

Phyllodes Tumor of the Breast: A Retrospective Study of Clinicopathological Factors Associated with Local Recurrence

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Abstract:

Background: Phyllodes tumors are uncommon breast neoplasms with diverse biological behavior and clinical presentations, leading to a potential for recurrence. However, the specific clinicopathological risk factors associated with local recurrence remain unclear. To address this gap, this study aimed to analyze the relationship between clinicopathological features and recurrence status in patients with breast phyllodes tumors.

Materials and Methods: This single Hospital-based, retrospective study was conducted on 113 histopathologically proven women with phyllodes tumors who were referred to our center, from January 2016 to December 2018. Clinical and pathological features, local and regional recurrence, distant metastasis, and overall survival were determined. SPSS 15.0 statistical software was used for analysis.

Results: The mean age of patients with phyllodes tumors (PTs) at diagnosis was 41.5 years (range: 24-69 years). Of these, 71 (68.1%) were 40 years old or younger, while 42 (34.5%) were older than 40. Tumor histology was benign in 24 (21.2%) patients, borderline in 27 (23.9%), and malignant in 62 (54.9%). We found a significant correlation between tumor size and tumor grade. The overall five-year recurrence-free survival rate was 65%. However, the five-year recurrence-free survival rates for benign, borderline, and malignant phyllodes tumors were 76%, 64%, and 60%, respectively. We found that both type of surgery and tumor size exceeding 10 cm significantly contributed to recurrence. Notably, patients who underwent lumpectomies had a higher recurrence rate than those who underwent mastectomies.

Conclusion: Wide local excision seems to be the initial procedure of choice for all PTs, and mastectomy for recurrent tumours. Further studies are needed to define the role of adjuvant therapies.

Keywords: Breast, Phyllodes tumors, clinicopathological factors, Recurrence.

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Introduction

Phyllodes tumors (PTs) are uncommon fibroepithelial breast lesions classified as benign, borderline, and malignant based on the degree of cellular atypia, stromal overgrowth, and mitotic activity. [1] Borderline and malignant tumors have a higher potential for local recurrence. [2] Although initially described in 1774, these tumors were first fully classified as "cystosarcoma phyllodes" by Johannes Muller in 1838. [3]

While fibroadenomas and phyllodes tumors (PTs) may not show obvious differences in clinical characteristics and mammograms, they arise from distinct origins. PTs develop in the breast stroma, which contains adipose tissue and ligaments surrounding ducts, lobules, blood, and lymphatic vessels, unlike breast carcinomas that originate within the ducts and lobules. Phyllodes tumors exhibit a characteristic leaf-like shape (phyllode) due to their composition of gelatinous solid and cystic areas with infarct and necrotic regions. While

the first case of metastasis for PTs was reported in the American Journal of Cancer by Lee and Pack in 1931, further studies revealed an additional difference: fibroadenomas exhibit polyclonality in both epithelial and stromal cells, whereas PTs display polyclonality only in epithelial cells and monoclonality in stromal cells. These findings suggest that fibroadenomas are hyperplastic lesions, not neoplasms, whereas PTs are indeed neoplasms arising from the breast stroma.

Phyllodes tumors (PTs) primarily affect women aged 35-55, with early recognition through clinical presentation being crucial for diagnosis. While most PTs appear benign and grow rapidly, they can reach massive sizes (40-50 cm) as reported in literature [8,9]. Despite relying on mammography, ultrasonography, MRI, and Doppler sonography, accurate diagnosis remains challenging due to limited specificity [6,7]. Fine needle aspiration (FNA) and core needle biopsy offer greater

confirmation, especially when encountering tumors with abundant cellular stroma and epithelial elements. The National Comprehensive Cancer Network (NCCN) guidelines recommend wide excision with a margin of at least 1 cm for effective PT management, as narrower margins increase the risk of local recurrence. Mastectomy is not unequivocally indicated. While adjuvant radiotherapy and chemotherapy demonstrate effectiveness in treating sarcomas [8-12], their role in PT treatment remains ambiguous. The rarity of phyllodes tumors, lack of patients and research about its pathology, clinical diagnostic tests and management methods, as well as the difficulty with differentiation between PTs and fibroadenomas, even after pictorial tests and FNA, necessitate additional research in order to obtain an agreement for diagnosis and therapeutic options for these tumors.

This study retrospectively analyzed clinicopathological features, diagnostic modalities, therapeutic interventions, and their associated outcomes to identify factors associated with recurrent phyllodes tumors (PTs) of the breast.

Materials and Methods

This single-institution, retrospective study analyzed all phyllodes tumors (PTs) of the breast treated at the Acharya Harihar Post Graduate Institute of Cancer, Cuttack (formerly known as Acharya Harihar Regional Cancer Centre), a tertiary cancer care center, between January 1, 2016, and December 31, 2018. Patient data, including demographics, clinical information, and pathological findings, were extracted from individual medical charts. Pathology

reports provided details on histological type and World Health Organization (WHO) tumor grade. Treatment modalities (surgery, radiotherapy, systemic therapy, combined-modality treatment, or observation) were also evaluated for each patient.

Five years follow up data were assessed. Disease-free survival was defined as the date of surgery until the time of any first locoregional or distant metastasis. Continuous variables were summarized as mean and range; categorical variables were summarized as *n* and percentage (%). The associations among the categorical data were examined using the Chi-square test. All tests were conducted at a two-sided significance level of 0.05, with no adjustments made for multiple comparisons.

Results

113 histopathologically proven phyllode tumor (PT) cases were encountered over a three-year period from January 2016 to December 2018. At diagnosis, the mean age of the PT cases was 41.5 years (range, 24-69 years). Among the patients, 71 (68.1%) were ≤40 years old, while 42 (34.5%) were >40 years old.

Among 113 patients, 24 (21.2%) had benign tumors, 27 (23.9%) had borderline tumors, and 62 (54.9%) had malignant tumors. We investigated the correlation between various clinical variables and tumor grade, finding a significant association between tumor size and grade. Fine needle aspiration data was available for 92% of the patients. The pathological analysis of these patients revealed 28% with fibroadenomas and 13% with phyllodes tumors. The remaining 75% of patients with FNA did not have phyllodes tumors (Table 1)

Table 1: Variables related to phyllodes tumors.

Clinical variables		Total (N=113)		Benign (N=24)		Borderline (N=27)		Malignant (N=62)		P value
		n	%	n	%	n	%	n	%	
Age	<20	0	0	0	0.0	0	0.0	0	0	0.1
	21-30	12	10.6	5	20.8	6	22.2	1	1.6	
	31-40	59	57.5	12	50.0	11	40.7	36	58.1	
	41-50	28	22.1	5	20.8	6	22.2	17	27.4	
	>50	14	12.4	2	8.3	4	14.8	8	12.9	
Tumor size	>5cm	78	71.7	10	41.7	24	88.9	44	71.0	0.001
	<5cm	35	31.0	14	58.3	3	11.1	18	29.0	
Tumor Location	Left	43	38.1	6	25.0	15	55.6	22	35.5	0.3
	Right	69	61.1	18	75.0	12	44.4	39	62.9	
	Both	1	0.9	0	0.0	0	0.0	1	1.6	
FNAC result	Fibroadenoma	32	28.3	12	50.0	12	44.4	8	12.9	0.001
	Fibrocystic disease	6	5.3	2	8.3	2	7.4	2	3.2	
	Phyllodes tumor	15	13.3	3	12.5	3	11.1	9	14.5	
	Positive for malignancy	21	18.6	0	0.0	0	0.0	21	33.9	
	suspicious for malignancy	26	23.0	2	8.3	8	29.6	16	25.8	
	No malignancy	2	1.8	2	8.3	0	0.0	0	0.0	
	Inadequate	1	0.9	1	4.2	0	0.0	0	0.0	

	Missed data	10	8.8	2	8.3	2	7.4	6	9.7	
Surgical methods	Lumpectomy	34	30.1	18	75.0	12	44.4	4	6.5	0.001
	Wide local excision	38	33.6	4	16.7	12	44.4	22	35.5	
	Mastectomy	41	36.3	2	8.3	3	11.1	36	58.1	
Adjuvant therapy	Yes	13	11.5	0	0.0	0	0.0	13	21.0	0.02
	No	58	51.3	16	66.7	14	51.9	28	45.2	
	Missed data	42	37.2	8	33.3	13	48.1	21	33.9	
Recurrence	Yes	25	22.1	4	16.7	5	18.5	16	25.8	0.5
	No	47	41.6	13	54.2	9	33.3	25	40.3	
	Unknown	41	36.3	7	29.2	13	48.1	21	33.9	
Local Recurrence	Yes	19	16.8	4	16.7	5	18.5	10	16.1	0.6
	No	53	46.9	13	54.2	9	33.3	31	50.0	
	Unknown	41	36.3	7	29.2	13	48.1	21	33.9	
Distance metastasis	Yes	6	5.3	0	0.0	0	0.0	6	9.7	0.4
	No	66	58.4	17	70.8	14	51.9	35	56.5	
	Unknown	41	36.3	7	29.2	13	48.1	21	33.9	

All patients in our study received surgery as their primary treatment. Table 1 shows that 72 patients (63.71%) underwent breast-conserving surgery, including 34 (30%) who had lumpectomy and 38 (33.9%) who had wide excision. Mastectomy was performed on the remaining 41 patients (36%). Adjuvant therapy was administered to 13 patients (11.5%).

Five-year follow-up data (from surgery date to December 2018) were extracted for 72 of the 113

included cases, with 25 experiencing recurrence and 47 experiencing no recurrence. The overall five-year recurrence-free survival rate was 65%. However, for benign, borderline, and malignant phyllodes tumors, the five-year recurrence-free survival rates were 76%, 64%, and 60%, respectively. We compared the different clinical variable with recurrence status (Table 2). The association between surgical procedures and recurrence was found to be statistically significant (P=0.02)

Table 2: Relationship between different clinicopathological factors and local recurrence of phylloid tumors.

Clinical variables		Recurrence Status(N=72)				P value
		Yes (N=25)		No (N=47)		
		n	%	n	%	
Age	≤40	11	44	28	59.6	0.6
	>40	14	56	19	40.4	
Site	Left	10	40	14	29.8	0.3
	Right	15	60	33	70.2	
Tumor size	>10 cm	16	64	17	36.2	0.02
	<10 cm	9	36	30	63.8	
Tumor grade	Benign	4	16	13	27.7	0.5
	Borderline	5	20	9	19.1	
	Malignant	16	64	25	53.2	
Surgery	Lumpectomy	14	56	12	25.5	0.02
	WLE	7	28	13	27.7	
	Mastectomy	4	16	22	46.8	
Surgical margin	Positive	13	52	26	55.3	0.7
	Negative	12	48	21	44.7	
Borders	Circumscribed/pushing	8	32	24	51.1	0.1
	Infiltrative	17	68	23	48.9	
Intra-tumoral necrosis	Yes	10	40	13	27.7	0.2
	No	15	60	34	72.3	
Adjuvant therapy	Yes	8	32	22	46.8	0.1
	No	17	68	25	53.2	

Discussion

We used the 2019 WHO criteria to classify phyllodes tumors (PTs) and found that most patients had malignant PTs, followed by borderline and

benign tumors. PTs can occur in all age groups, but the average age at presentation is 45 years old. The majority of cases (79.6%) were between 20 and 50 years old, with a peak incidence between 40 and 45 years. In a study by Mishra et al., women aged 35 to

55 were most affected. Sawalhi and Al-Shatti reported a mean age of 39.8 years.

Previous Indian studies reported benign lesions more commonly in younger patients (median age 34 years) compared to borderline and malignant cases, which tended to occur in a slightly older age group (median age 51 years) [15]. However, our study did not find a significant difference. Currently, no single clinical parameter can definitively differentiate the three PT categories, although tumor size may offer some insight. While the average tumor size is 5 cm, lesions up to 40 cm have been documented. The relationship between size and malignancy is debated, but rapid growth appears associated with malignant tumors [16]. In our series, 41% of patients had tumors larger than 10 cm, and 67% of these were malignant. Interestingly, our study found a higher prevalence of right-sided lesions compared to left-sided PTs, consistent with observations in other studies [15, 17, 18]. Among our 113 cases, only one instance of bilateral tumors was observed. Notably, Macdonald et al. [19] reported four cases of bilateral tumors in their study of 13 patients.

Clinically, patients in this series presented with a round, mobile, and painless breast mass, either primary or recurrent. No axillary lymph node metastasis was detected. This aligns with the typical presentation, as most patients show non-palpable axillary lymph nodes at diagnosis due to the primarily hematogenous metastatic spread of these tumors. The most common sites of metastasis, as reported in the literature [20], are the lungs, pleura, and bones, with axillary lymph node involvement occurring in only 2%.

In the current study, as in most others, fine-needle aspiration (FNA) had low sensitivity for diagnosing phyllodes tumors. Ramakant et al. [21] reported similar findings, stating that fine-needle aspiration cytology (FNAC) was not beneficial. In our series of patients with phyllodes tumors, only 13% could be correctly diagnosed as benign. FNA accuracy was higher for malignant phyllodes tumors compared to benign ones, mirroring the findings of Bandyopadhyay et al. [22], who reported that FNAC did not reliably differentiate fibroadenomas from phyllodes tumors.

Several studies reported varying rates of surgical approaches and lymph node involvement. Kim et al. [23] found primary excisions in 94.4% of patients, while Blanco et al. [24] and our study observed mastectomies in 6% and 37%, respectively. Lymph node involvement was rare, with none found in our study, one in Staren et al.'s [25] research, and single cases reported by Minkowitz et al. [26] and Muttarak et al. [27]. Macdonald et al. [19] found the highest rate at 1% (8/498 patients).

Spitaleri et al. [28], in a recent study of 83 articles and 5,530 patients, reported that local recurrence of

phyllodes tumors was independent of histology. Their finding, however, contrasts with our results. In this study, the local recurrence rate for benign, borderline, and malignant tumors was 23%, 35%, and 39%, respectively.

Previous studies reported a five-year disease-free survival rate of 90% for patients with benign tumors, compared to 69% for borderline and 61% for malignant phyllodes tumors [29]. In our study, the five-year recurrence-free survival rates for patients with benign, borderline, and malignant tumors were 76%, 64%, and 60%, respectively.

In our current study, larger tumor size (>10cm) and specific surgical procedures were significantly correlated with local recurrence. Previous studies have found that stromal overgrowth increases the probability of local recurrence by sevenfold, a margin <1cm increases the risk fivefold, and a tumor size >10cm increases the prevalence fourfold compared to smaller tumors [15]. Therefore, large breast lumps should be considered in the clinical differential diagnosis, and patients require long-term follow-up with education on breast self-examination (SBE) for early detection.

The extent of surgery for this disease remains controversial due to the tumor's rarity and the heterogeneity of management approaches across different centers. However, wide local excision (WLE) is currently recommended as the primary surgical procedure for all histological types of phyllodes tumors (PTs) due to their rarely multifocal nature. Mastectomy is indicated for larger (>10cm), malignant, or recurrent disease. Axillary lymphadenectomy is reserved for clinically suspicious cases only, as PT primarily metastasizes hematogenously and axillary involvement is infrequent (<10%). Breast reconstruction can be considered as an additional procedure alongside WLE or simple mastectomy, particularly in younger patients with PT [30].

Currently, radical mastectomy is no longer the primary treatment for phyllodes tumors (PT) due to their tendency to spread through the bloodstream (hematogenous dissemination). Therefore, removing lymph nodes (auxiliary lymph node dissection) isn't typically recommended.

For tumors without prior metastasis, localized removal of the tumor with a healthy margin (1-2 cm) is preferred to prevent recurrence. Unfortunately, there's no effective treatment available for PT with existing metastases.

To diagnose the type of PT before surgery, a core needle biopsy (tru-cut biopsy) is recommended for large breast lumps. While wide local excision is considered the best approach for benign and borderline PT, malignant PT may require a simple

mastectomy. Regardless of the treatment method, long-term follow-up is crucial for all PT cases [15].

Conclusion

Type of surgery and tumor size >10cm contributed significantly to the recurrence of PTs where patients who underwent only lumpectomies had a higher recurrence than patients who underwent mastectomies. WLE or even mastectomy should be conducted for borderline/malignant PTs with large mass.

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