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Indian Journal of Pathology and Oncology

Journal homepage: www.ijpo.co.in

Case Series

Borderline phyllodes tumor – A saga of recurrences and malignant transformation

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Abstract

Background: Phyllodes tumors (PTs) of the breast are rare fibroepithelial neoplasms with variable biological behaviour. While most cases are benign, some recur with increasing aggressiveness and histologic transformation. This study evaluates a case series of borderline phyllodes tumors from last 10 years records and their morphological evolution.

Materials and Methods: A retrospective cohort study was conducted on recurrent phyllodes tumors, which were initially diagnosed as either benign or borderline. The records of last 10 years were retrieved. Out of total number of 30 diagnosed phyllodes tumors, 5 were recurrent. Their slides were reviewed and morphological parameters were evaluated. The clinical demographic parameters, clinical parameters including interval between the first diagnosis and recurrence and surgical margins were also evaluated.

Results: Among these five cases, three showed transformation to sarcoma, over a period of 1-5years, one of them in first recurrence itself,another in second recurrence and third in third recurrence. One case has heterologous elements in form of well differentiated liposarcoma. With each recurrence, there was a progressive reduction in the epithelial component. One case remained borderline phyllodes even after three recurrences, and one of them transformed from benign to borderline Phyllodes tumors. In four out of five cases the stromal hypercellularity was seen in the first presentation. Extent of surgical margins had no bearing on recurrence; however infiltrative margins were seen in two cases, on initial presentation.

Conclusion: Phyllodes tumors may evolve into more aggressive histologic subtypes upon recurrence, often with diminishing epithelial elements. Early recognition of these changes is essential for prognosis and management planning with close follow ups.

Keywords: Phyllodes tumors, Tumor recurrence, Histological progression, Malignant transformation.

Received: 26-06-2025; **Accepted:** 20-09-2025; **Available Online**: 17-10-2025

1. Introduction

Phyllodes tumors (PTs) are uncommon fibroepithelial breast neoplasms accounting for less than 1% of all breast tumors.[1-5] They display a wide spectrum of biological behaviour, ranging from benign to frankly malignant forms. Although complete surgical excision is generally curative in benign PTs, a subset may recur and undergo histological progression, raising clinical and therapeutic challenges.

Recurrence is a well-documented feature of PTs and may be associated with increasing stromal cellularity, atypia, and loss of epithelial components.[3-6] Malignant transformation, though rare, has been reported, particularly in long-standing or recurrent cases.[4] In this study, we present five cases of PTs with longitudinal follow-up to assess patterns of recurrence and morphological evolution. Notably, five of the cases had shown recurrence in our series, and several demonstrated progression from benign or borderline PTs to malignant phyllodes. Although phyllodes tumors primarily undergo stromal (sarcomatous) transformationin 10–20% of PTs, epithelial malignancy within PTs is rare**,** occurring in less than 1% of all cases.[7,8]

This study underscores the importance of vigilant follow-up in patients with PTs and highlights the need for awareness of their potential for histologic transformation over time.

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https://doi.org/10.18231/j.ijpo.12006.1759139906

Careful evaluation of the surgical specimen is needed to study the surgical margins, stromal cellularity, stroma to epithelial component ratio, mitosis, necrosis and heterologous elements in case of malignant transformation.

2. Case Series (Table 1)

2.1. Case 1

A 46 year female presented with a mass in the scar of size 6x4cm. It was excised, sent for HPE section showed presence of hypercellular stroma, leaf like pattern, with infiltrative margins and was diagnosed as Borderline phyllodes. Her previous excision slides were reviewed which was characteristic of Benign Phyllodes with a clear margin all around.

2.2. Case 2

A 60 year old female presented with a lump in scar measuring 6x5cm, with features of borderline phyllodes. The tumor was locally infiltrative with margins varying from 0.1cm to 1 cm. Section of previous excision mass was consistent with borderline phyllodes. Patient was kept on follow up and after 2 years, she again presented with a scar recurrence. Sections showed proliferation of spindle cells in bundles and fascicles with moderate anisocytosis, mitosis 6-7/10 hpf and infiltrative borders. Epithelial elements were not identified. Tumor was vimentin positive, and SMA negative. Case was reported as sarcomatous transformation in phyllodes – Fibrosarcoma.

2.3. Case 3

A 35 year female first presented with lump of 6x6 cm. On HPE examination section shows hypercellular stroma & stromal overgrowth, bundle, with mild anisocytosis, and low mitotic activity and reported as borderline phyllodes. The patient was kept on follow up, it showed scar recurrence, on hpe examination showed similar features of Borderline phyllodes with pushing margins and reaching focally up to surgical margins. She again presented 3 years later, with similar histologic features.

2.4. Case 4

A 35 year female presented as scar recurrence with lump of 8x10 cm, on HPE, sections showed, bundles and fascicles of plump ovoid spindle cells with blunt tipped nucleus and mild to moderate anisocytosis. A few epithelial cyst were seen towards the periphery. Previous excision slides were reviewed which was consistent with Borderline Phyllodes. Tumor was CD 34 Negative, Desmin and SMA positive with high Ki 67 index. It was thus diagnosed as sarcomatous transformation of phyllodes tumor- Leiomyosarcoma.

2.5. Case 5

A 60 year female presented lump of 5x4.5 cm size, with pushing margins and showed presence of hypercellular stroma, moderate anisocytosis, low mitotic activity and focal epithelial component. It was diagnosed as Borderline phyllodes. Case was kept on follow up, showed recurrence after 4 years as scar recurrence with lump of 6x8 cm, on HPE examination section showed admixture of lipoblast with spindle cell proliferation, surrounding residual PTs. Tumor showed positivity for S100 MDM2 and with high Ki 67 index. It was thus diagnosed as sarcomatous transformation of phyllodes tumor - Liposarcoma.

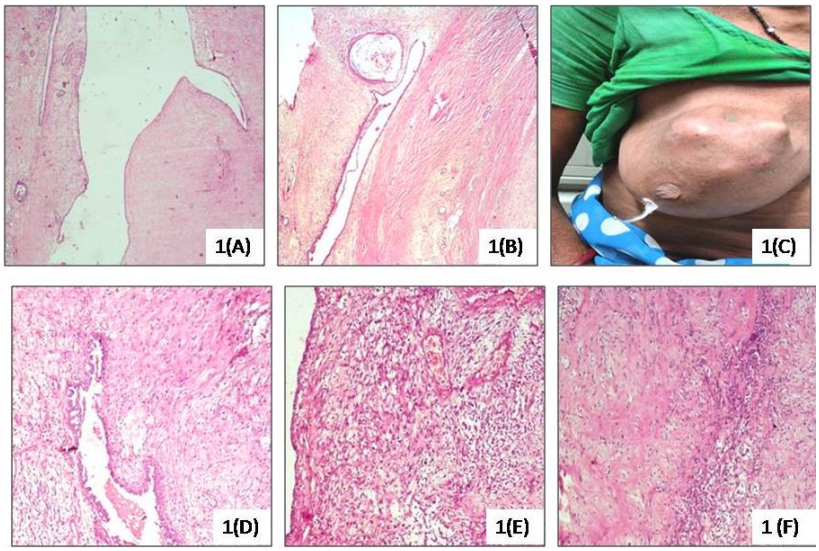

Figure 1: A): Leaf like pattern with surrounding stroma in the first presentation H&E X400, 1. **B):** Squamous lined cyst H&E X400, 1. **C):** Clinical photograph of recurrent lesion showing large multinodular swelling in the vicinity of the scar, 1. **D):** Shows areas of hypercellular stroma, H&E X400 1. **E):** Angiogenesis with anisocytosis frequent mitosis, H&E X400 1. **F):** Myxoid changes H&E X400

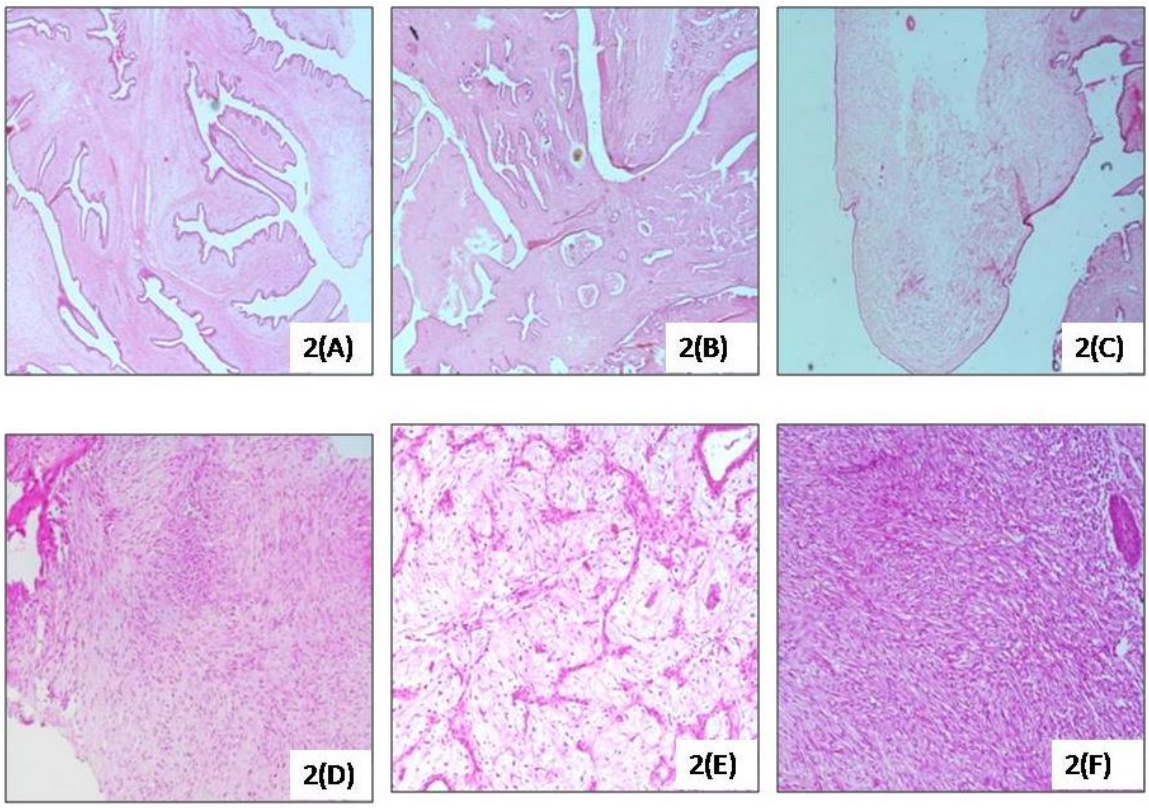

Figure 2: (A&B): First presentation exaggerated intracanalicular pattern, with cystically dilated gland, H&E X100. **C):** Second presentation, Leaf like pattern, H&E X100. **D,E&F):** Third presentation; showing stromal overgrowth & hypercellular stroma, H&E X100. **F):** Bundle & fascicles, mild to moderate anisocytosis, frequent mitosis. H&E X400

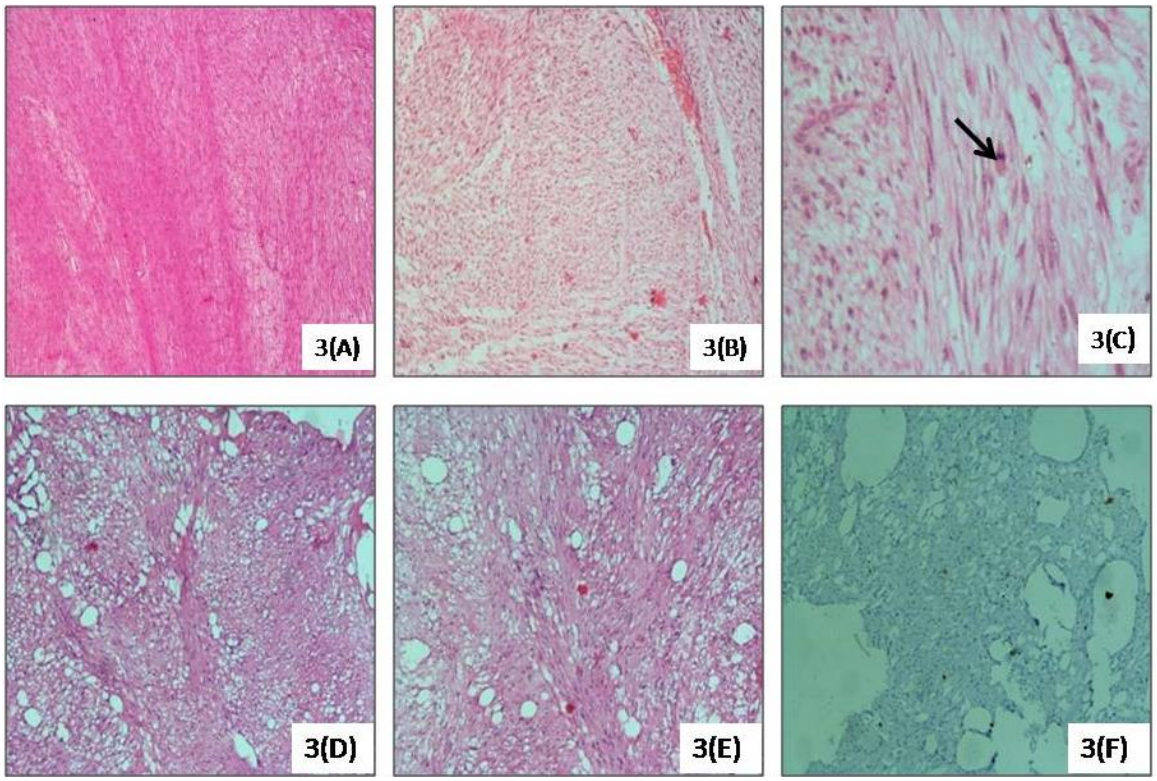

Figure 3: A): First presentation Stromal overgrowth H&E X100. **B):** Second presentation Hypercellular stroma & stromal overgrowth H&E X100. **C):** Bundle and fascicles, mild anisocytosis and mitosis low, (arrow) H&E X400. **D&E)**: Third presentation, Hypercellular stroma & stromal overgrowth H&E X100. **F):** Showing low Ki-67 X100

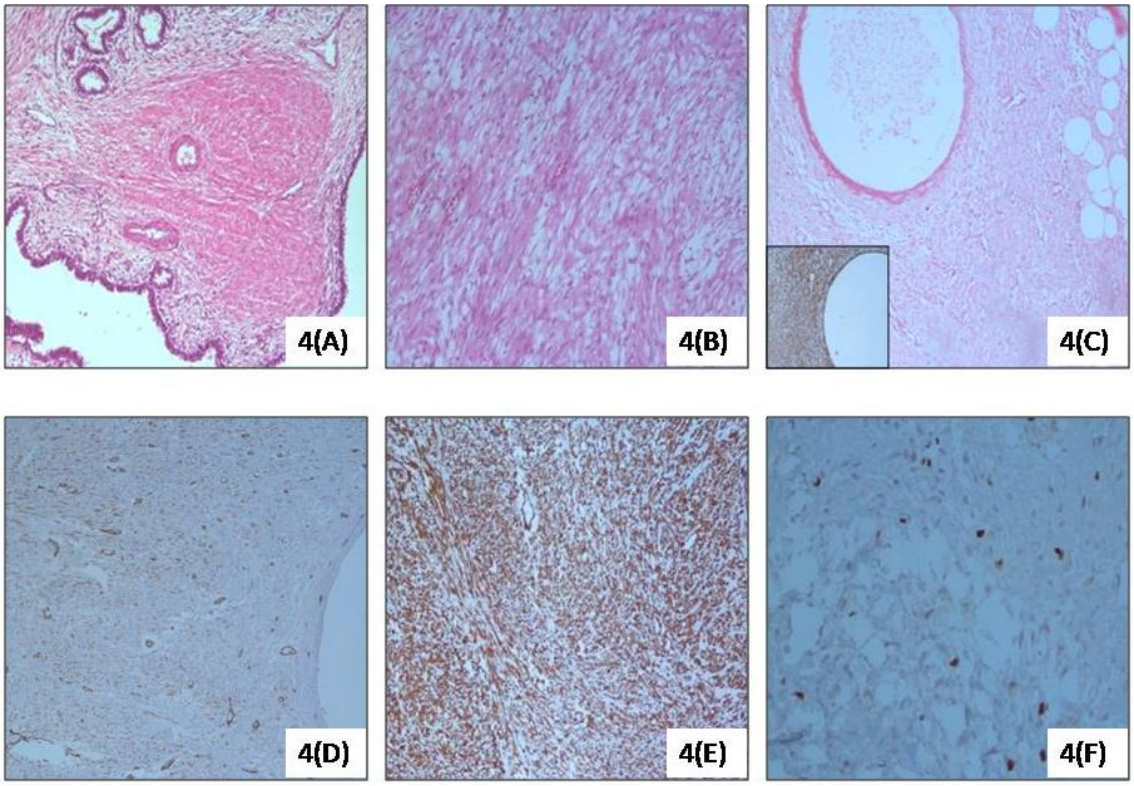

Figure 4: A): First presentation Leaf like pattern with surrounding stroma H&E X100. **B):** Second presentation showing hypercellular stroma & stromal overgrowth H&E X400. **C):** Plump ovoid stromal cells, with a residual cyst) H&E X400 & SMA in (inset). **D):** CD 34 negative stroma with internal control X100. **E):** CD 99 –Positivity X400. **F):** Ki-67 > 10% X400

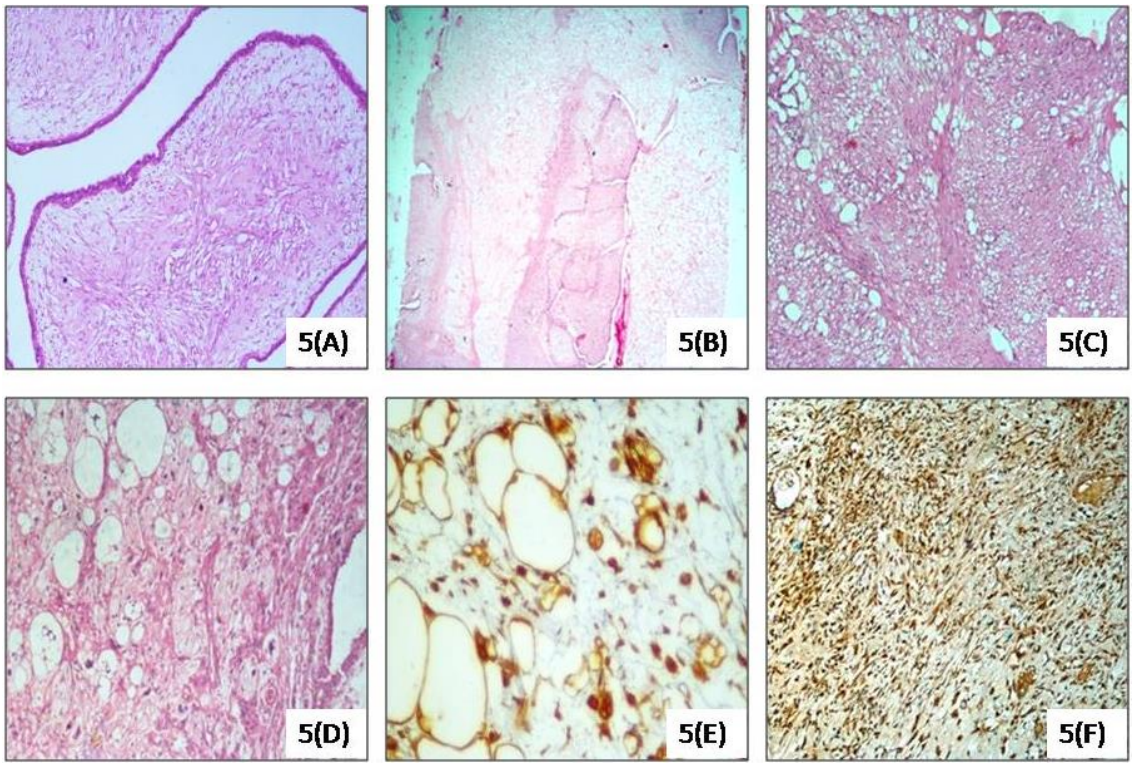

Figure 5: A): First presentaion leaf like pattern H&E X100. **B):** Second prsentation liposarcomatous area surrounding the residual phyllodes focus H&E X20. **C):** Admixture of lipoblast with spindle cell H&E X100. **D):** High power of same, H&E X400. **E):** S-100 Positivity X400. **F):** MDM2 positivity X400

Table 1: Case details

S. No	Age	Sex	Focality	Size	BIRADS	Recurrence	Recurrence interval	Stromal overgrowth	Stromal atypia	Leaf like pattern, staghorn pattern	Cystic change	Myxoid changes	Mitosis	Necrosis	Margins	Diagnosis
Case 1	46 year	Female	Unifocal	6x6 cm	4	Single		Heterogenous	Absent	Present	Squamous lined Present	Present	< 4/10 hpf	Absent	Pushing	Benign Phyllodes
				6x4 cm			After 1 year	Homogenous	Focal	Present	Present	Present	4-5/10 hpf	Absent	Infiltrative	Borderline Phyllodes
Case 2	60 year	Female	Unifocal	6x5 cm	4	Thrice		Focal	Absent	Present	Present	Absent	< 4/10 hpf	Absent	Pushing	Benign Phyllodes
				8x8 cm			After 1 year	Present	Present	Present	Absent	Absent	5-6/10 hpf	Absent	Infiltrative	Borderline Phyllodes
				10x10 cm			After 2 year	Marked	Present	Absent	Absent	Absent	6-7/10 hpf	Present	Infiltrative	Sarcoma
Case 3	35 year	Female	Bifocal Skin ulceration	6x6 cm	3	Thrice	After 1 year	Present	Focal	Present	Absent	Absent	5-6/10 hpf	Absent	Pushing with focally infiltrative	Borderline Phyllodes
				10x8 cm			After 2 year	Marked	Present	Present	Absent	Absent	5-6/10 hpf	Absent	Pushing with focally infiltrative	Borderline Phyllodes
				10x10 cm			After 3 year	Marked	Present	Present	Present	Absent	5-6/10 hpf	Absent	Pushing with focally infiltrative	Borderline Phyllodes
Case 4	35 year	Female	Unifocal	6x5 cm	4	Single		Marked	Moderate	Present	Two dilated cysts toward periphery	Present	<5/10 hpf	Absent	Infiltrative	Borderline Phyllodes
				8x10 cm			After 5 year	Marked	Maked	Absent	Absent	Absent	<5/10 hpf	Absent	Infiltrative	Sarcoma
Case 5	60 years	Female	Unifocal	5x4.5 cm	2	Single		Focal	Absent	Present	Absent	Absent	<5/10 hpf	Absent	Pushing	BorderlinePhyllodes
				7x5 cm			After 4 year	Marked	Present	Absent	Absent	Absent	<5/10 hpf	Absent	Infiltrative	Liposarcoma

Table 2: Benign phyllodes haver to be differentiated from borderline and malignant phyllodes

S. No.	Histologic features	Benign	Borderline	Malignant
1	Tumour border	Well defined	Well defined, may be focally permeative	Malignant Permeative
2	Stromal cellularity	Cellular, usually mild, may be non-uniform or diffuse	Cellular, usually moderate, may be non-uniform or diffuse	Cellular, usually marked and diffuse
3	Stromal atypia	Mild or none	Mild or moderate	Marked
4	Mitotic activity	Usually low:<2.5 mitoses/mm? (<5 per 10 HPFS)	Usually frequent 2.5 to< 5 mitoses/mm^2 (5-9 per 10 HPFs)	Usually abundant: ≥ 5 mitoses/mm^2 ≥(10 per 10 HPFs)
5	Stromal overgrowth	Absent	Absent (or very focal)	Often present
6	Malignant heterologous elements	Absent	Absent	May be present
7	Distribution relative to all breast tumours	Uncommon	Rare	Rare
8	Relative proportion of all phyllodes tumours	60-75%	15-26%	8-20%

Adapted from WHO book: WHO criteria for benign, borderline & malignant phyllodes tumor

Table 3: Role of immunohistochemistry in phyllodes tumors

Diagnostic Context	IHC Markers	Interpretation / Utility
Juvenile Fibroadenoma vs Benign Phyllodes Tumor	CD34, SMA	Benign phyllodes shows increased stromal cellularity and atypia compared to juvenile fibroadenoma; CD34 helps in stromal evaluation
Grading of Phyllodes Tumor (Benign, Borderline, Malignant)	Ki-67	Ki-67 index increases from benign to malignant; Low (≤15%), Intermediate (16–30%), High (>30%)[19] useful for prognosis & treatment.
Malignant Phyllodes vs Metaplastic Carcinoma	Cytokeratin (CK), p63	CK/p63 positive in metaplastic carcinoma spindle cells; typically negative in PT stroma; PT may show focal p63 positivity
Malignant Phyllodes vs Breast Sarcoma	CD34, CK	CD34 positive in PT stroma, reduced in high-grade PTs; CK negative in sarcoma but helps confirm epithelial origin in PT
Phyllodes Tumor	CK	CK positivity limited to epithelial component confirms biphasic nature; stromal CK-negativity differentiates from MBC and sarcoma

3. Discussion

Phyllodes tumors accounts for less than 0.5% of all breast malignancies, with a median age of presentation around 45 years.[1,9,10] Benign PTs comprises 60% to 75% of all PT. The percentage of borderline PT ranges from 12% to 26% in different large series. And approximately 10% to 15% of PTs are malignant.[2] In ours study, 16.6% cases showed recurrence with 3.3% showed recurrence with benign to borderline, 3.3% remains borderline to borderline in every recurrences, 10% showed recurrence with malignant transformation. 83.3% showed no recurrence.

Phyllodes tumors most commonly occur in women between 45–49 years of age representing the peak incidence. There are no specific clinical features that reliably differentiate benign from malignant PTs. However, tumors exceeding 5 cm in size or those demonstrating a rapid growth trajectory should raise suspicion for malignancy. All cases in our series are of more than 5 cm size. Large tumors may present with skin ulceration or invasion into the chest wall, particularly in high-grade or long-standing lesions.[4]

Phyllodes tumors (PTs) typically arise unilaterally and can occur in any part of the breast, including the nipple and ectopic breast tissue. Bilateral involvement is extremely rare, with only a few cases reported in the literature. When bilateral PTs occurs it is generally asynchronous and are more frequently associated with malignant behaviour. Similarly, multifocal presentations are also uncommon and tend to exhibit more aggressive features.[5,11,12]

Phyllodes tumor is a well-circumscribed fibroepithelial neoplasm characterized by a prominent intracanalicular growth pattern with leaf-like stromal fronds lined by both luminal epithelial and myoepithelial cells, along with stromal hypercellularity.[10] Distinguishing phyllodes tumors from cellular or juvenile fibroadenomas can be challenging, as the latter may also exhibit a cellular stroma. Benign phyllodes tumors closely resemble intracanalicular fibroadenomas,

whereas malignant phyllodes tumors may mimic primary breast sarcomas or sarcomatoid carcinomas, making accurate diagnosis essential.[9]

Benign phyllodes haver to be differentiated from borderline and malignant phyllodes. (**Table 2**). According to the WHO classification, a diagnosis of malignant phyllodes tumor requires the presence of all five histologic criteria: marked stromal cellularity, pronounced stromal atypia, stromal overgrowth, infiltrative tumor borders, and ≥10 mitoses per 10 high-power fields and were followed for classifying our cases.

However lately, the refined criteria have been proposed, which require more validation.[13]

Borderline phyllodes tumors are characterized by frequent mitotic activity (5 to 9 mitoses per 10 high-power fields), moderate stromal cellularity, a circumscribed or focally infiltrative border, and notable stromal atypia. Stromal overgrowth is usually absent, but was seen in almost cases in our series.[10] Squamous cysts was seen in one case of borderline PTs similar to observation of other workers.[14]

The Ki-67 proliferation index in malignant phyllodes tumors shows considerable variability, ranging from 15% to 100%. In contrast, benign and borderline tumors usually exhibit Ki-67 expression in fewer than 10% of tumor nuclei, classifying them within the negative to mildly proliferative category.[15] CD34 may be useful in cases where the classical phyllodes tumor architecture is not clearly discernible. CD34 is usually negative in metaplastic carcinoma of the breast, aiding in its distinction from malignant phyllodes tumors, which often exhibit CD34 positivity. However, CD34 is typically negative in high-grade phyllodes tumors. Focal expression of cytokeratin (CKs) or p63 may be observed in malignant phyllodes tumors, but these findings should not override the diagnosis when characteristic histological architecture is present.[16]

Malignant transformation typically occurs in long-standing or recurrent benign or borderline PTs, predominantly involving the stromal component. Once sarcomatous transformation sets in, the tumor behaviour closely mimics that of high-grade soft tissue sarcomas, with significantly increased risk of hematogenous metastasis.[17]

Primary sarcomas of the breast are exceedingly rare, accounting for less than 0.1% of all malignant breast neoplasms. Sarcomatous transformation of a phyllodes tumor (PT) has been reported.[4] Sarcomatous differentiation arising from phyllodes tumors has been reported in fewer than 6% of cases.[18] In our case series 3 out of 30(10%) showed sarcomatous transformation. The epithelial portion is benign, whereas the stromal elements, composed of hyperproliferative fibroblasts arranged in abnormal patterns (mesh, spiral, or woven), are the neoplastic components of the tumor as compared to primary sarcoma.[19]

Histological subtypes of sarcoma observed in this context include:

Angiosarcoma: Characterized by an irregular vascular network, hyperchromatic and atypical nuclei, and confirmed via immunohistochemical staining for CD31, a sensitive and specific marker of angiogenic proliferation.[20]

Leiomyosarcoma: Exhibits a fascicular architecture of atypical spindle cells with cigar-shaped hyperchromatic nuclei and eosinophilic cytoplasm, showing immunoreactivity for smooth muscle actin (SMA) and desmin as in one of our cases.[20]

Fibrosarcoma: Composed of atypical spindle cells arranged in sheets and fascicles, often forming storiform or “herringbone” patterns, and diffusely positive for vimentin.as in one of our cases.[20]

Chondrosarcoma, osteosarcoma, rhabdomyosarcoma, and liposarcoma have also been rarely reported in this setting, with liposarcoma being particularly uncommon in the breast, however we found a case of Liposarcoma.[20] Immunohistochemistry plays a vital rolein categorization. (**Table 3**)

Recurrence of PTs may result from residual proliferative stromal elements following incomplete excision or may represent de novo tumors arising from extra-tumoral stromal hypercellularity, leading to the development of new benign phyllodes.[4]

The local recurrence rate has been reported to be about 20% in benign phyllodes, 14% to 25% in borderline and malignant phyllodes local recurrence ranges from 15% to 40%, and 9% to 27% metastasize to distant organs.[2]

The median interval to local recurrence after initial surgical excision is approximately 20 months, in our case series ranged from 1-4 years. The time from surgery to the onset of distant metastases varies widely, ranging from 2 to 57 months, with an average interval of 21 months.[22]

In benign and borderline phyllodes tumors, recurrence rates are similar following breast-conserving surgery (BCS) and mastectomy. However, in malignant phyllodes tumors (MPTs), BCS is associated with a significantly higher risk of local recurrence compared to mastectomy.Margin status or width does not significantly impact recurrence risk. Although NCCN recommends a 1-cm margin, this is based on limited evidence, and the optimal margin width remains uncertain due to conflicting retrospective data. In our cases a variable surgical margin of 1mm to 1cm could be maintained because of size but there was no association of surgical margin with recurrences.[1] Positive surgical margins and large tumor size still remain the most critical predictors of recurrence. While multiple recurrences are rare, complete surgical excision remains the cornerstone of treatment.

Adjuvant radiotherapy is selectively employed in cases of recurrence or where high-risk histologic features are present.[1,3,6] Adjuvant radiotherapy, though not routinely indicated in primary phyllodes tumors, may be considered in locoregional recurrences to reduce local relapse risk, without impacting overall survival. None of the patient in our series received chemotherapy. Chemotherapy and hormonal therapy lack proven benefit, and repeat surgical excision remains the cornerstone for recurrent cases.[6]

MED12 mutations are early events in fibroepithelial tumorigenesis, seen in ~50–70% of fibroadenomas and benign PTs. In contrast, TERT promoter mutations, often co-occurring with RB1 and CDKN2A loss, are more frequent in borderline and malignant PTs, contributing to genomic instability. Malignant PTs exhibit additional alterations including TP53, NRAS, and PI3K/Akt/mTOR pathway activation, as well as amplifications of EGFR, PDGFβ, IGF1R, and MET. PTEN, SMAD4, and SETD2 mutations and PD-L1 upregulation have also been observed, indicating potential roles in prognosis and immunotherapy.[23-25] These molecular studies were not conducted in our case series due to economic constraints.

4. Conclusion

Phyllodes tumors may evolve into more aggressive histologic subtypes upon recurrence, often with diminishing epithelial elements. Early recognition of these changes is essential for prognosis and management planning with close follow ups.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Cite this article: Sood N, Ruhi. Borderline phyllodes tumor – A saga of recurrences and malignant transformation. *Indian J Pathol Oncol*. 2025;12(3):258–266.