. Because statistical significance has not been obtained, these results cannot be directly implemented in clinical practice. However, if similar results are obtained in studies including a large number of patients, the obtained results can be applied in the clinical field to reduce the socioeconomic costs and unnecessary need for reoperations.

Our study had several limitations. First, the retrospective nature of our study introduced population bias. Second, the small number of studied patients and events decreased the reliability of the statistical analysis and study power. In particular, the associations were not reported in some histopathological factors that have already been reported to affect recurrence, such as mitosis, stromal overgrowth, stromal cellularity, and infiltrative tumor border, because the number of total patients and patients who were recured was small [14,15]. Third, there was a lack of uniform commentary on the

histopathological features in the pathology reports. Not all the pathological diagnoses were made by a single pathologist, the diagnostic criteria may have been updated, or newly developed diagnostic tools may have been introduced during the study period. Therefore, future studies should include a larger number of patients from multiple centers.

In this study, we suggest that the resection margin status of benign phyllodes tumors does not significantly affect recurrence. Follow-up imaging at short intervals without additional surgery is also a feasible clinical option when the surgical resection margin is positive or less than 1 cm wide. By carrying out further research and including more patients, the treatment of benign phyllodes tumors should be established to reduce the unnecessary need for reoperations.

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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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