Predictive Factors of Early Recurrence in Patients with Phyllodes Tumor of the Breast

 Bharadhwaj Ravindhran, Sendhil Rajan

Clinic of General Surgery, St. John's Medical College Hospital, Bangalore, Karnataka, India

ABSTRACT

Objective: Phyllodes tumor (PT) is a rare entity accounting for 1% of breast neoplasms with a high propensity of recurrence. This study aimed to identify factors that are predictive of early recurrence in patients with PT.

Materials and Methods: This study reviewed clinical data of patients with PT (n=57) treated at our tertiary care referral center in South India between February 2010 and December 2019. The Pearson χ^2 test was used to investigate the relationship between patient's clinical features and tumor histotypes. Survival curves were obtained using the Kaplan-Meier method based on the log-rank test. Multivariate Cox regression analyses were performed to identify predictors of early recurrence or local recurrence-free-interval (LRFI).

Results: The mean age was 38.3 [standard deviation (SD)=13.6] years, and the mean follow-up was 18 (SD=13.5) months. The median tumor size was 5 cm (interquartile range 3 and range: 3–22 cm). Moreover, 64.9% (n=37) of the tumors were benign, 21.1% (n=12) were borderline, and 14% (n=8) were malignant. Of the 57 patients, 17 (29.8%) developed local recurrence and one developed distant metastasis. Of the 17 patients, three were unwilling to undergo completion surgery. The median LRFI was 20 (range: 7–60) months. Multivariate cox regression analyses showed that mitotic rate >10/high power field [hazard ratio (HR) 0.147; p=0.04], stromal overgrowth (HR: 4.904; p=0.05), margin status (HR: 0.037; p<0.001), and preoperative neutrophil-to-lymphocyte ratio [(NLR), HR: 4.891; p=0.04)] were significant predictors of LRFI.

Conclusion: A high mitotic rate, positive margin, stromal overgrowth, and NLR >3.5 were associated with early recurrence. These attributes mandate stringent follow-up, especially in a resource-limited setting.

Keywords: Aftercare, local neoplasm recurrence, phyllodes tumor

Introduction

Phyllodes tumor (PT) is a rare neoplasm that accounts for only 1% of all breast neoplasms in women (1, 2). The World Health Organization (WHO) Classification of Tumors of the Breast distinguishes three histological subtypes of PTs: benign, borderline, and malignant (3). The biological behavior, clinical course, and recurrence rates of the three subtypes of PT vary widely among different reports (4-6). Most studies have investigated different cohorts of patients with various prognostic factors which could possibly predict the aforementioned outcomes (7-10).

Close follow-up of patients, especially those with tumors such as PT which have a high recurrence rate, is critical for optimal outcomes (11). However, in low- and middle-income countries (LMIC), follow-up of patients is poor because of many reasons. Therefore, identification of patients who are at a higher risk of early recurrence may help in decreasing morbidities associated with PT. Therefore, this study aimed to investigate possible predictive factors that may influence early recurrence or local recurrence-free interval (LRFI) in PT.

Materials and Methods

Patient Selection

This historical cohort study included all patients diagnosed with PT at our tertiary care referral center between February 2010 and December 2019 with complete clinicopathological data and follow-up records. All factors including age, tumor size, pathological parameters (e.g., stromal hypercellularity, mitosis, stromal atypia, stromal overgrowth, borders, necrosis, hemorrhage, epithelial hyperplasia, presence of giant cell tumors, and pathologic mitosis), histotype, local recurrence sites, and distant metastasis sites were recorded.

Corresponding Author:
Sendhil Rajan; sendhil1986@gmail.com

The surgical approaches were classified into excision, wide local excision (WLE), mastectomy, and mastectomy with axillary clearance. Excision [performed for apparently benign findings, based on investigations such as fine-needle aspiration cytology (FNAC) and/or ultrasonography] refers to enucleation or removal of the tumor, with margins of <1 cm; WLE means that the entire tumor was completely dissected with the intention of taking a rim of breast tissue using the no-see technique, with clear margins of at least ≥1 cm. The histopathological diagnoses of all cases were assessed based on established histological criteria defined by the WHO Classification of Tumors of the Breast in 2012 (3). The margin status was determined as follows: a positive margin was defined as the presence of tumor cells at the surgical margin, a close margin was defined as the presence of tumor cells <1 cm from the closest surgical margin, and a clear margin was defined as the presence of tumor cells >1 cm from the closest surgical margin. LRFI was defined as the period from the date of surgery to the date of diagnosis of local recurrence.

Approval of the institutional ethics review board of our institution was taken along with a waiver of consent due to the retrospective study design.

Based on previous studies (12-14) and their recommendation for axillary clearance in clinically detected lymph nodes in PT (7, 15), we decided to perform lymph node dissection in all patients with borderline/malignant disease and palpable lymph nodes.

Protocol for Patients who Developed Recurrence

Completion mastectomy was performed in patients who underwent WLE. In patients who underwent mastectomy, chest wall excision with margins >1 cm was also performed. These patients also underwent reconstruction if required. Patients with aggressive tumors on histopathology were treated with radiation therapy based on the discussion with the multidisciplinary tumor board.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 16.0 software (SPSS Inc., Chicago, IL, USA). The Pearson χ^2 test was used to investigate the relationship between categorical variables. Survival curves were obtained using the Kaplan-Meier method based on the log-rank test. Univariate and multivariate cox regression analyses were performed to identify variables that were predictive of LRFI, and $p < 0.05$ was considered significant.

Results

The mean age of the cohort was 38.3 [standard deviation (SD): 13.6, range: 13–67] years, and the mean follow-up duration was 18 (SD=13.5) months. The median tumor size was 5 cm [interquartile range (IQR 3), range: 3–22 cm]. Moreover, 64.9% (n=37) of the tumors were benign, 21.1% (n=12) were borderline, and 14% (n=8) were malignant. Of the 57 patients, 42.1% (n=24) underwent WLE, 26.3% (n=15) (who had benign findings on FNAC) underwent excision, and 31.6% (n=18) underwent mastectomy.

Key Points

- PT is associated with a high rate of recurrence, and identification of patients who are at a higher risk of developing early recurrence could help in decreasing morbidities associated with PT.

- Our historical cohort analysis of a series of large PTs show that mitotic rate >10/high power field (hpf) [hazard ratio (HR): 0.147; p=0.04], stromal overgrowth (HR: 4.904; p=0.05), margin status (HR: 0.037; p<0.001), and preoperative NLR (HR: 4.891; p=0.04) were significant predictors of early recurrence.

- Identification of these factors and stringent follow-up could help in early identification of recurrence, especially in a resource-limited setting such as in our center where patient compliance to regular follow-up is still a problem.

Of the 57 patients, 17 (29.8%) developed local recurrence. More than half (9/17) of the patients who had a recurrence had FNAC findings suggestive of fibroadenoma or benign disease. One patient with local recurrence also developed distant metastasis. No significant differences were found between the groups with respect to the age at diagnosis or laterality between the groups. Of the 17 patients, three were unwilling to undergo completion surgery. In patients who developed local recurrence, the median age at diagnosis of the primary tumor was 42 (IQR 21) years, the median duration prior to presentation was 134 (IQR 309) days, and the median size of the primary tumor was 7 (range: 3–22) cm. Moreover, 41% (n=7) of recurrent tumors were benign, 29.4% (n=5) were borderline, and 29.4% (n=5) were malignant. The median LRFI was 20 (range: 7–60) months (Table 1). Multivariate Cox regression analyses showed that mitotic rate >10/hpf (HR: 0.147; p=0.04), stromal overgrowth (HR: 4.904; p=0.05), margin status (HR: 0.037; p<0.001), and preoperative NLR (HR: 4.891; p=0.04) were significant predictors of LRFI (Table 2). Survival curves are shown in Figure 1.

Discussion and Conclusion

Previous reports have shown that the local recurrence rates of PTs ranged from 12% to 32% (average ~15%). In this study, the recurrence rate at our center is almost twice the average (6, 8, 9, 16, 17). This finding may be attributable to the larger tumor size at presentation, longer duration of lump, and aggressive tumor biology. In this study, more than one-fourth of the patients had a preoperative benign FNAC, thus influencing not only the type of surgery (excision vs WLE), but also the extent of surgical margin. In our cohort, the local recurrence rates were 18.9% (n=7), 41.6% (n=5), and 62.5% (n=5) for the benign, borderline, and malignant subtypes, respectively.

According to a multivariate cox regression analysis, the predictive factors for LRFI were high mitotic rate, stromal overgrowth, NLR >3.5, and margin status. The HR of 4.90 for stromal overgrowth was the highest among the four factors closely followed by NLR >3.5 (HR=4.89). It appears that the stromal component significantly affects the recurrence and LRFI in PTs. The margin status, which is an indicator of adequate surgical clearance (HR=3.79), was also an important factor for LRFI.

To our knowledge, this study is one of the first to investigate the LRFI in PT and could possibly help in recognizing patients at a higher risk of developing early recurrence following surgery for PT. Patients with the above risk factors could be followed up closely. Patients with an aggressive tumor type with close or positive margins should undergo

Table 1. Comparison of attributes between patients with or without tumor recurrence

Feature	Patients without recurrence (n=40)	Patients with recurrence (n=17)	p
Age at diagnosis			
Median (IQR)	34.5 (17.5)	42 (21.5)	0.16
Duration of lump, median (IQR)	40 (65.5)	134 (309)	0.01
Left breast	24 (60%)	9 (52.9%)	0.77
Right breast	16 (40%)	7 (47.1%)	
Tumor size-Largest dimension (cm), mean ± SD	5.15±2.12	8.6±5.5	0.008
Benign	30 (75%)	7 (41.2%)	
Borderline	7 (17.5%)	5 (29.4%)	0.03
Malignant	3 (7.5%)	5 (29.4%)	
Lumpectomy	14 (35%)	1 (5.9%)	
Wide local excision	18 (45%)	6 (35.2%)	0.005
Mastectomy	4 (10%)	7 (41.2%)	
Mastectomy with axillary clearance	4 (10%)	3 (17.6%)	
Clear margin	29 (72.5%)	2 (11.8%)	
Close margin	8 (20%)	5 (29.4%)	<0.001
Positive margin	3 (7.5%)	10 (58.8%)	
NLR >3.5	27 (67.5%)	6 (37.3%)	0.04
NLR <3.5	13 (32.5%)	11 (64.7%)	
Stromal overgrowth			
Minimal	7 (17.5%)	2 (11.8%)	
Moderate	24 (60%)	9 (52.9)	0.5
Marked	9 (22.5%)	6 (35.3%)	
Mitotic figures/Hpf			
0–4	29 (72.5%)	5 (29.4%)	
5–9	6 (15%)	7 (41.2%)	0.01
>10	5 (12.5%)	5 (29.4%)	

Hpf: High power field; NLR: Neutrophil-to-lymphocyte ratio; IQR: Interquartile range; SD: Standard deviation; n: Number

completion surgery at the earliest, which could reduce the morbidity associated with PT.

Study limitations include a retrospective study design and associated inherent bias. Many of our patients were diagnosed to have fibroadenomas on FNAC, which was later proven to be PT. This could be the reason for a high recurrence rate in patients with a benign PT in our series. A preoperative diagnosis of fibroadenoma or a missed diagnosis of PT probably resulted in an inadequate surgical margin. Prospective validation of these data with a core-biopsy proven diagnosis of PT is necessary to confirm the efficacy of these parameters as predictors of early recurrence.

In summary, we found that stromal overgrowth, high mitotic rate, NLR >3.5 and margin status are associated with a shorter LRFI and therefore may predict earlier recurrence. The identification of these risk factors in patients with PT followed by close follow-up are critical for early recognition of local recurrence which may help improve the overall outcome, especially in an LMIC setting.
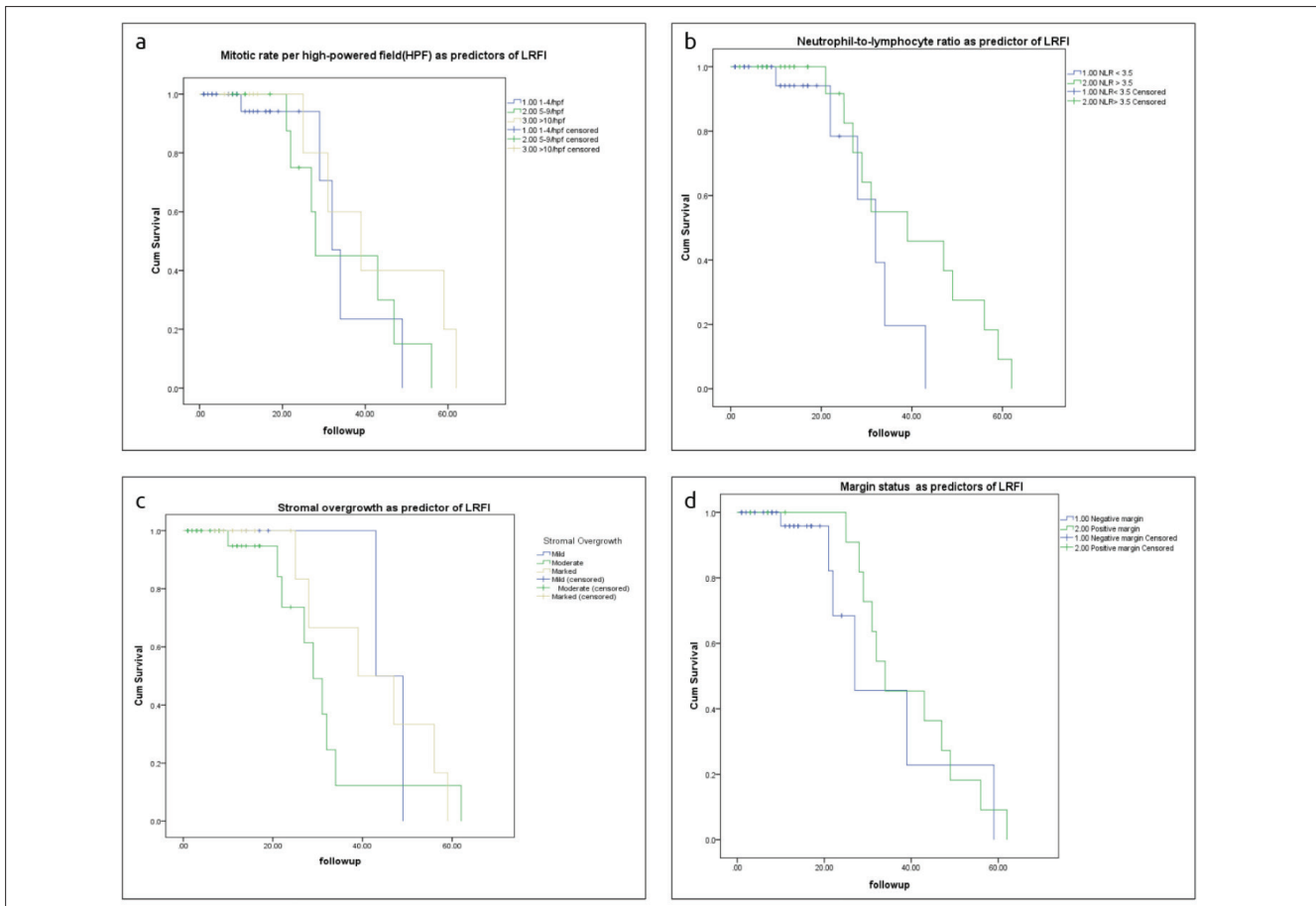
Figure 1. a-d. Local recurrence-free interval survival curves stratified by margin status, high mitotic rate, neutrophil-to-lymphocyte ratio >3.5, and stromal over growth

LRFI: Local recurrence-free interval; HPF: High-powered field; NLF: Neutrophil-to-lymphocyte; Cum: Cummulative

Table 2. Cox regression analysis of variables as predictors of local recurrence-free interval

Factor	Sig.	Exp (B)	95.0% CI for Exp (B)	
			Lower	Upper
Mitotic figures per high power field	0.038	1.475	0.8	2.736
Stromal overgrowth	0.047	4.904	1.023	23.509
Nuclear atypia	0.537	0.441	0.033	5.939
Cellular atypia	0.471	0.528	0.093	3.000
Close/positive margin	<0.001	3.796	0.8	5.179
Neutrophil-to-lymphocyte ratio >3.5	0.045	4.891	1.034	7.142
Platelet-to-lymphocyte ratio >190	0.761	0.791	0.174	3.591

CI: Confidence interval; Sig: Significance

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