



Margin Width and Local Recurrence in Patients with Phyllodes Tumors of the Breast

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ABSTRACT

Background. Optimal surgical margin width for patients with phyllodes tumors (PTs) of the breast remains debated. The aim of this study was to assess the influence of margin width on long-term local recurrence risk.

Patients and Methods. This was a single-institution retrospective review of patients with confirmed PT treated from 2008–2015. Margins were defined as positive (ink on tumor), narrow (no tumor at inked margin but < 10mm), or widely free (\geq 10mm). LR rates were estimated by the Kaplan–Meier method.

Results. Among 117 female patients, histology included 55 (47%) benign, 29 (25%) borderline, and 33 (28%) malignant PT. Final margins were positive in 16 (14%), narrow in 32 (27%), widely free in 64 (55%), and unknown in 5 (4%) patients. Compared with margins > 10 mm, patients with positive and narrow margins had a higher LR risk [HR 10.57 (95% CI 2.48–45.02) and HR 5.66 (95% CI 1.19–26.99), respectively]. Among benign PTs, the 10-year LR-free rates were 100%, 94%, and 66% for widely negative, narrow, and positive margins, respectively ($p = 0.056$). For borderline/malignant PT, the 10-year LR-free rates were 93% and 57% for widely negative and narrow margins, respectively ($p =$

0.02), with no difference in LR between narrow and positive margin groups ($p = 1.00$).

Conclusions. For benign PTs, a margin of no ink on tumor appears sufficient to optimize local control. In patients with borderline or malignant PTs, achieving a wide surgical margin may remain important as narrower margins were associated with LR rates comparable to those with positive margins.

Keywords Phyllodes tumor · Breast sarcoma · Surgical margin · Local recurrence · Long-term outcomes

Phyllodes tumors (PTs) are rare fibroepithelial neoplasms of the breast accounting for less than 1% of breast tumors with a wide scope of biologic behaviors, ranging from benign to malignant.¹ Usually presenting as a palpable breast mass, the diagnosis includes clinical, radiological, and histopathological evaluation. For pathologic diagnosis, the World Health Organization defines PTs as benign, borderline, or malignant on the basis of stromal cellularity, stromal atypia, mitotic activity, stromal overgrowth, tumor margin appearance, and presence of heterologous elements.^{2,3} Currently, the most accepted treatment is surgical excision without lymph node staging. Systemic chemotherapy is used for select malignant PTs and for patients with metastatic PTs.⁴ Adjuvant radiation therapy (RT) is typically reserved for patients with malignant tumors, but can also be used in borderline PT, on the basis of principles similar to those of other soft tissue sarcomas.⁴

One of the most debated aspects of PT surgical management is margin width. While a margin width of 10 mm has been the standard based on early reports of higher rates of local recurrence (LR) with narrower margins,⁵ more recent studies have suggested that narrower margins (< 10 mm) may be sufficient.⁶⁻⁹ Currently, the literature is discordant, given a substantial number of studies showing a prognostic impact of margin status on LR risk.¹⁰⁻¹² Notably, comparison with the recommended 10 mm margin width is not included in many studies. Inadequate length of follow-up is an important factor to consider, as most PT studies have follow-up of less than 5 years.^{6,10,13-15} Additionally, given the prognostic relevance of histologic classification in PT, accuracy of pathologic classification is an important consideration. The literature suggests low concordance between pathologists when assigning PT grade.¹⁶ Given the rarity of these tumors and the resultant challenges in classification, the use of experienced and specialized pathologists to review and confirm diagnosis is critical.

The aim of this study was to assess the influence of margin width on long-term local recurrence risk for PT. To avoid the potential confounding effect of histologic misclassification on the association of margin width and local recurrence, we reviewed our institutional experience with PTs that had all been reviewed by an expert group of breast pathologists.

PATIENTS AND METHODS

Selection of Patient Cohort

This was a retrospective review of patients with PTs treated at MD Anderson Cancer Center (MDACC) from 2008 to 2015. Cases with a diagnosis of PT were retrieved from the surgical pathology file. Patients who met the following criteria were included: (i) age >18 years, (ii) pathology reviewed at MD Anderson with confirmation of phyllodes diagnosis, (iii) the diagnosis was not deemed an incidental finding on excision for another lesion, and (iv) at least 1 year of follow-up at our institution following diagnosis. Pathologic review was performed by breast pathologists with consultation to soft tissue pathology at the discretion of the interpreting pathologist. Patients were excluded if they had a concomitant breast cancer diagnosis, not including ductal carcinoma in situ (DCIS). Patients with a previous breast cancer diagnosis were included if they were at least 5 years from prior diagnosis.

Patient demographics and management decisions including presurgical clinical information and imaging, biopsies, type of surgery, pathologic information such as tumor size and margins, adjuvant therapy (RT and/or cytotoxic chemotherapy), follow-up period, recurrence, and fibroadenoma history were obtained from the electronic medical record. Type of surgery was identified as breast-conserving surgery

or mastectomy. Margin width was captured as a continuous variable but categorized for purposes of analysis as positive (ink on tumor), narrow (no tumor at inked margin but less than < 10 mm), widely free (\geq 10 mm), or margin width unknown. For patients who underwent re-excision without any residual findings, margin width was classified as widely free. Follow-up was captured from the medical record if seen by provider within the MD Anderson system or if patient completed a cancer status survey. Time to recurrence was calculated from date of surgery.

Statistical Analysis

Descriptive statistics [frequency distribution, mean (\pm standard deviation), and median (range)] were used to summarize patient characteristics.¹⁷ The distributions of time to local recurrence (TTLR), time to distant recurrence (TTDR), and overall survival (OS) were estimated by the Kaplan–Meier method¹⁸ along with the 95% confidence interval using the method by Kalbfleisch and Prentice.¹⁹ TTLR was defined as the time from surgery to the time of local recurrence; TTDR was defined as the time from surgery to the time of regional or distant recurrence; OS was defined as the time from diagnosis or surgery to death. For events that had not occurred by the time of data analysis, times were censored at the last contact at which the patient was known to be local/regional/distant recurrence free for TTLR/TTDR or the last time the patient was known to be alive for OS. Log-rank test²⁰ was performed to test the difference in survival between groups. Regression analyses of survival data based on the Cox proportional hazards model²¹ were conducted on TTLR, TTDR, and OS in multivariable setting using backward selection approach on the covariates, with a p -value < 0.05 in univariate setting. As a sensitivity analysis, competing risk analysis of local recurrence was conducted with regional/distant recurrence and/or death as competing risk factors.

RESULTS

Cohort Demographics

Our review of the pathology database identified 117 patients that met the inclusion criteria. There were five patients with benign PT for whom only core needle biopsy pathologic slides were reviewed internally, which was felt to be conclusive for benign PT. For the remainder of the patients with benign PT and for all patients with borderline or malignant tumors, the surgical specimen was internally reviewed at MD Anderson. All patients were women and the median age at diagnosis was 44 years (range 19, 82 years), Table 1. The median tumor size was 3.0 cm (range 0.8, 9.2 cm). Breast-conserving therapy was performed in 97 patients

TABLE 1 Baseline patient demographics

Characteristic	n = 117
Age at Diagnosis (years), average (range)	44 (19, 82)
Diagnosis by needle biopsy (85 patients)	
Fibroadenoma	7 (6%)
Benign fibroepithelial lesion	28 (24%)
Phyllodes tumor (unspecified)	22 (19%)
Benign phyllodes tumor	8 (7%)
Borderline phyllodes tumor	2 (2%)
Malignant phyllodes tumor	7 (6%)
Other	11 (9%)
Diagnosis by excision (32 patients)	
Tumor size by imaging	
Not reported	29 (25%)
< 5 cm	69 (59%)
≥ 5 cm	19 (16%)
Type of surgery	
Mastectomy	20 (17%)
BCT	97 (83%)
Axillary surgery	
Yes	8 (7%)
No	109 (93%)
Surgical pathology diagnosis	
Benign phyllodes tumor	55 (47%)
Borderline phyllodes tumor	29 (25%)
Malignant phyllodes tumor	33 (28%)
Margins	
Negative	101 (86%)
Positive	16 (14%)
Margin category	
Widely free (≥ 10 mm)	64 (55%)
Narrow (> tumor at inked margin but < 10 mm)	32 (27%)
Positive (ink on tumor)	16 (14%)
Margin width unknown	5 (4%)
Adjuvant chemotherapy	
Yes	10 (9%)
No	107 (91%)
Adjuvant radiation therapy	
Yes	18 (15%)
No	99 (85%)
Local recurrence*	
Yes	13 (11%)
No	104 (89%)
Distant recurrence*	
Yes	10 (9%)
No	108 (91%)

*Three patients had recurrence at multiple sites (i.e., both local and distant recurrences).

(83%). Final surgical pathology was distributed as follows: 55 (47%) benign PT, 29 (25%) borderline PT, and 33 (28%) malignant PT. Overall, final margins were noted to be positive in 16 (14%) patients, narrow (> tumor on ink but < 10 mm) in 32 (27%), and widely free (≥ 10 mm) in 64 (55%). Three patients underwent re-excision for close or positive margins: one patient with benign PT with a close margin (< 1 mm) underwent re-excision to find 2 mm of residual benign phyllodes tumor and widely negative final margins, one patient with benign PT with a positive margin for whom the re-excision specimen was not able to be ascertained, and one patient with borderline PT with a positive margin who underwent re-excision and had no residual disease on final margin assessment.

Most patients did not receive adjuvant treatment, with 10 (9%) receiving adjuvant chemotherapy and 18 (15%) receiving adjuvant RT. All patients who received chemotherapy had malignant PT. Of the 18 patients who received RT, 17 (94%) had malignant PT, with 1 patient having a borderline PT. In total, 15 (83%) of the patients who received RT had a negative margin, with 2 having narrow margins and 1 with unknown margin width. Median follow-up time was 85 months for all patients.

Local Recurrence Events

Overall, 5- and 10-year LR-free rates for our cohort were 87% (95% CI 78–93%) and 86% (95% CI 76–91%), respectively. Significant differences were observed on the basis of histology with lower rates of LR for benign PT ($n = 3$) as compared with borderline/malignant tumors ($n = 10$) with 10-year local recurrence-free rates of 92% (95% CI 77–97%) versus 80% (95% CI 65–89%), respectively ($p = 0.036$, Fig. 1A). LR rates were also significantly lower in patients with margin width equal to or greater than 10 mm as compared with narrow or positive margins, with 10-year LR-free rates of 95% (95% CI 85–98%), 84% (95% CI 62–94%), and 58% (95% CI 25–81%) for widely free, narrow and positive margins, respectively ($p = 0.013$, Fig. 1B). Clinicopathologic details for patients who experienced local recurrence are listed in Supplementary Table S1.

In univariate analysis, margin status and histology impacted local recurrence, while age, receipt of RT or chemotherapy, tumor size, and type of surgery (BCT versus mastectomy) did not. In multivariable analysis, margin status and histology remained independently associated with risk of LR (Table 2). Patients with borderline and malignant histology were nearly six times more likely to experience local recurrence [HR 5.799 (95% CI 1.482–22.696), $p = 0.0012$] compared with benign histology. As compared with patients with widely free margins (> 10 mm), patients with a positive margin had more than ten times the likelihood of LR [HR 10.571 (95% CI 2.482–45.022), $p = 0.0014$] and those with

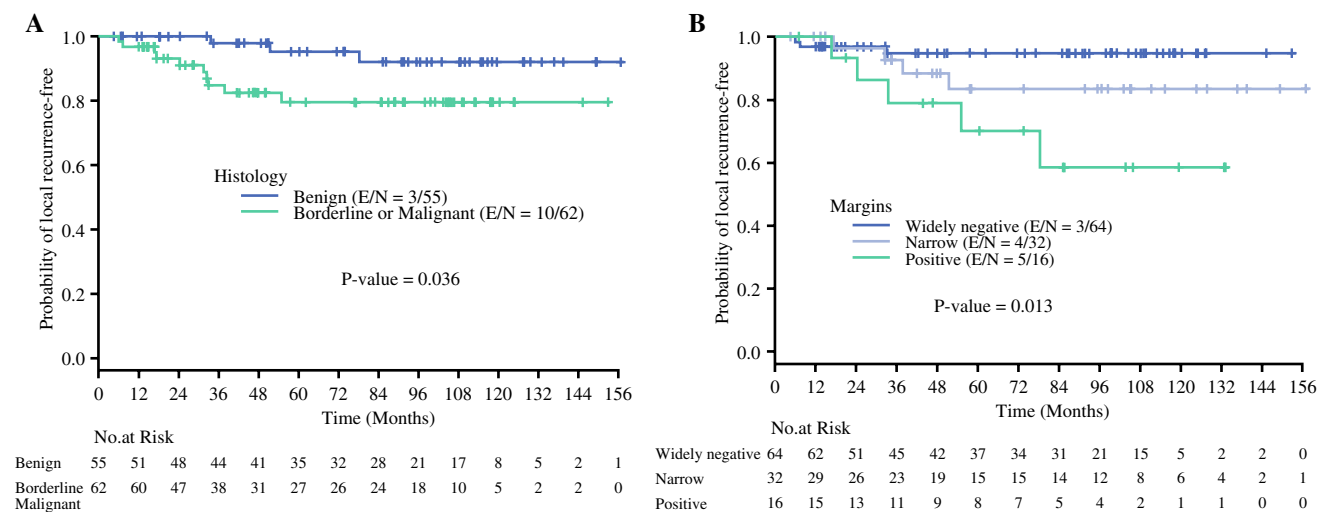


FIG. 1 A Kaplan–Meier curve of time-to-local recurrence by histologic subtype; B Kaplan–Meier curve of time-to-local recurrence by surgical margin width

a narrow (< 10 mm) had almost a sixfold greater risk of LR [HR 5.664 (95% CI 1.189–26.986), $p = 0.0295$]. The findings were similar in the competing risk analyses.

Association of Margins and Local Recurrence by Histologic Subtype

We next evaluated the impact of margin width on LR within histologic classifications of PT (Fig. 2A, B). For these analyses, patients with negative margins but without known width of resection margin were excluded ($n = 5$). Among the 51 patients with benign PTs, LR was noted in 2 (20%) of 10 patients with positive margins and 1 (4%) of 23 patients with narrow (< 10 mm) resection margins (Table 3). The patient with a narrow margin had a margin width of < 1 mm. There were no local recurrences reported in the 18 (35%) of 51 patients with widely negative margins of 10 mm. This corresponds to 5-year LR-free rates of 88% (95% CI 39–98%) for patients with positive margins, 94% (95% CI 63–99%) for patients with narrow margins and 100% for patients with widely negative margins (Fig. 2A, $p = 0.056$). In patients with borderline PT ($n = 29$), LR occurred in 1 (25%) of 4, 3 (50%) of 6, and 0 (0%) of 19 patients with positive, narrow, and widely free resection margins, respectively. The patients with narrow margins had widths of 1, 2, and 4 mm. In the malignant PT cohort ($n = 32$), LR were noted in 2 (100%) of 2 patients with positive margins, 0 (0%) of 3 patients with narrow margins, and 3 (11%) of 27 patients with widely free margins (Table 4).

In a combined analysis of borderline and malignant phyllodes tumors, the 5-year LR-free rate was 44% (95% CI 7–78%) for those with positive margins, 57% (95% CI 17–84%) for those with narrow margins, and 93% (95% CI

78–98%) for those with widely negative margins (Fig. 2B, $p = 0.008$). Tables 3 and 4 present a summary of TTLR by surgical margin status for the two histologic subgroups. In a separate analysis of borderline and malignant phyllodes tumors independently, the differences in time-to-local recurrence between margin subgroups were suggestive of benefit to wider excision margins, although the small sample size and variable follow-up time in the subsets of interest preclude definitive conclusions. Similarly, we did not assess risk of LR within only malignant PT patients who did or did not receive RT, and the difference was not statistically significant. Of the 11 patients who developed recurrence and for whom we had available pathology related to the recurrence, 1 patient experienced upgrade in histologic subtype (from borderline to malignant PT).

Distant Recurrence and Overall Survival

The overall distant recurrence rates were low, with 92% distant recurrence-free survival at 5 years. Distant recurrence rates were significantly impacted by histologic subtype, with 5-year distant recurrence-free survival rates of 100%, 96% (95% CI 73–99%), and 72% (95% CI 52–85%) for benign, borderline, and malignant PT, respectively ($p < 0.01$). Margin status did not impact distant recurrence, with 5-year distant recurrence-free survival rates of 100%, 100%, and 84% (95% CI 72–92%) for positive, narrow, and widely negative margins, respectively ($p = 0.078$).

The 5- and 10-year OS rates from the date of surgery for all patients in the study were 93% (95% CI 86–97%) and 90% (95% CI 81–95%), respectively. A total of ten patients died, including one patient with benign PT, one with borderline PT, and eight with malignant PT. The one patient with

TABLE 2 Associations between clinicopathologic factors, treatment, and local recurrence in univariate and multivariate Cox proportional hazard models

Variable		Univariate			Multivariate		
		Hazard ratio (95% CI)	<i>p</i> -Value for comparison with reference	<i>p</i> -Value for overall effect	Hazard ratio (95% CI)	<i>p</i> -Value for comparison with reference	<i>p</i> -Value for overall effect
Age at surgery	> 50 versus ≤ 50	0.503 (0.11, 2.268)	0.3710	0.3710			
Histology	Malignant versus benign	4.354 (1.087, 17.441)	0.0378	0.1144			
	Borderline versus Benign	2.904 (0.648, 13.006)	0.1634				
	Borderline/malignant versus benign	3.630 (0.997, 13.215)	0.0505	0.0505	5.799 (1.482, 22.696)	0.0116	0.0116
Margin category	Positive (tumor on ink) versus widely free (≥ 10 mm)	6.796 (1.623, 28.458)	0.0087	0.0304	10.571 (2.482, 45.002)	0.0014	0.0059
	Narrow (> tumor on ink but < 10 mm) versus Widely free (≥ 10 mm)	2.708 (0.606, 12.105)	0.1922		5.664 (1.189, 26.986)	0.0295	
	Positive (tumor on ink) versus narrow (> tumor on ink but < 10 mm)	2.509 (0.674, 9.349)	0.1704		1.867 (0.492, 7.087)	0.3592	
Margins	Positive versus negative	3.991 (1.305, 12.207)	0.0152	0.0152			
Tumor size by imaging	≥ 5 cm versus < 5 cm	0.824 (0.096, 7.067)	0.8598	0.8598			
Adjuvant radiation	Yes versus no	0.576 (0.075, 4.433)	0.5960	0.5960			
Adjuvant chemotherapy	Yes versus no	0.362 (0.019, 6.789)	0.4966	0.4966			
Axillary surgery	Mastectomy versus BCT	0.963 (0.213, 4.345)	0.9605	0.9605			

benign PT died of other causes, the cause of death for the one patient with borderline PT was unknown, and seven of the eight patients with malignant PT died from their disease. The 5-year OS rate was 100% for patients with benign PT, 96% (95% CI 74–99%) for patients with borderline PT, and 79% (95% CI 58–90%) for patients with malignant PT ($p < 0.01$; Fig. 3). Margin status did not impact OS.

DISCUSSION

Phyllodes tumors of the breast present a clinical challenge given their rare occurrence. Our study aimed to analyze surgical margins and related outcomes for a cohort of 117 pathologically confirmed PTs of the breast with long-term follow-up. Both histologic subtype and margin status were independently associated with increased risk of local

recurrence. On the basis of our analyses, margin width did impact local control for PT of the breast. For benign PT, a negative margin is advised to reduce local recurrence, although the width of the margin appears to be less relevant. However, for borderline and malignant PT, a 10 mm margin width has been historically recommended and appears to remain important on the basis of our findings, as narrower margins were associated with local recurrence rates comparable to those with positive margins.

National Comprehensive Cancer Network (NCCN) guidelines for PT of the breast state that for a diagnosis of benign phyllodes tumor by an excisional biopsy, clinical follow-up for 3 years is appropriate.⁴ These guidelines do not require a negative margin. In our series, patients with tumor at the inked margin had higher rates of local recurrence, but this was not statistically significant. Notably, the overall

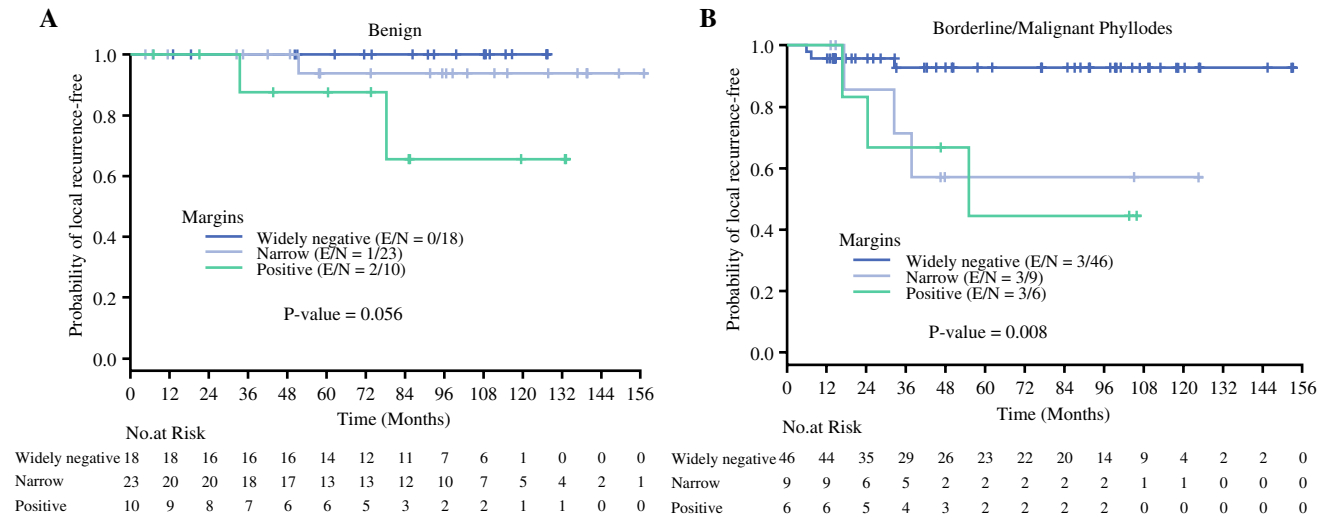


FIG. 2 A Kaplan–Meier curve of time-to-local recurrence by surgical margin width for patients with benign phyllodes tumors; B Kaplan–Meier curve of time-to-local recurrence by surgical margin width for patients with borderline or malignant phyllodes tumors

TABLE 3 Summary of time-to-local recurrence by surgical margin status in patients with benign phyllodes tumors

Margin category	Median FU (months)	Event/total	Median time-to-local recurrence (months)	3-year Local recurrence-free rate	5-year local recurrence-free rate	10-year local recurrence-free rate
Widely free (≥ 10 mm)	91.1 (62.5, 108.4)	0/18	NR	1	1	1
Negative ($>$ tumor on ink but < 10 mm)	95.4 (48.8, 111.3)	1/23	NR	1	0.94 (0.63, 0.99)	0.94 (0.63, 0.99)
Positive (tumor on ink)	73.5 (7.2, 119.5)	2/10	NR (33.58, NR)	0.88 (0.39, 0.98)	0.88 (0.39, 0.98)	0.66 (0.16, 0.91)

NR not reached

TABLE 4 Summary of time-to-local recurrence by surgical margin status in patients with borderline or malignant phyllodes tumors

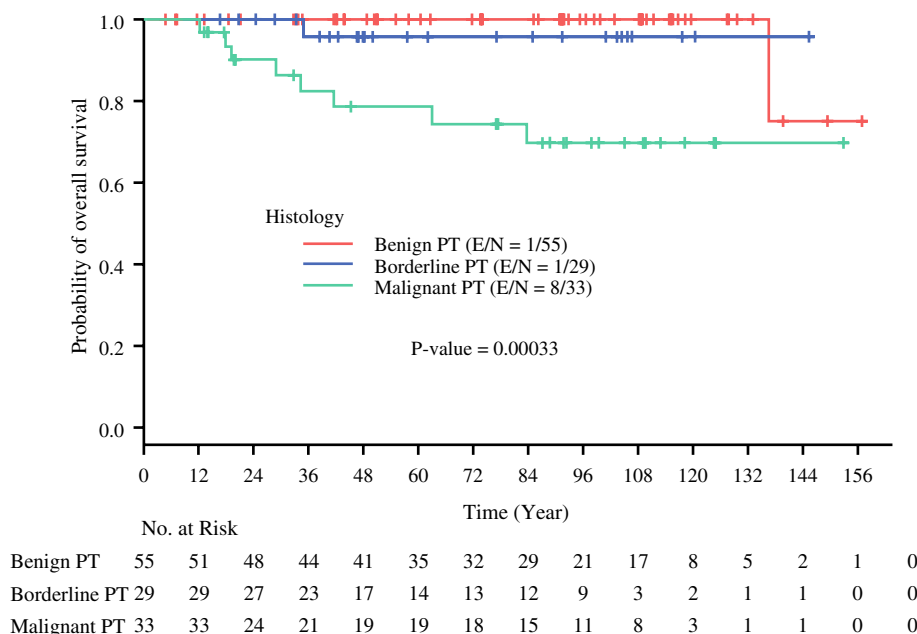
Margin category	Median FU (months)	Event/total	Median time-to-local recurrence (months)	3-year local recurrence-free rate	5-year local recurrence-free rate	10-year local recurrence-free rate
Widely free (≥ 10 mm)	77 (41.6, 91.5)	3/46	NR	0.93 (0.78, 0.98)	0.93 (0.78, 0.98)	0.93 (0.78, 0.98)
Negative ($>$ tumor on ink but < 10 mm)	47.7 (13.3, 124.6)	3/9	NR (17.31, NR)	0.71 (0.26, 0.92)	0.57 (0.17, 0.84)	0.57 (0.17, 0.84)
Positive (tumor on ink)	103.6 (46.7, 105.9)	3/6	55 (16.79, NR)	0.67 (0.19, 0.9)	0.44 (0.07, 0.78)	N/A

NR not reached

local recurrence rate for patients with benign PT was low (5.9%). The large difference in 10-year local recurrence rates between positive and negative margins (66% versus $> 90\%$) may reflect a true increase in risk of recurrence for patients

with tumor at the inked margin, but larger patient numbers would be required to determine this. In the largest available series of patients with benign PT by van Olmen et al. ($n = 1908$), the authors found a higher local recurrence rate in

FIG. 3 Kaplan–Meier curve of overall survival from the date of surgery by histologic subtype; solid line is the point estimate and dashed lines are lower and upper 95% confidence intervals



patients with positive compared with negative margins (8.9 versus 4.0%).²² Moutte et al. also reported a local recurrence rate of 33% following margin positive excision, with no local recurrences noted among any of the patients with negative margins.²³ Conversely, in the multi-institutional cohort study by Rosenberger et al., there was no evidence to suggest a difference in local recurrence rates between a positive margin, a final negative margin < 2 mm, and > 2 mm margin.⁶ Similarly, Bohrani-Khomani et al. reported no difference in local control among patients with benign PT in the Danish Pathology Register with margins < 1 mm, 1–5 mm, or greater than 5 mm.⁸

The reasons for discordance between the studies is not entirely clear, however, it could be related to duration of follow-up or variation in reporting of histopathologic details. Given the well-recognized challenge of histologic classification of fibroepithelial tumors, we limited our cohort to those whose pathology had been internally reviewed at our institution, thus reducing the risk of misclassification of cases aggregated from a wide range of practice settings. Additional contributory factors that may explain the differences between our data and the case series reported by Bohrani-Khomani is the aggregation of positive and close (< 1 mm) margin cases in the analysis, thus potentially obscuring the recurrence rate attributable to a positive margin. A similar margin threshold was used by Kim et al., who noted no effect of positive margins on LR in benign PTs where a positive margin was defined as margin width ≤ 1 mm.⁷ These differences with respect to the definition and significance of positive margins notwithstanding, our data adds to the growing body of evidence that wider negative margins are not necessarily preferable to narrower negative margins in

surgical management of benign PT.¹⁰ The lack of evidence that local recurrence impacts survival for benign PT and the low rates of histologic upgrade should be taken into account when discussing reoperation for positive margins.^{8,9,22}

For borderline and malignant PTs, our data suggest the historical 10 mm margin width may remain important, given that narrower margins were associated with LR rates comparable to those with positive margins. The NCCN guidelines note that wide excision without axillary staging is required, which is defined as intention to obtain surgical margins ≥ 1 cm without an absolute indication for mastectomy if lumpectomy fails to achieve a 1 cm margin width.⁴ Our study suggests narrow (< 10 mm) margins result in an increased LR risk substantial enough to suggest that pursuing additional surgery to achieve wider margins (i.e., mastectomy if segmental mastectomy is not feasible) may be warranted. This is further supported by the lack of strong evidence or standardized guidelines, suggesting that the addition of RT after narrow or positive margin excision can achieve similar local control to surgical resection with widely negative margins. NCCN guidelines currently suggest consideration of RT when recurrence would result in significant morbidity.⁴ In our study, there was no significant difference in LR risk when comparing outcomes for those treated with RT with those who did not receive RT. However, the number of patients who received RT in our cohort was small (15%).

A number of recent studies have reported an association between positive margins and recurrence without further consideration of margin width^{7,10,11,24} and/or specific consideration of margin width within the context of borderline and malignant tumors.^{10,11} While most reports in the literature, especially the older literature, have assessed the

association between margin and LR independent of subtype, the more recent studies that have considered margin width in the context of histologic subtype rarely compare with the historical standard of 10 mm.⁶ In a large study of borderline and malignant PT from the Netherlands ($n = 921$), Bartels et al. found increased rates of LR with positive margins but suggest that narrow margins (0–1 mm) are not associated with increased risk of LR compared with margins > 1 mm.²⁴ Another recent study by Yoon et al. compared LR within subtypes on the basis of margins in a similar manner as the present analysis, noting no difference in risk of LR based on margin status.²⁵ However, only 5% of patients in this study had malignant PT, which has the highest risk of recurrence, and all patients with malignant PT received RT.

While our data suggest improved local control with wider margins for borderline and malignant tumors, we note that our cohort lacked patients with margins between 5–10 mm. Thus, while we found margin width < 5 mm to be associated with worse local control, and > 10 mm to be associated with low rates of local failure (5-year local recurrence free rate of 57% versus 93%, respectively), we were unable to determine whether a margin threshold of 5 mm may be sufficient for this population of patients. Neron et al. studied surgical margins for malignant PTs and found that margins of 3–7 mm compared with > 8 mm did not impact LR but did find a benefit in LR-free survival for patients that underwent mastectomy.²⁶ These data suggest that narrower margins, less than 1 cm, but wider than 5 mm, may be sufficient for borderline and malignant PTs, but more comprehensive assessments with larger patient cohorts are needed.

Our study has limitations. In the multivariate model of LR, histologic subtype and surgical margin were included with a total of three degrees of freedom. This may cause overfitting given there were only 13 LR events. Therefore, one needs to interpret this result with caution. Further, while we have the added value of expert pathology review in the attempt to avoid the confounding variable of histologic misclassification, this is a relatively small, single-institution cohort subject to selection bias inherent in retrospective reviews. The rarity of this tumor type makes it difficult to obtain large cohorts, but a larger analysis evaluating narrower margin cutoffs may be beneficial. It would also be of value to analyze the patients with borderline and malignant phyllodes tumors independently given the histologic differences and clinical behavior between these subtypes, however, this requires larger patient cohorts than the present study.

CONCLUSIONS

Our study identified 117 patients with PTs of the breast pathologically confirmed at our institution. We found that margin status remains important for local control. With our

study findings and a review of the current guidelines, for benign PT, we suggest that a no ink on tumor standard is appropriate. For borderline and malignant PTs, the current 10 mm guideline seems appropriate, given that the local recurrence rate for resection with narrower margins was comparable to that for patients with positive margins in our study.

SUPPLEMENTARY INFORMATION The online version contains supplementary material available at <https://doi.org/10.1245/s10434-024-15892-8>.

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REFERENCES

1. Rayzah M. Phyllodes Tumors of the breast: a literature review. *Cureus*. Sep 7 2020;12(9):e10288. <https://doi.org/10.7759/cureus.10288>
2. Azzopardi JG, Chepick OF, Hartmann WH, et al. The World Health Organization histological typing of breast tumors—Second edition. *Am J Clin Pathol*. 1982;78(6):806–16. <https://doi.org/10.1093/ajcp/78.6.806>.
3. Zhang Y, Kleer CG. Phyllodes tumor of the breast: histopathologic features, differential diagnosis, and molecular/genetic updates. *Arch Pathol Lab Med*. 2016;140(7):665–71. <https://doi.org/10.5858/arpa.2016-0042-RA>.
4. NCCN clinical breast guidelines in oncology. Breast cancer. Version 4.2020. Nation Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
5. Mangi AA, Smith BL, Gadd MA, Tanabe KK, Ott MJ, Souba WW. Surgical management of phyllodes tumors. *Arch Surg*. May 1999;134(5):487–92; discussion 492–3. <https://doi.org/10.1001/archsurg.134.5.487>
6. Rosenberger LH, Thomas SM, Nimbkar SN, et al. Contemporary multi-institutional cohort of 550 cases of phyllodes tumors (2007–2017) demonstrates a need for more individualized margin guidelines. *J Clin Oncol*. 2021;39(3):178–89. <https://doi.org/10.1200/JCO.20.02647>.
7. Kim S, Kim JY, Kim DH, Jung WH, Koo JS. Analysis of phyllodes tumor recurrence according to the histologic grade. *Breast Cancer Res Treat*. 2013;141(3):353–63. <https://doi.org/10.1007/s10549-013-2684-x>.
8. Borhani-Khomani K, Talman ML, Kroman N, Tvedskov TF. Risk of local recurrence of benign and borderline phyllodes tumors: a Danish population-based retrospective study. *Ann Surg Oncol*. 2016;23(5):1543–8. <https://doi.org/10.1245/s10434-015-5041-y>.
9. Yom CK, Han W, Kim S-W, Park SY, Park IA, Noh D-Y. Reappraisal of conventional risk stratification for local recurrence based on clinical outcomes in 285 resected phyllodes tumors of the breast. *Ann Surg Oncol*. 2015;22(9):2912–8. <https://doi.org/10.1245/s10434-015-4395-5>.

10. Lu Y, Chen Y, Zhu L, et al. Local recurrence of benign, borderline, and malignant phyllodes tumors of the breast: a systematic review and meta-analysis. *Ann Surg Oncol.* 2019;26(5):1263–75. <https://doi.org/10.1245/s10434-018-07134-5>.
11. Co M, Chen C, Tsang JY, Tse G, Kwong A. Mammary phyllodes tumour: a 15-year multicentre clinical review. *J Clin Pathol.* 2018;71(6):493–7. <https://doi.org/10.1136/jclinpath-2017-204827>.
12. Toussaint A, Piaget-Rossel R, Stormacq C, Mathevet P, Lepigeon K, Taffe P. Width of margins in phyllodes tumors of the breast: the controversy drags on? A systematic review and meta-analysis. *Breast Cancer Res Treat.* 2021;185:21.
13. Zhou ZR, Wang CC, Sun XJ, et al. Prognostic factors in breast phyllodes tumors: a nomogram based on a retrospective cohort study of 404 patients. *Cancer Med.* 2018;7(4):1030–42. <https://doi.org/10.1002/cam4.1327>.
14. Cowan ML, Argani P, Cimino-Mathews A. Benign and low-grade fibroepithelial neoplasms of the breast have low recurrence rate after positive surgical margins. *Mod Pathol.* 2016;29(3):259–65. <https://doi.org/10.1038/modpathol.2015.157>.
15. Sevinc AI, Aksoy SO, Guray Durak M, Balci P. Is the extent of surgical resection important in patient outcome in benign and borderline phyllodes tumors of the breast? *Turk J Med Sci.* 2018;48(1):28–33. <https://doi.org/10.3906/sag-1704-47>.
16. Lawton TJ, Acs G, Argani P, et al. Interobserver variability by pathologists in the distinction between cellular fibroadenomas and phyllodes tumors. *Int J Surg Pathol.* 2014;22(8):695–8. <https://doi.org/10.1177/1066896914548763>.
17. Woolson RaC, WR. *Statistical Methods for the Analysis of Biomedical Data.* 2nd Edition ed. Wiley, New York, 2002.
18. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53(282):457–81. <https://doi.org/10.1080/01621459.1958.10501452>.
19. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data.* Wiley; 1980.
20. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep.* 1966;50(3):163–70.
21. Cox D. Regression models and life tables (with discussion). *J R Stat. Soc. B* 34:187, 220, 197
22. van Olmen JP, Beerthuis AWJ, Bekers EM, et al. Management of benign phyllodes tumors: a Dutch population-based retrospective cohort between 1989 and 2022. *Ann Surg Oncol.* 2023;30(13):8344–52. <https://doi.org/10.1245/s10434-023-14128-5>.
23. Moutte A, Chopin N, Faure C, et al. Surgical management of benign and borderline phyllodes tumors of the breast. *Breast J.* 2016;22(5):547–52. <https://doi.org/10.1111/tbj.12623>.
24. Bartels SAL, van Olmen JP, Scholten AN, et al. Real-world data on malignant and borderline phyllodes tumors of the breast: a population-based study of all 921 cases in the Netherlands (1989–2020). *Eur J Cancer.* 2024;201:113924. <https://doi.org/10.1016/j.ejca.2024.113924>.
25. Yoon KH, Kang E, Kim EK, Park SY, Shin HC. Recurrence is not associated with margin status in phyllodes tumor. *Ann Surg Oncol.* 2023;30(4):2154–61. <https://doi.org/10.1245/s10434-022-12997-w>.
26. Neron M, Sajous C, Thezenas S, et al. Surgical margins and adjuvant therapies in malignant phyllodes tumors of the breast: a multicenter retrospective study. *Ann Surg Oncol.* 2020;27(6):1818–27. <https://doi.org/10.1245/s10434-020-08217-y>.

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