

Histomorphological analysis of phyllodes tumors at a tertiary care center



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ABSTRACT

Background: Phyllodes tumors (PT) are rare biphasic neoplastic breast lesions. They account for 0.3–0.5% of female breast tumours¹ and have an incidence of about 2.1 per million, the peak of which occurs in women aged 45–49 years. There is sometimes difficulty in dividing tumors into the three recognized grades based on histomorphological features. It is because of the subjective variation and absence of a definitive grading system. More importantly, they do not always correlate with clinical outcome in terms of predicting recurrence, malignant transformation, metastasis, and overall survival. **Aims and Objectives:** (1) The aim of the study was to study the clinicopathological and histomorphological features of the PT and classify the tumors based on 2019 WHO classification. **Materials and Methods:** This study was done in the Department of Pathology at Government General Hospital Nizamabad. Total 68 cases are included in this study over a period of 5 years (3 1/2 years retrospective and 1 1/2 year prospective) from 2017 March to 2022 March. PT cases were analyzed based on 2019 WHO classification criteria. The age of the patients, tumor locations, and the relevant details were obtained from the pathology records. **Results:** Of the 68 PT cases, 53 (78%) were classified as benign, 8 (12%) borderline and 7 (10%) malignant PT based on histomorphological features based on 2019 WHO classification. **Conclusion:** Our study showed that tumors occurring in older age group with a large tumor size and the presence of malignant heterologous elements, infiltrating borders, and surgical margins < 1 cm were usually malignant phyllodes.

Key words: Benign phyllodes, Borderline phyllodes, Malignant phyllodes, WHO 2019 classification

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INTRODUCTION

Phyllodes tumors (PTs) of the breast are rare biphasic tumors accounting for 0.3–0.5% of all breast tumors. These patients usually present with a large and well-circumscribed painless mass with rapid growth, without nodal involvement and typically affects women within the fourth or fifth decade of life.^{1,2} PT histologically resemble intracanalicular fibroadenomas, characterized by a double-layered epithelial component arranged in clefts surrounded by a hyper cellular stromal/mesenchymal component which in combination elaborate leaf-like structures.

The 2019 WHO classification of breast tumors³ classifies PT as benign, borderline, and malignant according to five morphological parameters: Stromal atypia, stromal

cellularity, stromal overgrowth, mitotic count, and tumor borders.⁴ These three subsets of tumor represent 60%, 20%, and 20% of all PTs, respectively.⁵ This morphological risk assessment scheme has some limitations related to the subjectivity and operator dependence of the evaluation, the absence of standardized cutoff points for individual histological parameters and the possible presence of heterogeneous foci within the same neoplasm.⁶

PTs usually have an indolent behavior and a good prognosis; they may exhibit a heterogeneous clinical outcome. Local recurrences can occur in all cases of PT with an overall rate of 21%. The recurrence rate is however within a range of 10–17% for benign, 14–25% for borderline, and 23–30% for malignant cases according to the fifth edition of WHO classification.⁴ Distant recurrences are rarer and occur in

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borderline and malignant PT. Some clinical, pathological, and surgical factors have been investigated to predict the risk of recurrence, with controversial results.⁷

The National Comprehensive Cancer Network Guidelines V.3.2020 recommends wide excision without axillary staging for malignant PT. The guidelines also specify that for malignant or borderline cases, wide excision means excision with the intention of obtaining margins of >1 cm. Narrow margins are associated with increased risk of local recurrence; however, they are not an absolute indication for mastectomy when partial mastectomy fails to achieve a margin width of ≥ 1 cm. No randomized trials have evaluated the role of neo/adjuvant chemotherapy and adjuvant radiotherapy in these patients.⁸

Aims and objectives

The aim of the present study is to analyze the clinicopathological and histomorphological features of the Phyllodes Tumour and classify it according to 2019 WHO classification.

MATERIALS AND METHODS

The present study is a both retrospective and prospective study conducted at Government General Hospital Nizamabad in the Department of Pathology. Total duration of the study is 5 years, out of this 3 ½ years was retrospective, from 2017 March to 2020 September and 1 ½ year of prospective study from October 2020 to March 2022. The total number of case studied is 68. The patient details were retrieved from pathology records such as age of the patients, tumor locations, laterality, and the relevant details were obtained and were analyzed. We included histologically proven cases of PT of the breast lesions, and excluded cases other than phyllodes such as fibroadenoma, inflammatory breast lesions, infiltrating duct cell carcinomas, sarcomas, and metastatic deposits.

Inclusion criteria

Histologically proven cases of PT of the breast were included in the study.

Exclusion criteria

Breast lesions other than PT of the breast were excluded from the study.

In our study, all the cases underwent fine-needle aspiration cytology (FNAC) procedure followed by simple mastectomy without axillary lymph node excision.

The specimens were fixed in 10% neutral buffered formalin. They were examined grossly according to the

standard guidelines, with special emphasis on the tumor size and lymph node status, location, and laterality of lesion. The specimens were grossed and sections were taken from representative sites. These sections were then processed in tissue processor and embedded in paraffin wax. Four-to-five-micron thick sections were prepared from the corresponding paraffin blocks, on albumin coated slides for Hematoxylin and Eosin staining. The histological type of tumor was assessed and categorized as benign, borderline, and malignant based on presence of histomorphological features according to the 2019 WHO criteria. In few doubtful cases, immunohistochemistry of ki67 and p53 were employed to differentiate malignant phyllodes from borderline phyllodes.

RESULTS

This study was conducted from March 2017 to March 2022. A total of 68 breast phyllodes cases were studied. The observations such as age, laterality, and histological type were tabulated. The mean and median of each category were analyzed.

Out of the 68 PT cases, 53 (78%) were classified as benign, 8 (12%) borderline, and 7 (10%) malignant PT based on histomorphology. The mean age of the benign group was 48 years (min: 25 years, max: 65 years), while it was 52 years (min: 36 years, max: 65 years) in the borderline, 63 years (min: 41, max: 70) in the malignant (Table 1). In the present study, the right breast was more commonly involved accounting for 68% of cases whereas the left breast phyllodes accounted for 32% (Figure 1).

Table 1: Age-wise distribution in phyllodes tumour

Age	Benign (%)	Borderline (%)	Malignant (%)
25–40	7 (13)	2 (25)	0
41–55	42 (79)	5 (62)	3 (43)
56–70	4 (8)	1 (13)	4 (8)

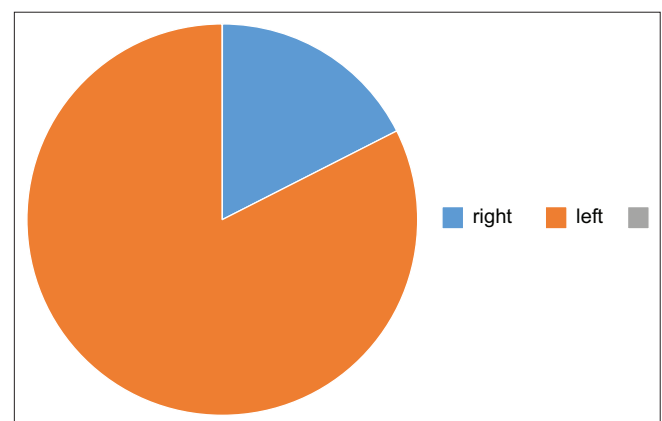


Figure 1: Laterality distribution of phyllodes tumor

FNAC

Cytology of PT shows hypercellular stroma with ductal epithelial cells clusters.

Gross

In the present study, minimum tumor size is 2 cm and maximum tumor size is 23 cm with a mean of 8.5 cm (Table 2). Cut section shows well circumscribed tumor grey-brown in color and fleshy and necrosis seen in few tumors along with cystic spaces (Figures 2 and 3).

All the benign PTs show glands and stroma with leaf-like projections, stroma showing hypercellularity adjacent to the epithelium, mitotic rate <4/hpf with mild nuclear atypia present (Figure 2). Borderline tumors show moderate stromal cellularity, hyperplasia and mitotic rate in between 4 and 10/hpf. Malignant PT show severe stromal cellularity, hyperplasia, marked atypia, and mitotic rate >10/hpf with infiltrating borders and no heterologous elements noted and margins are free (Figure 3). In few doubtful cases, IHC with Ki 67 was employed to differentiate borderline and malignant phyllodes (Figure 4).

DISCUSSION

PT are rare biphasic neoplasm that account for <1% of all breast neoplasms. Displaying a broad range of clinical and pathological behavior, PT should be regarded as a spectrum of biphasic neoplasms rather than a single disease entity.

Malignant PTs, if inadequately treated, have a propensity for rapid growth and metastatic spread. Benign PTs on clinical, radiological, and cytological examination are often indistinguishable from fibroadenomas and can be cured by local surgery. With the non-operative management of fibroadenomas widely adopted, the importance of PT today lies in the need to differentiate them from other benign breast lesions.⁹

Triple assessment by clinical, radiological, and cytological or histological examination forms the fundamental basis for the evaluation of all breast lumps. In patients with PT, all three aspects individually have a low sensitivity and, even in combination, the diagnostic accuracy is often poor.^{10,11}

On ultrasound examination, PTs often show smooth contours with low level homogenous internal echoes, intramural cysts, and the absence of posterior acoustic enhancement. As with mammography, no reliable ultrasonic indicators have been identified that differentiate between benign and malignant lesions.^{12,13} The role of magnetic resonance imaging in the assessment of PT and fibroadenomas remains to be defined.¹⁴

Table 2: Tumor size			
Tumor size	Benign (53)	Borderline (08)	Malignant (07)
<10 cm	41	02	00
10–20 cm	22	06	03
>20 cm	00	00	04

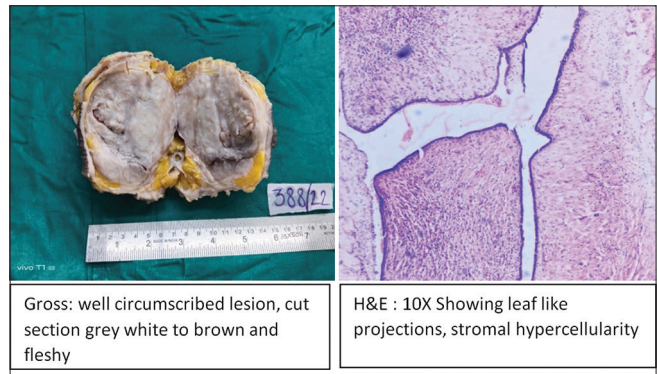


Figure 2: Benign phyllodes tumor-gross and H and E

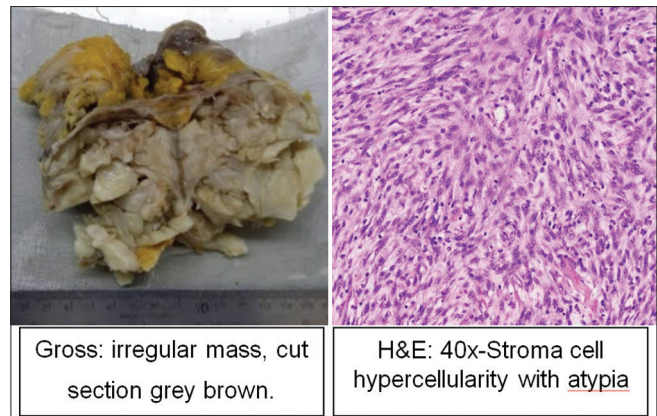


Figure 3: Malignant phyllodes tumor - gross and H and E

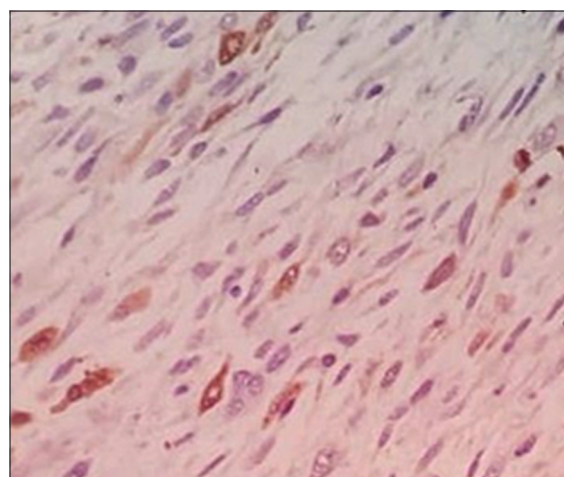


Figure 4: Ki67-x40 showing expression in malignant phyllodes tumor

An accurate cytological diagnosis of PT by fine needle aspiration can be difficult cytologically. It is often easier to differentiate benign from malignant PTs than to separate

benign PTs from fibroadenomas. In the correct clinical setting, the presence of both epithelial and stromal elements within the cytological smear supports the diagnosis. Epithelial cells may, however, be absent from specimens taken from malignant lesions. The presence of cohesive stromal cells, isolated mesenchymal cells, clusters of hyperplastic duct cells, foreign body giant cells, stromal fragments, and bipolar naked nuclei and the absence of apocrine metaplasia are highly suggestive of a PT and yet the value of FNAC in the diagnosis of PT remains controversial, with an overall accuracy of about 63%.^{15,16}

A wide range of histological features is seen within PT with heterogeneity existing within the same lesion. Predicting the biological behavior of PTs remains a challenge in pathology. Various grading systems have been proposed, but none is universally accepted. The threshold for number of mitoses required for classification into each subgroup of PT varies from one grading system to another. Stromal overgrowth has been defined as marked stromal proliferation to the point where the epithelial component is absent in at least one low-power field. Infiltration into adjacent tissue is a feature of malignant PTs, whereas benign PTs tend to having pushing rather than infiltrative margins.

Adequate sampling is important, with at least one block for every 1 cm of maximal tumor dimension. The grading should be based on the areas of highest cellular activity and most florid architectural pattern. Follow-up studies to determine the behavior of PTs have demonstrated the inadequacy of histological criteria alone in predicting biological behavior.¹⁷

Prognosis and predictive factors

Most PTs behave in a benign fashion, with local recurrences occurring in a small proportion of cases. Very rarely about 2% or less overall, the tumor may metastasize, mainly in the cases of tumors of malignant grade. Local recurrences can occur in all PTs, at an overall rate of 21%, with ranges of 10–17%, 14–25%, and 23–30% for benign, borderline, and malignant PTs, respectively. These recurrences may mirror the microscopic pattern of the original tumor or show dedifferentiation with microscopic upgrading in 25–75% of cases.

Many histological features have been reported to possess predictive value for local recurrences in PT, and status of surgical margins at the previous excision appears to be the most reliable. Other less consistent predictors include stromal overgrowth, classification/grade, and necrosis. A recent study found that, apart from surgical margins, histological parameters that had an independent impact on recurrence were stromal overgrowth and atypia, with mitotic activity being almost significant.^{18,19}

Limitations of the study

No IHC marker was done to differentiate from the sarcoma.

In our study, there are no cases of recurrence as we did not do follow-up, we do not have data regarding recurrence.

CONCLUSION

1. PTs is a benign biphasic breast tumor that is composed of cellular spindle stroma with epithelial elements.
2. The neoplastic component of the tumor is the stroma, which determines its behavior.
3. There is sometimes difficulty in dividing tumors into the three recognized grades benign, borderline, and malignant PTs based on histological features.
4. In these situations, Ki67 and p53 are helpful to differentiate benign, borderline, and malignant PT.

In the present study, we found that older age group, with a large tumor size and the presence of malignant heterologous elements and infiltrating borders, was found in malignant PT.

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Authors' Contributions:

ML - Concept and design of the study; **MIA** - Concept and drafting of manuscript; **SS** - Design of study and preparation of manuscript; **ML** - Concept of study and revision of manuscript; **SVSP** - reviewed literature and preparation of manuscript; **SS** - Data collection and statistical analysis.

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