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Long-Term Outcomes After Surgical Treatment of Malignant and Borderline Phyllodes Tumors of the Breast

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Abstract

Background.—Malignant and borderline phyllodes tumors (PTs) are rare, and little is known about their long-term prognosis. This study sought to evaluate recurrence rates and identify factors associated with local and distant failure.

Methods.—From 1957 to 2017, this study identified 124 patients with 125 PTs (86 malignant and 39 borderline). Recurrence rates and survival were assessed using the Kaplan-Meier method and correlated with clinicopathologic factors using the log-rank test.

Results.—The median age of the patients was 44 years, and the median tumor size was 5 cm. Breast-conserving surgery was performed for 57 % of the patients. During a median follow-up period of 7.1 years, 14 patients experienced a locoregional recurrence (LRR), with a 10-year cumulative LRR incidence of 12 %. In the univariable analysis, age younger than 40 years ($p = 0.02$) and close or positive margins ($p = 0.001$) were associated with increased risk of LRR. Seven patients experienced distant disease, all occurring as malignant PTs. The 10-year distant recurrence-free survival rate was 94 %. Uniformly poor pathologic features consisting of marked stromal cellularity, stromal overgrowth, infiltrative borders, and 10 or more mitoses per 10 high-power fields (hpf) were identified in 25 PTs (20 %), and all distant recurrences occurred in this group. For the patients who did not have uniformly poor features, the 10-year disease-specific rate was 100 %, and the overall survival rate was 94 % compared with 66 % and 57 %, respectively, among those with poor features.

Conclusion.—Malignant and borderline PTs without uniformly poor histologic features have an excellent prognosis after surgical resection, with a 10-year disease-specific survival rate of 100 %.

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The presence of uniformly poor pathologic features predicts a poor prognosis. Efforts should be directed toward new treatment approaches for these tumors.

Malignant phyllodes tumors (PTs) are rare neoplasms of the breast, with an estimated annual incidence of 2.1 cases per 1,000,000 women.¹ The primary treatment for malignant PT is complete surgical excision using either breast-conserving surgery (BCS) or mastectomy,^{2,3} with little known benefit from adjuvant chemotherapy or radiation therapy.⁴⁻⁶

Due to the rarity of malignant PT, little is known about its long-term prognosis. The reported local failure rate ranges from 10 % to 65 %, and the reported distant failure rate ranges from 5 % to 30 %.⁷⁻¹³ Furthermore, clinicopathologic factors associated with recurrence are inconsistent in the literature, providing little guidance on how patients should be counseled regarding prognosis after surgical excision. Current single-institution data are limited by small sample size,^{4,14,15} and publications using larger national databases lack detailed pathologic data that can be linked to outcomes.^{2,5}

Notably, the boundary between malignant and borderline PT is ill defined because these tumors demonstrate overlapping histologic features.¹⁶ In addition, the grading of PT has changed over time, so the uncertainties concerning the prognosis and management of malignant PT are equally applicable to borderline tumors. In this report, we review our single-institution experience with malignant and borderline PTs during a 50-year period to evaluate recurrence rates and survival, and to identify factors associated with local and distant failure.

METHODS

After institutional review board approval, we reviewed the cancer registry records at Memorial Sloan Kettering Cancer Center (MSK) for patients with malignant or borderline PT. Between April 1957 and July 2017, we identified 124 patients with 125 malignant or borderline PTs who had definitive surgery at MSK. Clinical, pathologic, and follow-up data were obtained by chart review.

Available pathology slides (43 of 125 cases, 34 %) were re-reviewed by a breast pathologist. One of these cases was reclassified from malignant to borderline. For the remaining cases, characterization of the tumors was based on the original pathology report.

Tumors were classified as borderline or malignant based on different grading schemes throughout the study period using pathologic characteristics such as stromal cellularity, stromal overgrowth, tumor borders, number of mitoses, and necrosis. Stromal cellularity was categorized as marked if there were confluent areas of densely overlapping stromal nuclei, or as mild to moderate if there was a slight to intermediate increase in stromal cells with evenly spaced nuclei or some overlapping nuclei. Stromal overgrowth was defined as the presence of stroma without epithelium in at least one low-power field as observed with a $\times 4$ microscopic objective.

The tumor border was characterized as infiltrative if invasion was noted, or as circumscribed/pushing if there was displacement of the breast parenchyma without invasion

or no breast parenchyma displacement. Mitotic count was calculated as the number of mitoses observed over 10 high-power fields (hpf) and stratified according to a cutoff 10 or more per 10 hpf. Tumor necrosis was defined as the presence of ghosts of tumor cells retaining phyllodes architecture within the tumor. The excision margin was recorded as close or positive if the tumor was present at or within 1 mm of the inked tissue edge. Margins of 1 mm or wider were recorded as negative. Margin status was determined from the last surgical procedure.

Locoregional recurrence was defined as recurrence in the breast or chest wall or within the ipsilateral regional nodal basins. Distant disease was defined as metastatic disease or inoperable locoregional disease extending directly into the chest cavity. Time to recurrence or death was calculated from the date of surgical resection.

Continuous variables were summarized using median (range), and categorical variables were summarized using frequency (%).

Comparisons between borderline and malignant histology groups were tested using the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. The Kaplan-Meier method was used to estimate distant recurrence-free survival (DRFS), disease-specific survival (DSS) defined as time from surgery to death from disease, and overall survival (OS). The cumulative incidence of local recurrence (LR) was estimated using one minus the Kaplan-Meier estimate of local recurrence-free survival. The log-rank test was used for comparisons between borderline and malignant histology groups. Univariable hazard ratios were estimated using Cox regression. Patients with uniformly poor pathologic features were defined as those with marked stromal cellularity, stromal overgrowth, infiltrative borders, and 10 mitoses or more per 10 hpf. A *p* value lower than 0.05 was considered statistically significant. All statistical analyses were performed using R version 3.4.2 (R Core Development Team, Vienna, Austria).

RESULTS

Clinicopathologic Characteristics

Of the 124 patients with malignant or borderline PT, 1 had a bilateral tumor, for a total of 125 cases, of which 86 were malignant and 39 were borderline. Table 1<T1> shows the clinicopathologic characteristics of the study cohort overall and stratified by malignant and borderline histology.

The median patient age was 44 years (range, 13–83 years), and the median pathologic tumor size was 5 cm (range, 0.9–35 cm). The patients with malignant PT had larger tumors than those with borderline PT (median 5.3 vs 3 cm; *p* < 0.001), and were more likely to have poor pathologic features including marked stromal cellularity (*p* < 0.001), stromal overgrowth (*p* = 0.001), infiltrative borders (*p* = 0.006), and 10 or more mitoses per 10 hpf (*p* < 0.001).

Overall, 57 % of the patients were treated with BCS and 43 % with mastectomy. The majority (87 %) had a negative final excision margin. Adjuvant chemotherapy and radiotherapy were rarely used (for 1.6 % and 0.8 %, respectively).

Locoregional Recurrence

During a median follow-up period of 7.1 years (range, 0–32.2 years), 14 patients had experienced a locoregional recurrence (LRR), of which 12 were local, 1 was locoregional (breast + ipsilateral axilla), and 1 was regional (ipsilateral axilla). The entire cohort had a 5-year cumulative LRR incidence of 11 % (95 % confidence interval [CI], 5–17 %) and a 10-year cumulative LRR incidence of 12 % (95 % CI, 6–19 %) (Fig. 1A), with a similar 10-year LRR incidence between the patients with borderline (11 %) and those with malignant (13 %) PTs ($p = 0.87$, log-rank) (Fig. 1B).

Of 14 LRRs, 13 developed within 6 years, with the final LRR occurring nearly 14 years after surgery. In the univariable analysis, the factors associated with a higher incidence of LRR included age younger than 40 years (10-year cumulative incidence of 21 % [$n < 40$] vs 7 % [$n \geq 40$]; $p = 0.02$, log-rank) and close or positive margins (10-year cumulative incidence: 33 % [close /positive] vs 9 % [negative], $p = 0.001$, log-rank). Age was not significantly associated with type of surgery ($p = 0.26$) or margin status ($p = 0.26$). Individual histologic characteristics were not associated with LRR (Table 2). Overall, BCS demonstrated a higher 10-year cumulative incidence of LRR (16 %) than mastectomy (8 %), but this difference was not statistically significant ($p = 0.11$, log-rank) (Table 2). Among those with a negative final margin, the 10-year cumulative incidence of LRR was 12 % with BCS versus 6 % with mastectomy ($p = 0.17$, log-rank).

Distant Metastasis and Survival

Of the 124 patients, 7 experienced distant disease, 6 within 5 years of surgery. Two of the seven distant recurrences (DRs) were preceded by an LR. The distant metastatic sites included lung, brain, bone, epidural space, and direct local extension to the parasternal region/mediastinum. Overall, the 5-year DRFS was 95 % (95 % CI, 91–99 %) and the 10-year DRFS was 94 % (95 % CI, 89–98 %) (Fig. 2). No DR was observed in the patients who had borderline histology, with DR occurring only in patients whose tumors had uniformly poor pathologic features, including marked stromal cellularity, stromal overgrowth, infiltrative borders, and 10 or more mitoses per 10 hpf. These features were identified in only 25 (29 %) of 86 malignant PTs overall. None of the patients without uniformly poor pathologic features (100 patients altogether and 66 patients with complete data) experienced distant disease.

Six of the seven patients with distant disease died of their disease a median of 10 months (range, 1–17 months) after diagnosis of metastasis. For the entire cohort, the 10-year DSS was 94 % (95 % CI, 90–99 %), and the 10-year OS was 90 % (95 % CI, 83–96 %). For the patients without uniformly poor pathologic features, the 10-year DSS and OS were 100 % and 94 % (95 % CI, 87–100 %), respectively, compared with 66 % (95 % CI, 45–97 %) and 57 % (95 % CI, 37–88 %), respectively, for the patients with uniformly poor features (Fig. 3).

DISCUSSION

Given the rarity of malignant and borderline PTs, it often is difficult to counsel patients about appropriate surgical management and prognosis after surgical excision, and the long-term incidences of local and distant relapse remain uncertain. Our study aimed to evaluate a large cohort of patients with malignant or borderline PT from a single institution to understand the incidences and patterns of LR and DR better, and to identify reproducible factors associated with recurrence.

Overall, the 10-year incidence of LRR was approximately 12 % and did not vary between tumors classified as borderline or malignant, suggesting that individual histologic characteristics were not important predictors of local failure. However, LRR incidence was significantly higher for the patients younger than 40 years and for those with close or positive final surgical margins. Due to the small number of local failures, multivariable analysis could not be performed. However, we found no association between age and either surgery type or margin status, suggesting that these factors are not potential confounders of the association between age and LRR.

In a study of 192 patients with PT, Wei et al.¹⁷ similarly demonstrated a threefold increase in LRR among patients with a diagnosis before the age of 35 years compared with older patients, although this has not been reported in other studies.^{18–20} Given the small number of patients in our study younger than 40 years ($n = 42$), we do not suggest that these patients warrant more aggressive surgical management other than obtaining negative surgical margins. However, patients younger than 40 years should undergo continued surveillance with annual breast imaging as recommended for women age 40 years or older, to monitor for LR. Similar to our study, several other studies have demonstrated that close or positive margins are associated with an increased risk of LR among patients with PTs.^{10,13,19,21} Consequently, the National Comprehensive Cancer Network (NCCN) guidelines recommend excision of PT with a margin of 1 cm or wider³ to minimize the risk of LR. Although our study also demonstrated an increased risk of LR with close (defined as <1 mm) or positive margins, the ideal negative margin width after excision of PT has yet to be defined.

Among patients with benign PT, the 1-cm margin recommendation has been challenged, with several recent studies demonstrating similar rates of LR with narrow versus wider margins.^{15,22,23} However, these data cannot be extrapolated to malignant and borderline PT. Based on our data, at minimum, a margin of at least 1 mm after BCS or mastectomy was associated with a significantly lower 10-year risk of LR (9 %) than a margin smaller than 1 mm or a positive margin (33 %) ($p = 0.001$), a finding also observed in a recent multicenter Korean study of malignant and borderline PT.¹⁹ Efforts should be made to achieve a margin of at least a 1 mm when feasible to minimize the risk of LR.

We also found no significant reduction in LR with mastectomy, which potentially has the widest negative margin that can be obtained, compared with BCS, for patients with malignant or borderline PT. Although the 10-year incidence of LR was numerically higher for the patients undergoing margin-negative BCS than for those undergoing mastectomy (12 % vs 6 %; $p = 0.17$, log-rank), the rates of LR were acceptably low with either treatment.

These findings suggest that even among patients with malignant or borderline PT, BCS is an appropriate treatment option provided that negative margins can be achieved with an acceptable cosmetic outcome.

Most of our patients did not receive adjuvant radiotherapy, so we were unable to draw definitive conclusions regarding this treatment. However, given the low rates of LR observed in our study among the patients with negative margins after BCS and mastectomy without radiotherapy, it is unlikely that adjuvant radiotherapy would provide additional meaningful benefit for these patients, which accords with observations from other studies.^{2,5}

Overall, we found a low rate of DR for patients with malignant or borderline PT (10-year DRFS, 94 %). However, unlike local failures, which were not influenced by histologic features, all DRs occurred in patients with malignant PT whose tumors had uniformly poor pathologic features including marked stromal cellularity, stromal overgrowth, infiltrative borders, and 10 or more mitoses per 10 hpf. The majority (80 %) of the patients with malignant or borderline PT did not have uniformly poor histologic features, and those patients had a 10-year DSS of 100 % and an OS of 94 %, suggesting that surgery alone results in a negligible risk of distant failure for this subset.

The presence of uniformly poor pathologic features was seen in 29 % of the patients who had malignant PT and predicted a poor prognosis, with a 10-year DSS of 63 % and a 10-year OS of 57 %. Additionally, the development of distant metastasis led to death for six of seven patients at a median of 5 months after diagnosis of distant disease. The difference in prognosis observed between patients with and without uniformly poor features suggests that the current classification system may be inadequate for prognostication. Consideration should be given to creation of a new classification system whereby only tumors with uniformly poor features are considered “malignant” given their significant metastatic potential, and those lacking these features can be reclassified into a different “nonmalignant” category.

Although the presence of uniformly poor pathologic features can be used to identify patients at high risk for distant failure, no systemic therapy regimen currently is known to improve the outcome for patients with malignant PT. Further study of these patients on a molecular level is needed to potentially identify unique genetic alterations that could be targeted with novel therapies in the future.

Our study was limited by its retrospective nature and small sample size, which was largely related to the rarity of malignant and/borderline PT in the population. Additionally, we included patients with borderline histology in our study cohort due to the histologic similarities between borderline and malignant PT and differences in grading schemes during the long study period. Although the LRR rates between borderline and malignant PT were similar, DR occurred only in malignant PT with uniformly poor features. However, DR was not observed in patients with malignant/borderline PT who did not have uniformly poor features, arguing that the presence of multiple poor features is more important in determining prognosis than the histologic designation. Margin width was dichotomized in

our study as less than 1 mm (close) or a 1 mm or wider (negative), and, as a result, the relationship between local recurrence and margin width could not be examined.

Finally, only about one third of slides were available for re-review by a breast pathologist. Because histologic definitions for PT have changed over time, re-review of additional slides may have resulted in a revised histologic diagnosis for a proportion of cases, which could have had an impact on the study findings.

CONCLUSIONS

Overall, patients with malignant/borderline PT have a low LRR rate after surgical excision without adjuvant therapy, with similar rates observed for patients with borderline and malignant histologies. Higher rates were observed for patients younger than 40 years and those with close or positive margins. Young age does not mandate mastectomy for patients with malignant or borderline PT. However, young women should be monitored closely for recurrence after excision with annual breast imaging. Efforts should be made to achieve negative margins for all patients after surgery for malignant or borderline PT to minimize the risk of local failure. The ideal negative margin width has yet to be defined but should be at least 1 mm. In this study, distant recurrence was rare and occurred only in patients with uniformly poor pathologic features, such as marked stromal cellularity, stromal overgrowth, infiltrative borders, and 10 or more mitosis per 10 hpf. Malignant or borderline PTs without multiple poor histologic features have an excellent prognosis after surgical resection, with a 10-year DSS of 100 %. Uniformly poor pathologic features predict poor prognosis and represent a group of patients who require further study and novel treatment strategies.

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SYNOPSIS This study evaluated recurrence rates for malignant and borderline phyllodes tumors and identified factors associated with local and distant failure. Age younger than 40 years and positive margins were associated with an increased local failure risk, whereas the presence of multiple poor histologic features predicted distant failure.

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FIG. 1.

Cumulative incidence of locoregional recurrence (**A**) for all patients and (**B**) for those stratified by malignant versus borderline histology.

FIG. 2.
Distant recurrence-free survival for the entire cohort.

FIG. 3.
(A) Disease-specific survival and (B) overall survival by pathologic features.

TABLE 1

Clinicopathologic characteristics of the study cohort stratified by histology

Characteristic	Total (<i>n</i> = 125) <i>n</i> (%)	Malignant (<i>n</i> = 86) <i>n</i> (%)	Borderline (<i>n</i> = 39) <i>n</i> (%)	<i>p</i> Value
Median age: years (range)	44 (13–83)	43 (13–83)	44 (14–77)	0.8
Median pathologic tumor size: cm (range)	5 (0.9–35)	5.3 (0.9–35)	3 (0.9–22)	<0.001
Stromal cellularity ^a				<0.001
Mild/moderate	37 (30)	16 (19)	21 (54)	
Marked	70 (56)	55 (64)	15 (39)	
Stromal overgrowth ^a				0.001
No	58 (46)	31 (36)	27 (69)	
Yes	45 (36)	38 (44)	7 (18)	
Borders ^a				0.006
Circumscribed/pushing	43 (34)	23 (27)	20 (51)	
Infiltrative	68 (54)	54 (63)	14 (36)	
Mitosis ^a				< 0.001
<10	53 (42)	24 (28)	29 (74)	
10	48 (38)	44 (51)	4 (10)	
Necrosis ^a				0.03
No	93 (74)	58 (67)	35 (90)	
Yes	19 (15)	17 (20)	2 (5)	
Uniformly poor pathologic features ^a				<0.001
No	67 (54)	38 (44)	29 (74)	
Yes	25 (20)	25 (29)	0 (0)	
Surgery				0.003
Breast-conserving surgery	71 (57)	41 (48)	30 (77)	
Mastectomy	54 (43)	45 (52)	9 (23)	
Final margin				0.09
Negative	109 (87)	78 (91)	31 (79)	
Close/positive	16 (13)	8 (9)	8 (21)	

^aUnknown, stromal cellularity (*n* = 18), stromal overgrowth (*n* = 22), borders (*n* = 14), mitosis (*n* = 24), necrosis (*n* = 13), uniformly poor pathologic features (*n* = 33)

TABLE 2

Factors associated with locoregional recurrence

Characteristic	10-Year LRR cumulative incidence % (95 % CI)	HR (95 % CI)	<i>p</i> Value
Age (years)			0.02
<40	21 (7–33)	1.00	
40	7 (1–13)	0.3 (0.1–0.89)	
Histology			0.87
Borderline	11 (0–21)	1.00	
Malignant	13 (5–21)	0.91 (0.31–2.72)	
Stromal cellularity			0.25
Mild/moderate	8(0–17)	1.00	
Marked	17 (6–26)	2.11 (0.58–7.67)	
Stromal overgrowth			0.79
No	11 (2–19)	1.00	
Yes	13 (0–24)	0.84 (0.25–2.9)	
Borders			0.55
Circumscribed/pushing	15 (3–26)	1.00	
Infiltrative	13 (3–22)	0.73 (0.26–2.08)	
Mitosis			0.93
<0	12 (3–21)	1.00	
10	15 (1–27)	1.06 (0.33 – 3.35)	
Necrosis			0.47
No	12 (5–19)	1.00	
Yes	32 (0–62)	1.75 (0.38–8.13)	
Surgery			0.11
Breast-conserving surgery	16 (6–24)	1.00	
Mastectomy	8 (0–16)	0.37 (0.1–1.31)	
Final margin			0.001
Negative	9 (3–15)	1.00	
Close/positive	33 (5–53)	4.97 (1.66–14.88)	

LRR, locoregional recurrence; CI, confidence interval; HR, hazard ratio