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Contemporary Multi-Institutional Cohort of 550 Cases of Phyllodes Tumors (2007-2017) Demonstrates a Need for More Individualized Margin Guidelines

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abstract

PURPOSE Phyllodes tumors (PTs) are rare breast neoplasms, which have little granular data on margins. Current guidelines recommend ≥ 1 cm margins; however, recent data suggest narrower margins are sufficient, and for benign PT, a negative margin may not be necessary.

METHODS We performed an 11-institution contemporary (2007-2017) review of PT practices. Demographics, surgical, and histopathologic data were captured. Logistic regression was used to estimate the association of select covariates with local recurrence (LR).

RESULTS Of 550 PT patients, the majority underwent excisional biopsy (55.3%, n = 302/546) or lumpectomy (wide excision) (38.5%, n = 210/546). Median tumor size was 30 mm, 68.9% (n = 379) were benign, 19.6% (n = 108) borderline, and 10.5% (n = 58) malignant. Surgical margins were positive in 42% (n = 231) and negative in 57.3% (n = 311). A second operation was performed in 38.0% (n = 209) of the total cohort, including 51 patients with an initial *negative* margin (82.4% with < 2 mm), and 157 with an initial *positive* margin, with residual disease only found in six (2.9%). Notably, 32.0% (n = 74) of those with an initial positive margin did *not* undergo a second operation, among whom only 2.7% (n = 2) recurred. Recurrence occurred in 3.3% (n = 18) of the total cohort (n = 15 LR, n = 3 distant), at median follow-up of 36.7 months. LR (all PT grades) was not reduced with wider negative margin width (≥ 2 mm *v* < 2 mm: odds ratio [OR] = 0.39; 95% CI, 0.07 to 2.10; *P* = .27) or final margin status (positive *v* negative: OR = 0.96; 95% CI, 0.26 to 3.52; *P* = .96).

CONCLUSION In current practice, many patients are managed outside of current guidelines. For the entire cohort, a wider margin width was not associated with a reduced risk of LR. We do not recommend re-excision of a negative margin for benign PT, regardless of margin width, as a progressively wider surgical margin is unlikely to reduce LR.

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ASSOCIATED CONTENT

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INTRODUCTION

Phyllodes tumors (PTs) are rare breast neoplasms representing less than 1.0% of all breast lesions.[1,2] The WHO classifies PT as benign, borderline, and malignant based on multiple stratified histopathologic parameters including; (1) degree of stromal cellularity and (2) atypia, (3) presence of stromal overgrowth, (4) mitotic count, and (5) nature of the tumor border.[3-6] These histologic grades have variable rates of recurrence, and are subject to significant subjectivity in diagnosis. National Comprehensive Cancer Network (NCCN) treatment guidelines for *all* grades currently include: wide local excision, with the intent of obtaining surgical margins ≥ 1 cm, omission of axillary staging, and cautious consideration of adjuvant therapy.[7]

Local recurrence (LR) has been associated with *positive* surgical margins as seen in multiple large series.[8-14] Additional independent factors associated with LR are age, grade, tumor size, cellular atypia, stromal overgrowth, mitoses, fibroproliferation (fibroadenoma or fibroadenomatoid change in the surrounding breast tissue), necrosis, and breast-conserving surgery.[9-13,15,16] Adequate margin *width* is a matter of ongoing debate. Some large series[11,16-18] reveal a *tumor-free* margin *alone* may be adequate to prevent LR. Jang et al[11] found in a multivariate analysis that only a *positive* margin increased LR, with no significant increase if the margin width was as narrow as 1 mm or even 0.1 mm. Shaaban and Barthelmes[18] had similar findings, evaluating benign PT only, revealing no difference in recurrence rates between a 1- and 10-mm margin.

CONTEXT

Key Objective

This study sought to provide contemporary data from a multi-institutional network of comprehensive cancer centers with respect to margin management of phyllodes tumors and its impact on local recurrence, for which little granular data exist.

Knowledge Generated

Many patients are being managed outside current margin management guidelines, including omission of re-excisions for narrow, and even positive margins. A wider negative margin width was not associated with a reduced risk of local recurrence.

Relevance

Current data support the omission of re-excisions of a negative margin for benign phyllodes tumors, regardless of margin width. While we suspect a positive margin will similarly not impact local recurrence for benign phyllodes, we recommend awaiting forthcoming prospective data to support this hypothesis. These data highlight the need for prospective, cooperative group collaboration to provide substantial evidence necessary to revise national guidelines for margin management.

While positive margins have been an independent predictor of LR in many series, there is a growing body of literature to suggest avoiding a positive margin *may not be necessary*. A few large series found that the significance of positive margins is lost on multivariate analysis.[15,16] Additional notable series found no association of positive margins with LR for any PT grade,[19] for benign and benign or borderline,[20] PT.[21] Finally, a recent meta-analysis found that positive surgical margins were only associated with an increased LR risk for malignant PT.[22]

We sought to provide data representative of contemporary practice patterns at comprehensive cancer centers with respect to margins. This study was also intended to provide foundation data to aid in the design of a prospective, national tumor registry to determine the safety of more narrow margins than currently supported by national guidelines.

METHODS

Data were collected from 11 institutions reviewing PT management from 2007 to 2017. After institutional review board approval from each site, all adult women who underwent definitive surgical management for an initial PT were included. Patient demographics, obstetric and gynecologic factors, and management decisions including presurgical imaging, biopsies, type of surgery, surgeon's preoperative suspicion of phyllodes, and margin intent were identified. Extensive histopathologic data, final surgical margin status, and receipt of adjuvant therapies were retrieved from the electronic health record; central pathologic rereview was not performed.

Surgical margin was recorded for each operation as either (1) positive (*any* tumor touching ink) or (2) negative (*no* tumor touching ink). If the margin was recorded as negative, the measured width of the closest negative margin was recorded as; < 1 mm, $\geq$ 1-2 mm, $\geq$ 2-5 mm, $\geq$ 5-10 mm, ≥ 10 mm, or margin width unknown or not reported. For subsequent operations, an additional pathologic classification permitted the pathologic margin status to be recorded as no residual phyllodes tumor. Final margin width was classified based on the last surgical procedure, and when the final operation had no residual tumor, they were classified as having a final negative margin status with final margin width ≥ 2 mm, conservatively assuming a re-excision lumpectomy or mastectomy with no residual disease would have permitted at least 2 mm around the tumor bed. Patient's last known status was recorded for recurrence or death. Family history and genetic testing data from this cohort were previously published.[23]

Data were abstracted according to study protocol, and de-identified case data were aggregated at the coordinating center. Patient characteristics were summarized by either n (%) or median (interquartile range [IQR]), for all patients and by grade. Chi-square or Fisher's exact tests were used to test for differences between groups, as appropriate, and analysis of variance was used to test for differences between groups for continuous variables. Median follow-up time was estimated using the reverse Kaplan-Meier method.

Univariate logistic regression was used to estimate the association of select covariates with the likelihood of experiencing LR. No adjustments were made for multiple comparisons. Only patients with complete data were included in each model and effective sample sizes were included for all tables. Statistical analyses were conducted using SAS (v9.4 SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

We identified 550 women with PT from 11 institutions (n = 91, 71, 62, 58, 55, 51, 47, 41, 34, 31, and 9). Median

TABLE 1. Multicenter Phyllodes Tumor Patient Demographic, Obstetric, and Gynecologic Factors, 2007-2017

	Overall, N = 550[a]	Benign, n = 379 (68.9%)	Borderline, n = 108 (19.6%)	Malignant, n = 58 (10.5%)
Age at diagnosis, years, median (IQR)	44 (36-53)	42 (34-52)	49 (40-57)	50 (39-57)
Ethnicity				
Asian	47 (8.5%)	28 (59.6%)	16 (34.0%)	2 (4.3%)
Native Hawaiian/Pacific Islander	1 (0.2%)	1 (100%)	0 (0%)	0 (0%)
American Indian	5 (0.9%)	1 (20.0%)	1 (20.0%)	3 (60.0%)
Black/African American	85 (15.5%)	61 (71.8%)	13 (15.3%)	10 (11.8%)
White	326 (59.3%)	227 (69.6%)	64 (19.6%)	34 (10.4%)
Other	39 (7.1%)	25 (64.1%)	8 (20.5%)	6 (15.4%)
Hispanic or Latino	37 (6.7%)	28 (75.7%)	8 (21.6%)	1 (2.7%)
Not Hispanic or Latino	396 (72.0%)	258 (65.2%)	84 (21.2%)	50 (12.6%)
BMI, median (IQR)	27 (23-33)	26 (23-33)	28 (24-34)	29 (24-34)
Tobacco use				
Current smoker	51 (9.3%)	38 (74.5%)	8 (15.7%)	5 (9.8%)
Former smoker	75 (13.6%)	51 (68.0%)	14 (18.7%)	10 (13.3%)
Never smoker	387 (70.4%)	259 (66.9%)	81 (20.9%)	43 (11.1%)
Alcohol use				
Heavy drinker, > 7 drinks/wk	12 (2.2%)	9 (75.0%)	2 (16.7%)	1 (8.3%)
Moderate drinker, 3-7 drinks/wk	36 (6.5%)	19 (52.8%)	8 (22.2%)	9 (25.0%)
Light/no drinking, < 3 drinks/wk	422 (76.7%)	290 (68.7%)	83 (19.7%)	45 (10.7%)
Age of menarche, years, median (IQR)	13 (12-14)	12 (12-14)	13 (12-14)	12 (11-14)
Menopausal status				
Premenopausal	302 (54.9%)	229 (75.8%)	44 (14.6%)	27 (8.9%)
Perimenopausal	24 (4.4%)	14 (58.3%)	6 (25.0%)	4 (16.7%)
Postmenopausal	141 (25.6%)	84 (59.6%)	42 (29.8%)	15 (10.6%)
Age of menopause, years, median (IQR)	50 (45-52)	49 (44-52)	50 (45-52)	50 (47-52)
Prior ovarian removal				
None	476 (86.5%)	328 (68.9%)	92 (19.3%)	54 (11.3%)
One or both	44 (8.0%)	32 (8.4%)	9 (8.3%)	3 (5.2%)
Number of pregnancies, median (IQR)	2 (0-3)	2 (0-3)	2 (0-3)	2 (1-3)
Number of live births, median (IQR)	2 (1 to 3)	2 (1 to 3)	2 (1 to 2)	2 (1 to 2.5)
Mother's age of first live birth, years, median (IQR)	25 (20-30)	25 (20-30)	26 (20-30)	26 (19-29)
Breast feeding history				
Yes	109 (19.8%)	69 (63.3%)	26 (23.9%)	14 (12.8%)
No	47 (8.5%)	32 (68.1%)	5 (10.6%)	9 (19.2%)
Hormonal contraceptive use				
Yes	226 (41.1%)	168 (74.3%)	39 (17.3%)	19 (8.4%)
No	148 (26.9%)	95 (64.2%)	29 (19.6%)	22 (14.9%)
History of fertility treatments				
Yes	14 (2.5%)	11 (78.6%)	2 (14.3%)	1 (7.1%)
No	240 (43.6%)	162 (67.5%)	43 (17.9%)	33 (13.8%)

(continued on following page)

TABLE 1. Multicenter Phyllodes Tumor Patient Demographic, Obstetric, and Gynecologic Factors, 2007-2017 (continued)

	Overall, N = 550[a]	Benign, n = 379 (68.9%)	Borderline, n = 108 (19.6%)	Malignant, n = 58 (10.5%)
Hormone replacement therapy				
Yes, currently	26 (4.7%)	16 (61.5%)	7 (26.9%)	3 (11.5%)
Yes, in the past	22 (4.0%)	14 (63.6%)	6 (27.3%)	2 (9.1%)
No, never	320 (58.2%)	219 (68.4%)	60 (18.8%)	39 (12.2%)

NOTE. Data presented as n (%) unless otherwise specified. Column percentages are presented for variables overall, and row percentages are presented for all subgroups. Percentages may not add up to 100 due to rounding or missing values.

Abbreviations: BMI, body mass index; IQR, interquartile range.

[a]Cohort N = 550; however, benign, borderline, and malignant phyllodes tumor total n = 545, and 5 classified as unknown.

tumor size was 3.0 cm (IQR, 2.0 to 4.5 cm) with a range of 0.3-29.0 cm. PTs were classified as benign in 68.9% (n = 379), 19.6% borderline (n = 108), and 10.5% malignant (n = 58). Median age was 44 years (IQR, 36 to 53 years), the majority of whom were White (59.3%, n = 326), non-Hispanic (72.0%, n = 396), never smokers (70.4%, n = 387), and had light or no alcohol history (76.7%, n = 422). Median age of menarche was 13 years (IQR, 12 to 14 years), the median age of menopause was 50 years (IQR, 45 to 52), and the majority of women had a history of pregnancy (56.4%, n = 310) (Table 1).

Preoperative Evaluation and Diagnosis

The majority of women presented with a palpable mass (median 30 mm on exam; IQR, 20 to 50 mm; 10.5% nonpalpable). Imaging workup often included a preoperative mammogram (70.2%, n = 386) and or ultrasound (86.7%, n = 477), and rarely a breast magnetic resonance imaging (5.5%, n = 30). The majority underwent a presurgical biopsy (87.6%, n = 482), most of which involved a core needle biopsy (CNB) (81.3%, n = 447), and this frequently (63.3%, n = 348) suggested the diagnosis of a PT (eg, cannot exclude a phyllodes) (Table 2). The majority of surgeons (69.1%, n = 380) had a presurgical clinical suspicion of PT; however, they frequently did not pursue a wide margin at the index operation, as the surgeon's margin intent was recorded as an enucleation in 28.0% (n = 154) and a narrow margin in 15.8% (n = 87).

Operative Management, Tumor Characteristics, and Margins

Initial management included 54.9% (n = 302) having an excisional biopsy (no attempt at margins), 38.2% (n = 210) lumpectomy (wide local excision with attention to margins), and 6.2% (n = 34) mastectomy (47.1%, n = 16 with immediate reconstruction). Very few underwent lymph node evaluation (2.2%, n = 12) and all examined lymph nodes were negative (n = 10 sentinel lymph node biopsy [SLNB], n = 2 axillary lymph node dissection [ALND]) (Table 2). A second operation was performed in over a third of the total cohort (37.6%, n = 209), including 51 women with an initial *negative* margin who underwent surgery to obtain a wider negative margin (82.4% with an initial margin < 2 mm). Of those who underwent a second operation, 87.1% (n = 182) had a re-excision lumpectomy, 11.0% (n = 23) completed a mastectomy, 1.0% (n = 2) an excisional biopsy, and 1.0% (n = 2) was unknown. Residual disease was identified in six patients (2.9%), and very few underwent a third operation (n = 5) (Fig 1).

At the initial operation, margin status was negative in 56.5% (n = 311), and positive in 42% (n = 231). Of the 231 with an initial positive margin, 68.4% (n = 157) underwent a second operation. Conversely, a third of women (32.0%, n = 74) with an initial positive surgical margin did not undergo re-excision. At the completion of definitive surgical management, > 10% of women had a positive margin as their final margin status.

Recurrences, Adjuvant Therapy, and Outcomes

Recurrences occurred in 3.3% (n = 18) of the total cohort, with the majority occurring as LRs (n = 15), and very few with distant recurrences (n = 3). A histologic upgrade occurred in 20% (3 of 15) of LRs (two benign to borderline and one borderline to malignant). LR occurred at a median of 18.8 months, while distant recurrences occurred at 7.1 months, with an overall median follow-up of 36.7 months (95% CI, 33.0 to 43.9). LR by grade occurred in 1.3% (n = 5) of benign, 5.6% (n = 6) borderline, and 6.9% (n = 4) malignant PT. The final margin status of these 15 patients with an LR included two with final *positive* margins (one benign and one borderline), five with margins < 2 mm (two benign, two borderline, and one malignant), six with margins ≥ 2 mm (two benign, three borderline, and one malignant), and two had unknown, but negative, margin width (two malignant) (Table 3). LR rates by final margin status, margin width, and PT grade are shown in Table 4. On univariate logistic regression, LR was associated with malignant versus benign or borderline grade (odds ratio [OR] = 3.19; 95% CI, 1.63 to 6.21; $P = .001$), moderate or marked versus mild stromal atypia (OR = 8.58; 95% CI, 2.39 to 30.79; $P = .001$), present versus absent stromal overgrowth (OR = 3.78; 95% CI, 1.32 to 10.79; $P = .01$), and increased pathologic tumor size (OR = 1.01; 95% CI, 1.00 to 1.01; $P < .001$).

LR (*all* PT grades) was *not* associated with final margin status (positive *v* negative: OR = 0.96; 95% CI, 0.26 to

TABLE 2. Multicenter PT Diagnosis and Operative Management, 2007-2017

	Overall, N = 550	Benign, n = 379 (68.9%)	Borderline, n = 108 (19.6%)	Malignant, n = 58 (10.5%)
Laterality				
Left	313 (56.9%)	219 (57.8%)	60 (55.6%)	34 (58.6%)
Right	231 (42.0%)	159 (42%)	47 (43.5%)	24 (41.4%)
Any biopsy prior to initial operation				
Yes	482 (87.6%)	333 (87.9%)	95 (88%)	54 (93.1%)
Type of biopsy				
CNB	447 (81.3%)	310 (81.8%)	88 (81.5%)	49 (84.5%)
Fine needle aspiration	30 (5.5%)	22 (5.8%)	6 (5.6%)	2 (3.4%)
Incisional biopsy	5 (0.9%)	1 (0.3%)	1 (0.9%)	3 (5.2%)
Presurgical biopsy indicated possible PT				
Yes	348 (63.3%)	230 (60.7%)	72 (66.7%)	46 (79.3%)
Clinical suspicion at the time of initial operation				
Yes	380 (69.1%)	252 (66.5%)	79 (73.1%)	49 (84.5%)
Clinical suspicion for PT was attributed to[a]				
Presurgical biopsy	341 (89.7%)	224 (88.9%)	71 (89.9%)	46 (93.9%)
Overall size	54 (14.2%)	27 (10.7%)	12 (15.2%)	15 (30.6%)
Rapid growth	49 (12.9%)	26 (10.3%)	13 (16.5%)	10 (20.4%)
INITIAL operative management, n = 546[b]				
Excisional biopsy (no attempt at margins)	302 (55.3%)	235 (62%)	50 (46.3%)	16 (27.6%)
Lumpectomy (wide local excision with attention to margins)	210 (38.5%)	136 (35.9%)	49 (45.4%)	25 (43.1%)
Mastectomy	34 (6.2%)	8 (2.1%)	9 (8.3%)	17 (29.3%)
Total mastectomy	23	3	4	16
Skin-sparing mastectomy	4	2	2	0
Nipple-sparing mastectomy	7	3	3	1
Axillary surgery performed, n = 12, 2.2%				
SLNB	10 (83.3%)	2 (100%)	3 (100%)	5 (71.4%)
ALND	2 (16.7%)	0 (0%)	0 (0%)	2 (28.6%)
Number of *positive* nodes identified	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Margin status, following *INITIAL* operation				
Negative, *no ink on tumor*	310 (56.4%)	216 (57%)	55 (50.9%)	39 (67.2%)
Positive	231 (42.0%)	159 (42%)	53 (49.1%)	19 (32.8%)
SECOND operative management, n = 209[c]				
Excisional biopsy (no attempt at margins)	2 (1.0%)	2 (1.7%)	0 (0%)	0 (0%)
Lumpectomy (wide local excision with attention to margins) or margin re-excision	182 (87.9%)	115 (95.0%)	50 (87.7%)	17 (58.6%)
Mastectomy	23 (11.1%)	4 (3.3%)	7 (12.3%)	12 (41.4%)
Total mastectomy	14	3	4	7
Skin-sparing mastectomy	3	0	1	2
Nipple-sparing mastectomy	6	1	2	3

(continued on following page)

TABLE 2. Multicenter PT Diagnosis and Operative Management, 2007-2017 (continued)

	Overall, N = 550	Benign, n = 379 (68.9%)	Borderline, n = 108 (19.6%)	Malignant, n = 58 (10.5%)
THIRD operative management, n = 6[d]				
Excisional biopsy (no attempt at margins)	0	0	0	0
Lumpectomy (wide local excision with attention to margins) or margin re-excision	2 (33.3%)	0 (0%)	0 (0%)	2 (40.0%)
Mastectomy	4 (66.7%)	1 (100%)	0 (0%)	3 (60.0%)

NOTE. Data presented as n (%) unless otherwise specified. Column percentages are presented for variables overall, and row percentages are presented for all subgroups. Percentages may not add up to 100 due to rounding or missing values.

Abbreviations: ALND, axillary lymph node dissection; CNB, core needle biopsy; PT, phyllodes tumor; SLNB, sentinel lymph node biopsy.

[a]Percentages are out of total with clinical suspicion (n = 380).

[b]Percentages are out of total with known initial operation and classification (n = 546, n = 4 missing).

[c]Percentages are out of all patients who underwent a 2nd operation (n = 209).

[d]Percentages are out of all patients who underwent a 3rd operation (n = 7).

3.52; $P = .96$), or a wider negative margin width (≥ 2 mm $v <$ 2 mm: OR = 0.39; 95% CI, 0.07 to 2.10; $P = .27$). LR was also not associated with surgery type, mitoses, histologic tumor border, and age at diagnosis (Table 5).

Very few women received adjuvant chemotherapy (n = 5, 0.9%), endocrine therapy (n = 9, 1.6%), or radiation (n = 23, 4.2%), and thus, the influence of these therapies on LR could not be analyzed. At median follow-up of 36.7 months for the entire cohort, 96% were alive without disease (n = 528), and very few alive with local or metastatic disease (n = 11, 2%), or died of disease (n = 2, 0.4%).

DISCUSSION

In this multi-institutional study, including 550 women with PT, we describe contemporary management from 11 institutions, representing the largest published cohort in the United States. This study highlights the substantial variability in practice patterns among academic surgeons from comprehensive cancer centers regarding surgical decision making and margin management. In many cases, surgeons are completely omitting re-excisions not only for narrow margins, but also for *positive* margins, revealing nonadherence to NCCN guidelines, which continue to recommend a wide tumor-free margin of 1 cm or greater for all histologic grades.[7]

The definitive diagnosis of PT often occurs after surgical excision, due to diagnostic uncertainty of CNB and PT heterogeneity. In this series, the initial surgical margin was positive in 42%, despite a suggestive CNB in 63%, and a clinical suspicion of PT by the surgeon (eg, rapid growth, size, and core biopsy) in approximately 70%. This high rate of initial margin positivity may be attributed to surgeon selection of an excisional biopsy, with no regard to margins, in greater than half of the cases (55.3%). This high initial positive margin rate is seen in other large series[17,21] and is likely due to the fact that 30% of core biopsies suspicious for PT are ultimately a fibroadenoma on final pathology, while the converse is true in just 7%-9%.[14,17] These high rates of initial positive margins leave surgeons to ponder to re-excise or not to re-excise?

Of the 42% of patients in our series with initial positive margins, one third did not undergo margin re-excision, in opposition to national guidelines, leaving the final margin as positive. Moo et al[21] similarly identified a high percentage of initial positive margins (47%) following surgical excision of 216 benign PT, much in line with our finding of 42%. In their series, 56% also did *not* undergo additional surgery and no difference in LR was identified between women with positive or negative margins. They concluded that close follow-up in lieu of a re-excision should be considered for close and positive margins for benign PT, which data from this series would support.

The decision to omit re-excision seen in our series may be attributed to (1) an uncertain oncologic benefit, (2) the frequent lack of residual phyllodes identified on re-excision (2.5% herein), and (3) potential psychological stress or cosmetic detriment with additional surgery. By contrast, roughly 15% of women with an initial negative margin did undergo a second operation, presumably attempting to obtain the 1 cm margin NCCN recommendation in an attempt to reduce LR. This practice of margin re-excision was performed similarly for all PT grades. Overall, nearly 40% of women with PT are subjected to a second operation, without clear benefit. Our data demonstrate wide variability in management of margins and suggest that surgeons are following more recent evidence, suggesting a wide margin, or perhaps even a negative margin, may not be indicated.

In this retrospective series, we observed a very low rate of LR (2.7%). This is slightly lower than older series reported in the literature, but closer to other large, contemporary series. One recent very large series (N = 479) reported an LR of 6.3% with 8 years of follow-up.[20] While noting our low event rate, our series identified PT grade, tumor size, stromal atypia, and presence of stromal overgrowth as significant predictors of LR on univariate analysis, with stromal cellularity and

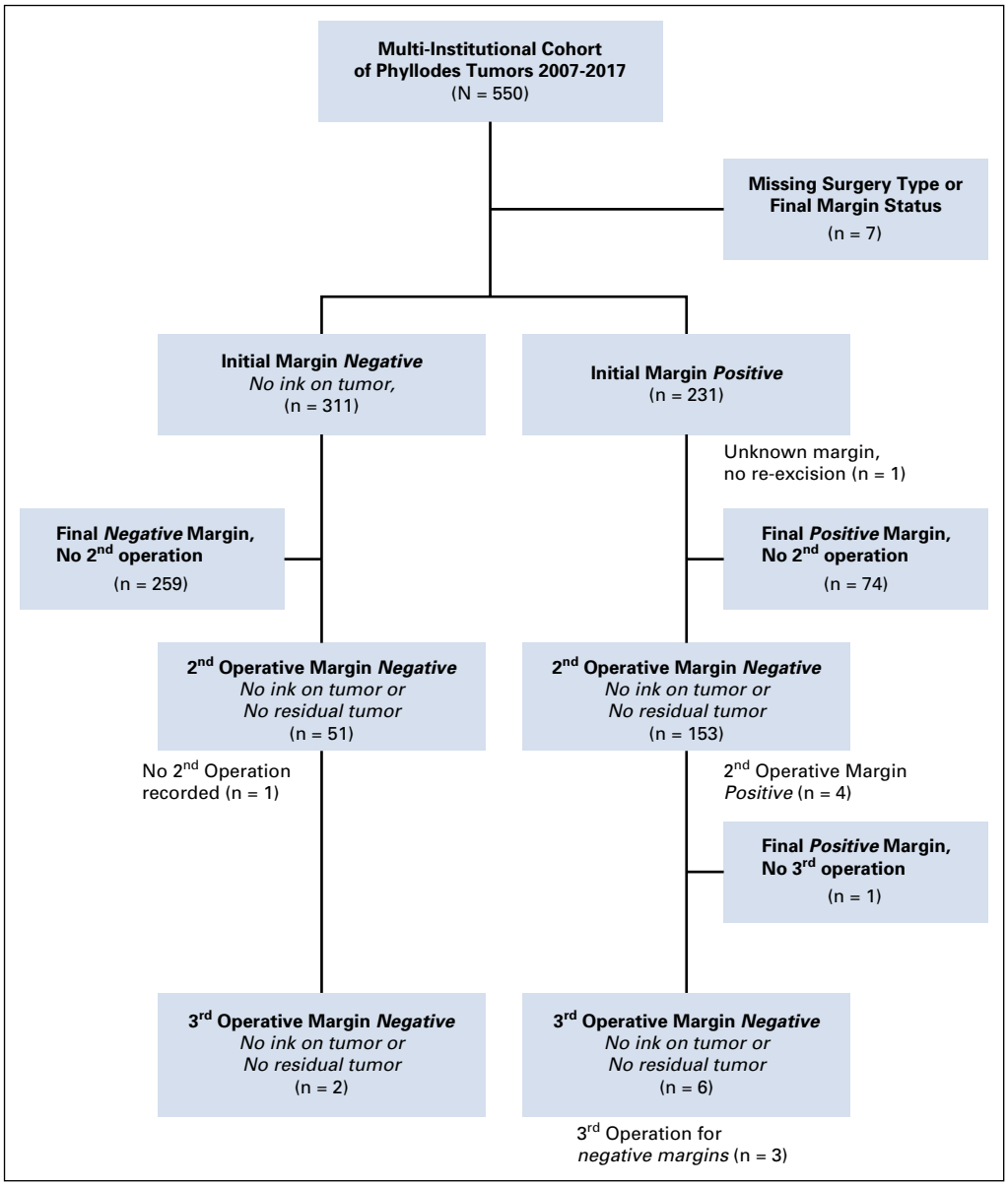

FIG 1. Patient flow diagram, multicenter phyllodes tumor management and margins, 2007-2017.

mitoses > 10 approaching significance. Notably, however, positive margins and margins < 2 mm were not associated with LR when evaluating all three PT subtypes together. Multivariate analysis was not feasible as the small number of local failures would only permit a single variable (with two levels) into the model without overfitting.

While many large series from around the world have found that positive margins matter, including Chen et al[24] (N = 172), Ben Hassouna et al[9] (N = 106), Cheng et al[8] (N = 182), Belkacemi et al[10] (N = 443), Spanheimer et al[25] (N = 125), Tan et al[12] (N = 605), Spitaleri et al[13] (N = 172), Jang et al[11] (N = 164), and Co et al[14] (N = 465); a growing number of large series indicate a negative margin may not be necessary, including Yom et al[16] (N = 285) and Kim et al[19] (N = 193), especially in the setting of a benign PT, such as Moo et al[21] (N = 246) and Lu et al[22] (2019 meta-analysis). The challenges with drawing any major conclusions from these data are (1) the rarity of the tumor and subjectivity of the diagnosis, (2) lack of prospective data, (3) commonly pooled analyses lumping all grades together, and (4) the single institutional or country-level data, with broad inclusion of cases that span multiple decades.[8,10,15,16,24-28] High-quality, prospective data from a national registry are needed to validate these contemporary results, update current national guidelines, and provide higher level evidence for a best practice.

TABLE 3. Final Negative Margin Width by Operative Type and LR by Grade

	Benign	Borderline	Malignant
Final *Negative* Margins (n = 468)	**n = 316**	**n = 96**	**n = 55**
Excisional biopsy (no attempt at margins) (n = 242)			
< 1 mm	32 (17.6%) [1]	3 (6.8%) [1]	0 (0%)
≥ 1-2 mm	9 (5.0%)	1 (2.3%)	1 (6.7%)
≥ 2 mm	107 (58.8%) [1]	38 (86.4%)	13 (86.7%)
Unknown	34 (18.7%)	2 (4.6%)	1 (6.7%)
Lumpectomy/wide local excision (n = 195)			
< 1 mm	25 (19.7%) [1]	5 (11.4%)	2 (8.3%) [1]
≥ 1-2 mm	7 (5.5%)	6 (13.6%) [1]	1 (4.2%)
≥ 2 mm	79 (62.2%) [1]	31 (70.5%) [3]	18 (75%) [1]
Unknown	16 (12.6%)	2 (4.6%)	3 (12.5%) [1]
Mastectomy (any) (n = 31)			
< 1 mm	1 (14.3%)	1 (12.5%)	2 (12.5%)
≥ 1-2 mm	0 (0%)	0 (0%)	2 (12.5%)
≥ 2 mm	5 (71.4%)	4 (50%)	7 (43.8%)
Unknown	1 (14.3%)	3 (37.5%)	5 (31.3%) [1]
Total LRs by grade[a]	[4] 1.3%	[5] 5.2%	[4] 7.3%

NOTE. [#] Patients with local recurrence (n = 15).

Abbreviation: LR, local recurrence.

[a]Two recurrences had initial *positive* margins, and had no 2nd operation (one benign and one borderline).

Very few patients in our series underwent nodal evaluation (2.2%), which is exceedingly lower than nationally reported rates of axillary staging (25.5% in SEER, 26.9% in the National Cancer Data Base),[29,30] revealing concordance with national guidelines and an understanding of PT by this academic cohort of surgeons. Of the 12 patients who underwent axillary staging, 83.3% had a SLNB only (92% performed with a mastectomy), and zero metastases were identified. Presence of metastases to axillary nodes is extremely rare, with rates between 0%[8,24,31,32] and 5%[9] in large PT series, and have been associated with synchronous ipsilateral adenocarcinoma.[33] Specifically, in older series, in which complete ALND were performed routinely, or for palpable adenopathy (present in 9%-17% of PT), < 1% identified nodal metastases.[34-36] If no concern exists for a synchronous invasive adenocarcinoma, the authors strongly support avoidance of axillary staging, including with mastectomy.

Despite radiation use for PT increasing over time, with currently reported rates of 10%-15%,[10,37-40] practice patterns in this academic cohort use considerably less adjuvant therapy as compared to national data sets (National Cancer Data Base and SEER). In our series, 4.2%, and 0.9% received adjuvant radiation and chemotherapy, respectively. While some data report a reduction in LR with radiation, no data have identified a benefit in disease-free or overall survival.[10,37-39,41] Currently, there are no prospective randomized data to support radiation use, and NCCN recommends consideration only where significant morbidity may occur with LR.[7] The authors do not support the use of radiation following breast conservation for prevention of LR, as there is a known association of PT with *TP53* mutations[42-45] and *RB1* mutations,[46,47] both of which are associated with increased risk of radiation-induced secondary malignancy.

We identified a histologic upgrade, or grade progression, in 20% of LR, consistent with other series.[8,12] This progression has been attributed to a number of factors including a potentially inadequately sampled initial tumor, dedifferentiation into a more aggressive subtype, altered epithelial and stromal interactions, and genomic aberrations. We did not identify any demographic or extremes of reproductive factors, including elevated lifetime estrogen exposure, supporting these are not endocrine driven tumors.

Our study has a number of notable strengths as this cohort represents one of the largest published series, with data pooled from major comprehensive cancer centers, during a contemporary time period. This suggests accuracy of PT tumor classification, and minimization of missing data. Academic breast pathologists recognize the necessity of adequate specimen sampling due to tumor heterogeneity; however, we did not specifically collect data regarding the number of slides per case, or overall extent of tumor sampling. As there is no College of American Pathologists synoptic reporting protocol for PTs, significant variability existed in the reporting of histopathologic details. Due to

TABLE 4. LR Rates by Final Margin Status, Margin Width, and Phyllodes Tumor Classification, 2007-2017

A. Final *Positive* Margin

	Overall, N = 75	Benign, n = 60 (80.0%)	Borderline, n = 12 (16.0%)	Malignant, n = 3 (4.0%)
Cases of LR	2	1	1	0
LR rate	2.7%	1.7%	8.3%	0%
Median follow-up, months[a]	27.5	31.0	24.0	—

B. Final *Negative* Margin, Final Margin Width < 2 mm

	Overall, N = 98	Benign, n = 74 (75.5%)	Borderline, n = 16 (16.3%)	Malignant, n = 8 (8.2%)
Cases of LR	5	2	2	1
LR rate	5.1%	2.7%	12.5%	12.5%
Median follow-up, months[a]	56.3	105.2	13.5	69.1

C. Final *Negative* Margin, Final Margin Width ≥ 2 mm

	Overall, N = 303[b]	Benign, n = 191 (63.0%)	Borderline, n = 73 (24.1%)	Malignant, n = 38 (12.5%)
Cases of LR	6	2	3	1
LR rate	2.0%	1.1%	4.1%	2.6%
Median follow-up, months[a]	66.1	71.9	58.0	74.2

NOTE. No residual tumor identified on re-excision operations were classified as having a margin ≥ 2 mm. Total LR, n = 15; however, n = 2 LR, malignant grade, had final negative margins, but *unknown* margin width, as seen above in Table 3. n = 7 had complete missing margin status. n = 67 had a negative margin, but measured margin width was not available.

Abbreviation: LR, local recurrence.

[a]Median follow-up time for the patients who had LR, not for all patients in each subgroup.

[b]n = 1 had final negative margin with final margin width ≥ 2 but unknown grade.

this lack of granular pathologic data, the number, and or extent, of close or positive margins were not able to be quantified. As previously reported, we acknowledge that some cases may have been missed during retrospective identification, as there is no specific International Classification of Diseases code for PT.[23] Our study is retrospective in nature with a relatively short median follow-up, which may limit identification of LRs, potentially contributing to our low event rate, limiting the ability to perform multivariate analysis.

In conclusion, as shown by this large multi-institutional series, most patients with PT are benign and can be managed successfully with breast conservation with an overall low risk of LR, which is not significantly impacted by margin status or width. The NCCN guidelines, which recommend a 1-cm wide margin for all PT, are reflective of broad principles based on lower-level evidence. With no prospective data in the literature, and conflicting large retrospective series on both ends of the margin spectrum, what constitutes an adequate margin for PT remains uncertain.

This series highlights the critical need for prospective, cooperative group collaboration to provide substantial evidence necessary to revise the national guidelines for margin management. While we endorse current margin recommendations for borderline and malignant PTs, guideline revision for benign PT should be considered, which comprise 70% of all PT, and are responsible for the majority (60%) of second operations. Based on the totality of available data, we do not recommend re-excision of a negative margin for benign PT, regardless of negative margin width, as progressively wider surgical margins do not reduce local or distant recurrences. While we suspect a positive margin will similarly not impact LR for benign PT, we recommend awaiting forthcoming prospective data to support this hypothesis.

TABLE 5. Logistic Regression Models Predicting Likelihood of Local Recurrence

Model	Predictor	N (# Events)	OR (95% CI)	*P*	Overall *P*
1	Final closest margin	401 (11)			.27
	< 2 mm		Ref		
	≥ 2 mm		0.388 (0.072 to 2.103)	.27	
2	Final margin status	543 (15)			.96
	Negative[a]		Ref		
	Positive		0.964 (0.264 to 3.518)	.96	
3	Phyllodes grade	545 (15)			**.001**
	Benign/borderline		Ref		
	Malignant		3.185 (1.633 to 6.213)	.001	
4	Surgery	546 (15)			.95
	Other[b]		Ref		
	Mastectomy		1.069 (0.123 to 9.272)	.95	
5	Stromal cellularity	252 (10)			.07
	Mild		Ref		
	Moderate/marked		6.759 (0.855 to 53.394)	.07	
6	Stromal atypia	227 (9)			**.001**
	Mild		Ref		
	Moderate/marked		8.581 (2.392 to 30.786)	.001	
7	Stromal overgrowth	237 (8)			**.01**
	Absent		Ref		
	Present		3.776 (1.321 to 10.794)	.01	
8	Mitoses per 10 hpf[c]	340 (12)			.14
	< 10		Ref		
	≥ 10		2.352 (0.759 to 7.284)	.14	
9	Histologic tumor border	248 (9)			.71
	Well-defined		Ref		
	Infiltrative		0.667 (0.08 to 5.576)	.71	
10	Pathologic tumor size	519 (14)	1.005 (1.003 to 1.008)	< .001	**< .001**
11	Age at diagnosis	546 (15)	0.999 (0.958 to 1.041)	.96	.96

NOTE. Each model was fit individually, and the correlation of patients treated at the same facility is accounted for in each model by inclusion of an exchangeable correlation structure in the context of the generalized estimating equations framework. Bold values are statistically significant.

Abbreviation: OR, odds ratio.

[a]Negative includes no ink on tumor and unknown/not reported when 2nd or 3rd operation margin is recorded as no residual phyllodes.

[b]Other includes excisional biopsy and lumpectomy.

[c]High-power fields.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Contemporary Multi-Institutional Cohort of 550 Cases of Phyllodes Tumors (2007-2017) Demonstrates a Need for More Individualized Margin Guidelines

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