

Review

Malignant phyllodes tumor of the breast: a systematic review

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Summary

Phyllodes tumors (PT) are fibroepithelial neoplasms of the breast showing a peculiar leaf-like appearance. They account for 0.3 to 1% of all primary breast tumors and 2.5% of all fibroepithelial breast tumors. PT are classified into benign, borderline and malignant based upon their stromal morphology with a distribution of 60%, 20%, and 20%, respectively. Malignant PT of the breast constitute an uncommon challenging group of fibroepithelial neoplasms. They have a relatively high tendency to recur, although distant metastasis is uncommon, and nearly exclusive to malignant PT. Adequate surgical resection remains the standard approach to achieve maximal local control. Giant malignant PT are rare and pose a diagnostic dilemma for pathologists, especially when comprised of sarcomatous elements. This review highlights the morphological features of PT detected in cytology and histology specimens and discusses diagnostic pitfalls and differential diagnosis.

Key words: fine needle aspiration, phyllodes tumor, malignant phyllodes tumor, breast disease, breast oncology, personalized medicine, pathology

Introduction

Phyllodes tumor (PT) is an uncommon breast neoplasm that exhibits variable biological behavior ranging from benign to malignant. Many PTs are characterized by rapid growth. PT have been defined as fibroepithelial neoplasms with an inherent ability to recur locally when diagnosed as borderline or malignant; metastasis is uncommon, nearly exclusive to malignant PT¹⁻³. PTs account for 0.3% to 1% of all primary breast tumors and 2.5% of fibroepithelial breast lesions; the remaining 97.5% are represented by fibroadenomas²⁻³. The relatively high recurrence rate of PTs, despite surgical resection, remains an unresolved management problem².

PTs were first described in 1838 by Johannes Müller as cystosarcoma phyllodes, mostly due to their leaf-like (phyllodal) tumoral projections into cystic spaces and their sarcomatous stromal appearance⁴. Nevertheless, this term is misleading because up to 70% of these tumors have a benign course and only rarely do they show cystic degeneration¹⁻². In 1931, the first case of a malignant PT with metastases to the lungs was reported, which revealed that these tumors could exhibit malignant behavior⁵. Re-

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cent literature reports that approximately 10% to 15% of PTs are malignant^{3,6-12}. Malignant PT have a significant potential for local recurrence (up to 30%) and the ability to metastasize. When PTs are larger than 10 cm in diameter, they have been classified as “giant” PTs, which account for about 20% of all PTs⁶. PT is the currently accepted nomenclature according to the World Health Organization (WHO), which classifies these tumors as benign, borderline, or malignant based on a combination of histological features including stromal cellularity, nuclear atypia, mitotic activity, stromal overgrowth, and tumor margin¹. The median and mean ages in which these tumors present are 45 years, which is about 15 years older than the age group for fibroadenoma. The average tumor size ranges from 4 to 5 cm, even though malignant PTs can grow to much larger sizes. PTs demonstrate a predilection for the upper outer quadrant of the breast, with only 3.4% demonstrating bilateral localization¹¹.

The distinction between PT and fibroadenoma by ultrasound (US) and mammography can be difficult^{11,13-17}. On mammography, a PT typically appears as a well circumscribed, hyperdense or isodense, round or oval mass. History of rapid growth, large size, and older age may be the only clinical findings in favor of a PT¹¹. Other features such as lobulated shape, heterogeneous internal echo pattern and absence of microcalcification are significant sonographic features used to favor PT over fibroadenomas. Of note, sonography cannot distinguish between malignant and benign PTs⁷⁻⁹. Major diagnostic challenges may also be encountered with the cytological diagnosis of PT, especially those that are malignant, as well

as discrimination of PT with sarcomatous overgrowth from mimics¹⁸⁻²⁴. This review focuses on the morphological features and potential pitfalls in the cytologic and histologic diagnosis of PT.

Cytopathology

Fine needle aspiration (FNA) has been proposed as an acceptable pre-operative modality for diagnosis of PT^{19,25-28}. Cytologically, these smears show cellular fibromyxoid stromal fragments composed of spindle cells, clusters or sheets of benign ductal epithelium without atypia, and admixed myoepithelial cells²⁵⁻²⁸. These features are also commonly seen in fibroadenomas (Tab. I). PT should be suspected when the following features are encountered: i) large hypercellular stromal fragments; ii) moderate to large numbers of dyscohesive stromal cells with elongated nuclei and scant to moderate cytoplasm admixed with a fibromyxoid stromal component; iii) significant atypia in individually distributed stromal cells including nuclear enlargement, pleomorphism, and mitotic figures, especially in malignant PT; iv) a low epithelial-to-stromal ratio; v) round epithelial fragments with mild atypia; and vii) columnar epithelial cells²⁵⁻²⁸. Despite the fact that grading is extremely difficult on FNA samples, the presence of the following should favor a malignant PT: high stromal cellularity, high degree of stromal nuclear atypia, mitotic figures, atypical single cells, multinucleated tumor cells, and heterologous differentiation of sarcomatous stroma exhibiting features of liposarcoma, osteosarcoma, chondrosarcoma, or rhabdomyosarcoma.

Table I. Cytological and histological features of fibroadenoma and phyllodes tumors.

	Fibroadenoma	Phyllodes Tumor (Benign)	Phyllodes tumor (borderline)	Phyllodes Tumor (Malignant)
Tumor border	Regular and well defined	Regular and well defined	Well defined or focally permeative	Permeative
Stromal cellularity	Variable	Mild	Moderately increased, can be focal	Diffuse and marked
Stromal atypia	Absent	Present-mild	Moderate	Present-severe
Mitotic figures	Absent	Present-low	Present-moderate	Present-high
Stromal overgrowth	Absent	Absent	Absent or very focal	Present
Patterns (cytology)	Solid and isolated cells Sheets with antler- or-staghorn shaped epithelial clusters	Solid-sheets and few isolated cells	Solid sheet few-moderate isolated cells	Solid sheets and increased atypical isolated cells.
Background (cytology)	Clean	Cellular	Moderately cellular	Highly cellular
Ductal hyperplasia (cytology)	Present	Absent	Absent	Absent
Nuclei (cytology)	Mild atypia	Mild atypia	Moderate atypia	Moderate-severe atypia
Bipolar nuclei in the background (cytology)	Present	Absent	Absent	Absent

The most important differential diagnoses include fibroadenoma with a prominent intracanalicular growth pattern and cellular stroma, spindle cell/metaplastic carcinoma, and primary or metastatic sarcomas^{1,25-28}. Given the overlap of cytological features for a benign PT and cellular fibroadenoma, these two biphasic fibroepithelial lesions cannot be reliably distinguished on FNA²⁹. Increased stromal cellularity favors a PT diagnosis. The diagnosis of a malignant PT depends on the amount of the epithelial component obtained by FNA sampling²⁷⁻²⁸. In challenging cases a core needle biopsy may be necessary to render a more definite diagnosis to guide subsequent patient management³⁰⁻³². The correct diagnosis can be supported by using immunohistochemistry. For example, the spindle cells in metaplastic carcinoma usually show positivity for keratins and p63, unlike the spindle cells of malignant PT where keratins are negative and p63 is positive in only 20% of tumors³³.

Histopathology

PT resemble intracanalicular fibroadenomas (i.e. double-layered epithelial component) arranged in leaf-like clefts surrounded by a hypercellular stromal

component¹⁻³. As mentioned, the WHO classifies PT into benign, borderline and malignant neoplasms¹. The difference is based on a combination of histological features (Tab. I) including the degree of stromal hypercellularity, overgrowth and atypia, numbers of mitoses, tumor border/margins, and the presence of malignant heterologous elements. Although the majority of PTs are benign, recurrences are not uncommon³⁴⁻³⁹. Moreover, hematogenous metastases can occur with malignant PT, although this is uncommon. A PT with a bland stromal component can mimic a fibroadenoma whereas a PT with stroma that appears overtly sarcomatous can be challenging to differentiate from a sarcoma. The main features in favor of a benign PT over fibroadenoma are the presence of more cellular stroma characterized by monomorphic spindle-cell nuclei and rare mitotic figures (< 5 mitoses per 10 high-power fields, HPF). Stromal cellularity is often higher in the areas immediately adjacent to epithelium³⁴⁻³⁹. There may be stromal hyalinization or myxoid change. The presence of necrosis can be seen in large PTs, along with occasional bizarre large stromal cells¹. Benign lipomatous, cartilaginous, and osseous metaplasia can be seen in PT; such features should not lead to a diagnosis of malignancy. Benign PTs are usu-

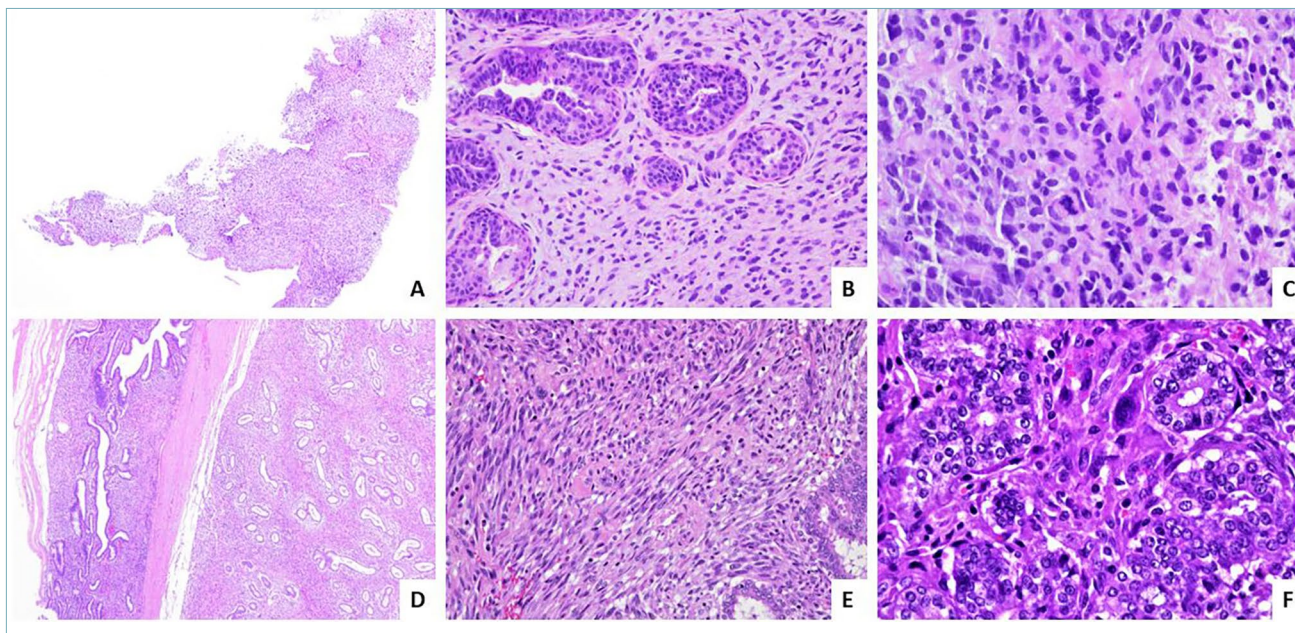


Figure 1. Morphological features of a benign phyllodes tumor (on surgical sample). (A, B, C, D) A surgical sample of a fibro-epithelial biphasic neoplasm constituted by well delimited or pushing margins into the surrounding tissue (A, B, HEx4), marked pericanalicular growth pattern and leaf-like formations (C, D, HEx10). We can observe only a focal increase of the stromal cellularity (D, HE x4). The spindle cell stromal nuclei are monomorphic and bland; mitoses are rare. The sample shows stromal heterogeneity with areas of sparse stromal cellularity and other areas with sclerosis and hyalinization (E, HEx10). A diagnosis of benign phyllodes tumor has been made.

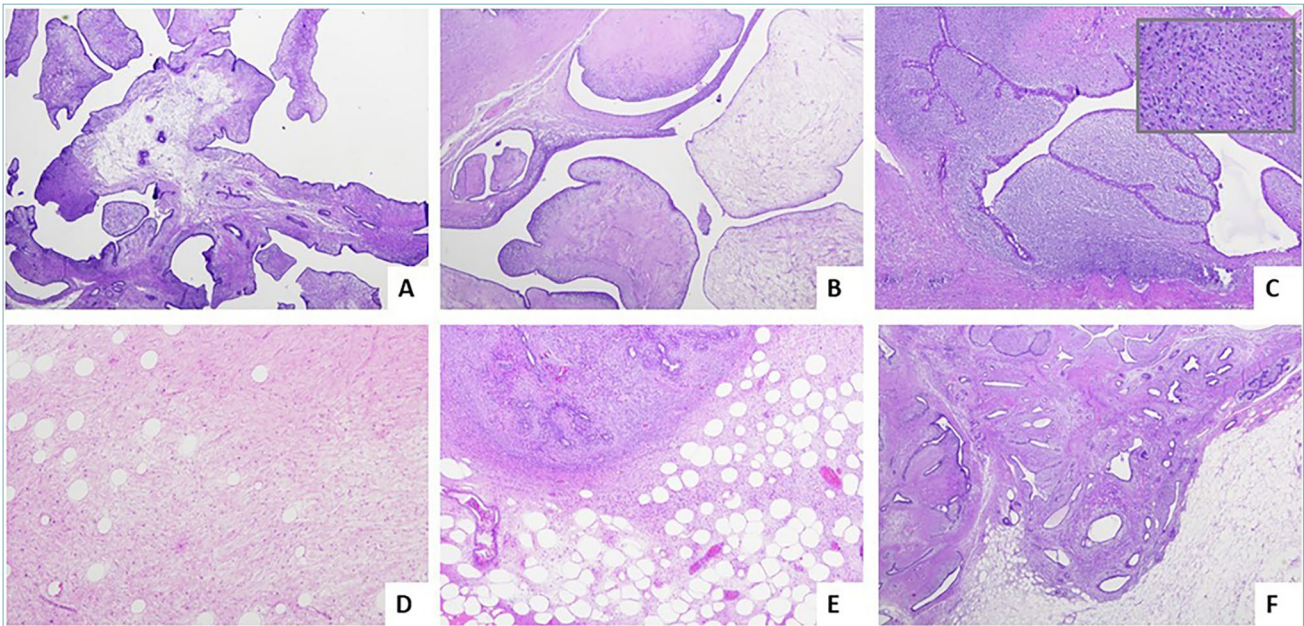


Figure 2. Morphological features of a borderline phyllodes tumor (on surgical sample). (A, B, C, D, E, F) Breast surgical sample with a borderline phyllodes tumor, characterized by the following features: marked pericanalicular pattern of growth (A, HEx4), stromal heterogeneity with sclerotic, edematous and more cellular areas (B, HEx4), non-uniform increase of stromal cellularity, with a periepithelial or subepithelial accentuation (C, HEx4), moderate stromal nuclear pleomorphism (insert on the right top in image C, HE 40X), with scattered fields with higher mitotic activity (up to 4-5 mitoses/10 HPF of 0.5 mm²), focal areas of stromal overgrowth (D, HEx4) and focally permeative borders with some tumoral buds protruding into the surrounding tissue (E,F HEx4). Epithelial component does not show significant atypia.

ally characterized by pushing, well-defined margins that only exhibit a small protruding component into the surrounding tissues^{1-3,40-42} (Fig. 1). Borderline PT is diagnosed when a PT shows some (but not all) of the features typically associated with a malignant PT¹ (Fig. 2). Similar to benign PT, borderline PT may recur locally, but they do not metastasize. Malignant PT is defined by the combination of marked nuclear pleomorphism of stromal cells, stromal overgrowth (defined by the absence of epithelial component in one low-power microscopic field), diffuse stromal cellularity with increased mitotic activity (> 10 per 10 HPF) and infiltrative borders¹ (Figs. 3-4). A diagnosis of malignant PT can also be made when malignant heterologous elements are present in the absence of other features. Distant metastases have been reported in up to 10% of malignant PTs with involvement in nearly all organs, especially the lung and skeleton⁶⁻¹⁰, (Fig. 4). Local axillary lymph node metastases are rare; hence, wide local excision or mastectomy with appropriate margins is the preferred clinical intervention⁴³⁻⁴⁶. Axillary node staging is not required because of rare lymph node involve-

ment^{3,21}. Data regarding sentinel lymph node biopsy in PTs are lacking, since metastatic spread of these tumors is primarily hematogenous. Patients with a giant PT may have clinically enlarged axillary lymph nodes suspicious for metastatic disease^{3,10,16,22}. Reported local recurrence rates in large patient cohorts were 11.2%, 15.9%, and 24.5% for benign, borderline, and malignant PT subtypes¹⁻³. The reported rates of distant metastases are 0%, < 2%, and 16% respectively for benign, borderline and malignant PT¹⁻³. Most patients with distant metastases also experience local recurrence^{7,12,13}. Malignant PTs have a high risk of metastasis ranging from 1.7 to 16%; patients with metastases rarely respond to chemotherapy and typically die within 3 years of initial treatment. Histological factors associated with the development of distant disease are: tumor size larger than 7 cm, infiltrative borders, marked stromal overgrowth, marked stromal cellularity, > 5 mitoses per 10 HPF, and necrosis^{9-11,16}. Heterologous elements do not appear to influence prognosis in malignant PT¹¹.

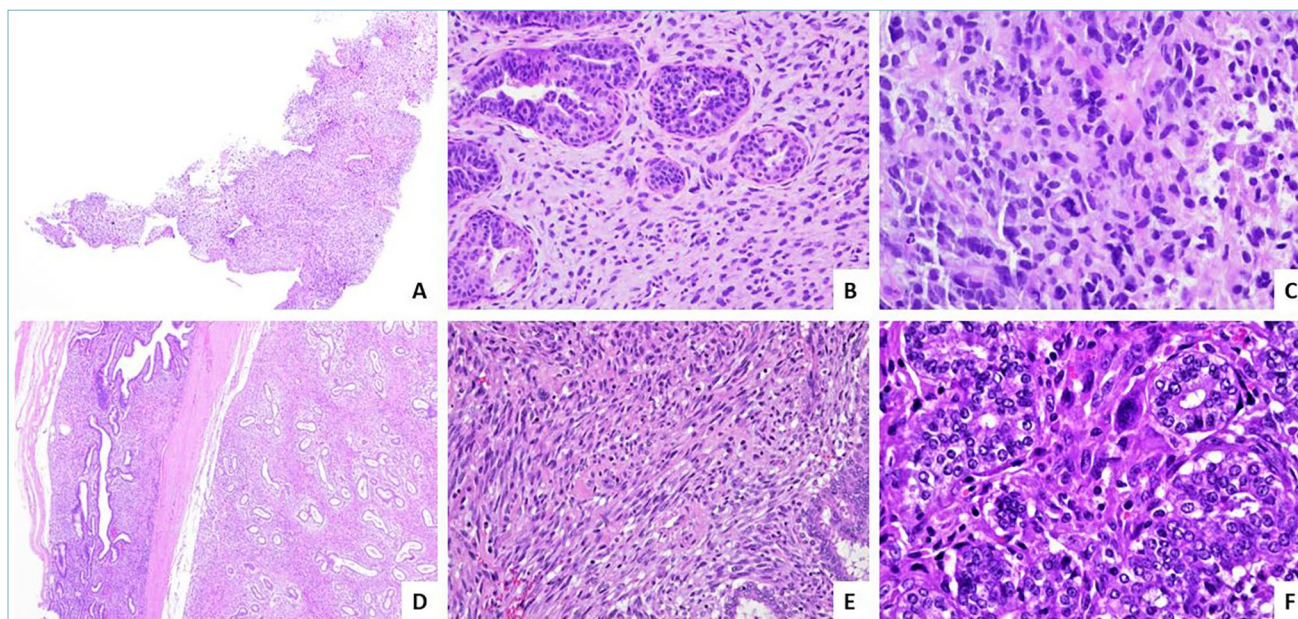


Figure 3. Morphological features of a malignant phyllodes tumor (on VABB and surgical sample). (A, B, C) A biopsy sample of a fibro-epithelial biphasic neoplasm constituted by increase stromal cellularity (an overview; A, HE x4). For moderate-severe nuclear atypia (B, HE x20) and presence of elevated mitotic index (C, HE x40), a diagnosis of malignant phyllodes tumor was made. (D) Breast surgical sample with the malignant phyllodes tumor diagnosed on the VABB observed and commented in A-B-C. We can note the following features: permeative margins into the surrounding breast parenchyma (D, HE x4), increased stromal cellularity, being usually diffuse (E, HE x20), with areas of stromal overgrowth and marked stromal nuclear pleomorphism (F, HE 40X), with scattered fields with brisk mitotic activity (up to 18 mitoses/10 HPF of 0.5 mm²). No malignant heterologous elements were observed.

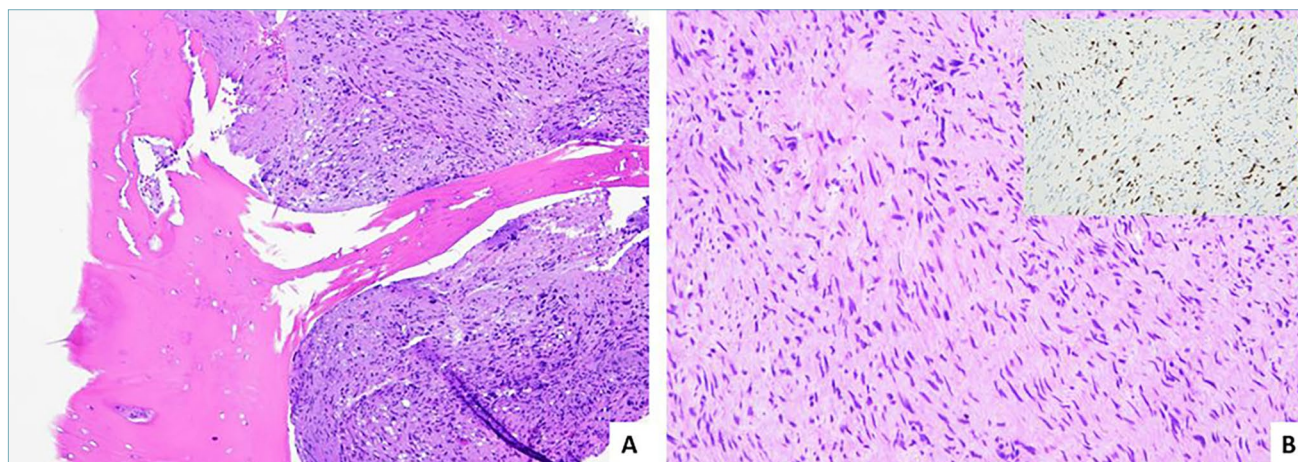


Figure 4. Vertebral metastasis of a malignant phyllodes tumor: histological and immunohistochemical findings. (A-B) After 1 year from histological diagnosis, the patient (affected from the malignant phyllodes tumor shown in Figure 1), experienced a vertebral metastases (on D3), constituted by a proliferation of spindle atypical cells (A, HE x10; B, HE x20), morphological resembling the primitive breast tumor, with a significant proliferative index (Ki-67: 20%, LSAB-HRP, x20; insert on the right top in image B).

Immunohistochemistry and genetic alterations

The correlation between genetic alterations and histological features has not been entirely clarified⁴⁷⁻⁵⁶. Sawyer et al. suggested a possible pathogenesis of PT in the epithelial-stromal interaction with stromal expression of β -catenin and insulin-like growth factors (IGF-I and II)⁴⁹⁻⁵⁰ and the epithelial overexpression of Wnt5a in benign/borderline PT, which might promote stromal overgrowth.

The immunohistochemical pattern is characterized by the expression of p53, Ki-67, CD117, EGFR, p16, and VEGF, which show the lowest positivity in benign PT and the highest in malignant PT⁵¹⁻⁵⁴.

Some recent studies have attempted to define a molecular classification for PT⁵⁷⁻⁶⁰. Lae et al. reported that high-grade (malignant) PTs had 1q gain and 13q loss while low-grade (benign/borderline) PTs had few or no alterations⁵⁷. Nevertheless, these results have not been confirmed by other authors⁵⁸⁻⁵⁹. The loss of 13q in PT suggests that the *RB1* gene could be relevant to PT oncogenesis or progression. Other authors have reported deletions of 9p21 associated with loss of p16INK4A protein expression in borderline/malignant PT⁶⁰.

Some authors studied breast cancer-related genes in fibroepithelial lesions, concluding that the profile of benign PTs is similar to fibroadenomas, whereas malignant PT was identified as claudin-low and basal-like⁶¹⁻⁶⁶. Recent studies have demonstrated that recurrent mediator complex subunit 12 (*MED12*) somatic mutations are frequently identified in both fibroadenomas (59-67%) and PTs (45-67%)^{62,66}. In addition, *MDM2* and *RARA* mutations may be early events in the pathogenesis of fibroadenoma and PT, whereas mutations in *FLNA* (28%), *SETD2* (21%), and *KMT2* (9%) have been observed only in PT⁶⁶⁻⁶⁹. Genome-wide analysis of DNA copy number variations and genomic sequencing have demonstrated significant numbers of amplifications and deletions. In addition to the loss of function mutation in *TP53*, deleterious mutations in *RB1* and *NF1*, mutations in *PIK3CA* and *ERBB4*, and high-level copy number variations of *EGFR* have been detected in borderline/malignant tumors; some of these pathways suggest possible therapeutic targets⁶⁹⁻⁷².

Differential diagnosis

The differential diagnosis varies according to the different PT histological patterns. As mentioned, benign PT and fibroadenoma exhibit overlapping histologic

features especially when they have a pronounced intracanalicular growth pattern^{1,3,79}. The detection of more cellular stroma, along with the formation of leaf-like processes, usually favors a benign PT. Stromal cellularity in PTs may be seen throughout the lesion or close to the leafy fronds. Of note, the presence of leaf-like processes may be found within intracanalicular fibroadenomas, although in such tumors these processes are usually scant, hypocellular and have an edematous stromal component. In some cases, an unequivocal distinction between fibroadenoma and benign PT is problematic, in which case a diagnosis of fibroadenoma is preferable in order to avoid any over-treatment. Lawton et al. highlighted the difficulty that exists in distinguishing some cellular fibroadenomas from PTs even for pathologists who are specialized in breast pathology⁴¹. Their paper included 21 cases of fibroepithelial lesions sent in consultation to the senior author that were challenging to classify as cellular fibroadenoma or PT⁴¹. In only two of these challenging cases was there uniform diagnostic agreement among experts⁴¹. Regarding the remaining 19 cases analyzed, when the diagnoses of fibroadenoma and benign PT were combined and separated from borderline and malignant PTs, there was 100% agreement in 53% of cases and 90% agreement in 79% of cases⁴¹. Malignant PTs can be misdiagnosed as exceptionally rare primary sarcomas of the breast⁷³⁻⁷⁴. The differential diagnosis is based on the detection of residual epithelial structures. Metaplastic carcinoma is another possible lesion to be added to the differential diagnosis, which can usually be resolved by using immunohistochemistry to demonstrate epithelial differentiation (i.e., broad-spectrum keratins)^{1,3,79}.

Role of core-needle biopsy

Some authors have deliberated over the role of core needle biopsy (CNB) in the diagnosis of PT versus fibroadenoma⁴⁷⁻⁴⁹. Komenaka et al. studied 57 CNB where a diagnosis of PT was considered. Their series included 25 cases diagnosed as fibroadenoma, 23 favoring PT, and 9 cases in which the final diagnosis was equivocal⁴⁷. Among the 25 cases diagnosed as fibroadenomas on CNB, only 2 (8%) were subsequently histologically diagnosed as PT. On the other hand, 19 of 23 cases (83%) diagnosed as PT on CNB were confirmed by follow-up histological examination. These data accordingly yielded 93% negative predictive value and 83% positive predictive value for CNB diagnosis. These data further confirmed that none of the cases in this series had a malignant diagnosis, and that correct pre-surgical diagnosis using CNB is

useful in personalizing management, thereby reducing the need for additional interventional procedures. This high concordance rate was not totally confirmed when Choi and Koo compared CNB and surgical excisions in 129 cases with histologically proven PT³². Their series included 90 benign PT, 30 borderline PT and 9 malignant PT. The benign PT group had 74.4% concordant diagnoses on CNB. The concordant rate for borderline PTs and malignant PTs was 26.6% and 44.4%, respectively on CNBs. The discordant diagnoses were underestimated in matched CNBs, especially in their stromal cellularity and mitotic counts. They concluded that CNB has some limitations in grading of PT, despite the fact that they reported a concordance rate for diagnosis between CNB and surgical excision of about 60%³².

Management

Although PT is mainly treated by surgical excision, there is reported evidence that all PTs can recur regardless of their histology, with the lowest incidences of recurrence observed in benign tumors and higher rates reported in borderline and malignant tumors^{8,13,15,17,18,22,76-78}. Local recurrence rates range from 15% to 40% among different types of PT^{3,15}. Nevertheless, surgical excision with breast conserving surgery (BCS) can offer adequate management, without causing significant cosmetic deformity⁹⁻¹¹. The National Comprehensive Cancer Network (NCCN) guidelines recommend at least a 1 cm excision margin or more as the best approach for conservative surgery¹². Cases with positive margins have a far higher local recurrence (LR) rates when compared to those with negative margins, highlighting the importance of achieving negative surgical margins at the initial surgical attempt regardless of PT histotype, and obviating the need for future mastectomy^{8,13,15,17,18,22,76-78}. The most common factors associated with local failure include not only positive margins, but also the presence of necrosis, stromal overgrowth, and larger tumor size. No difference was found in terms of LR between patients treated with BCS and mastectomy⁹⁻¹¹. A multicenter, large retrospective study on malignant PT management reported that a 3 mm margin threshold was adequate, with no impact of wider margins on overall survival (OS), while they recommended re-excision to obtain wider margins in cases with 0-1-2 mm margins¹³. The role of radiation therapy and chemotherapy remains undefined in the management of PT, which is further confounded due to a lack of randomized controlled data²⁴. Adjuvant radiotherapy may be ben-

eficial to reduce local recurrence and is sometimes considered for high risk malignant PT including those that are greater than 5 cm, have high stromal overgrowth, or more than 10 mitoses per HPF. Overall, radiotherapy has demonstrated a positive effect on local disease control, but without prolonging survival. The benefit of radiotherapy seems to be strongest for patients treated by BCS, especially when employed in patients with worse prognostic factors such as large tumor size or tumor necrosis. Further prospective studies are needed to demonstrate the efficacy of adjuvant therapy, since most data thus far have been retrospective^{13,25-26}. Chemotherapy has been used for recurrent and metastatic disease, without clear survival benefit. Patients with recurrent or metastatic PT are often treated in accordance with the guidelines for metastatic soft tissue sarcomas, as recommended by the NCCN⁴⁶. Prior studies reporting adjuvant chemotherapy did not improve metastasis-free survival^{9,13,27}. The potential role of endocrine therapy in this clinical setting is limited, as stromal cells constitute the neoplastic cell population in PTs and only exhibit low stromal expression of hormone receptors (ER, PR)¹. The reported 5-year survival rate for malignant PTs ranges from 54% to 82%, sometimes even up to 95.7%^{9,15}.

Conclusion

PT is a rare biphasic neoplasm of the breast, which belongs to the group of non-epithelial tumors. Malignant PT of the breast is a very rare disease. Although most PTs are benign, careful attention to worrisome clinical and radiological features is critical. Furthermore, reliable pre-surgical diagnosis on CNB can be difficult. The identification of PT based solely on their cytological features in FNA samples is controversial. More studies on histologic features and molecular correlations are needed to reach more accurate pre-surgical diagnosis. The role of genetic alterations in the acquisition of malignant characteristics and aggressive biologic behavior in PT is under investigation. Clearly, while much is known about the pathology and biology of PTs, more research is needed to refine diagnosis and improve treatment.

ABBREVIATIONS:

Malignant phyllodes tumor (MPT), Phyllodes tumor (PT), Multidisciplinary Meeting (MDM), Breast conserving surgery (BCS), Local recurrence (LR), Overall survival (OS).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

No competing financial interests exist for all the authors.

ETHICAL CONSIDERATION

All patients consented to their procedure. We received institutional (Catholic University of the Sacred Heart) ethics approval for this study.

AUTHORS' CONTRIBUTION

EDR, LP, JLH, planned conceived and designed the study, GL, MA, SA, GP, LN, EC, AAA conducted the evaluation and acquisition of data, PV, GL, MA, EDR, LP, JLH revised the draft and data.

References

- Tan PH. Fibroepithelial tumors and hamartomas of the breast. In Breast tumors. WHO classification of tumors. 5th Ed. IARC Press: Lyone 2019, pp. 165-176.
- Tse GM, Lee CS, Kung FY, et al. Hormonal receptors expression in epithelial cells of mammary phyllodes tumors correlates with pathologic grade of the tumor: a multicenter study of 143 cases. *Am J Clin Pathol* 2002;118:522-526. <https://doi.org/10.1309/D206-DLF8-WDNC-XJ8K>
- Rosen PP, Oberman HA. Tumors of the Mammary Gland. Washington, DC: Armed Forces Institute of Pathology 1993.
- Muller J. Uber den Feineren bau und die formen der krankhaften geschwulstre. Berlin G. Reimer 1838;54.
- Lee BJ, Pack GT. Giant intracanalicular fibroadenomomyxoma of the breast. The so-called cystosarcoma phyllodes mammae of Johannes Muller. *Am J Cancer* 1931;15:2583 <https://doi.org/10.1097/0000658-193101000-00034>
- Liang M, Ramaswamy B, Patterson CC, et al. Giant breast tumors: Surgical management of phyllodes tumors, potential for reconstructive surgery and a review of literature. *World J Surg Oncol* 2008;6:117. <https://doi.org/10.1186/1477-7819-6-117>
- Zhang Y, Kleer CG. Phyllodes tumor of the breast: histopathologic features, differential diagnosis, and molecular/genetic updates. *Arch Pathol Lab Med* 2016;140:665-671. <https://doi.org/10.5858/arpa.2016-0042-R>
- Liang MI, Ramaswamy B, Patterson CC, et al. Giant breast tumors: Surgical management of phyllodes tumors, potential for reconstructive surgery and a review of literature. *World J Surg Oncol* 2008;6:117. <https://doi.org/10.1186/1477-7819-6-117>
- Lakhani SR, Ellis IO, Schnitt SJ, et al., eds. World Health Organization Classification of Tumours of the Breast. Vol. 4. Lyon: IARC Press 2012.
- Noguchi S, Motomura K, Inaji H, Imaoka S, Koyama H. Clonal analysis of fibroadenoma and phyllodes tumor of the breast. *Cancer Res* 1993, 53:4071-74
- Papas Y, Asmar AE, Ghandour F, et al. Malignant phyllodes tumors of the breast: A comprehensive literature review. *Breast J* 2020;26:240-244
- Chao TC, Lo YF, Chen SC, et al. Sonographic features of phyllodes tumors of the breast. *Ultrasound Obstet Gynecol* 2002;20:64-71. <https://doi.org/10.1046/j.1469-0705.2002.00736.x>
- Asoglu O, Ugurlu MM, Blanchard K, et al. Risk factors for recurrence and death after primary surgical treatment of malignant phyllodes tumors. *Ann Surg Oncol* 2004;11:1011-1017. <https://doi.org/10.1245/ASO.2004.02.001>
- Barrio AV, Clark BD, Goldberg JI, et al. Clinicopathologic features and long-term outcomes of 293 phyllodes tumors of the breast. *Ann Surg Oncol* 2007;14:2961-2970. <https://doi.org/10.1245/s10434-007-9439-z>
- Kapiris I, Nasiri N, AHern R, et al. Outcome and predictive factors of local recurrence and distant metastases following primary surgical treatment of high-grade malignant phyllodes tumours of the breast. *Eur J Surg Oncol* 2001;27:723-730. <https://doi.org/10.1053/ejso.2001.1207>
- National Comprehensive Cancer Network. Phyllodes tumor, version 1.2018. Plymouth Meeting (PA): NCCN 2018.
- Neron M, Sajous C, Thezenas S, et al. Surgical margins and adjuvant therapies in malignant phyllodes tumors of the breast: a multicenter retrospective study. *Ann Surg Oncol* 2020;27:1818-1827. <https://doi.org/10.1245/s10434-020-08217-y>
- Ogunbiyi S, Perry A, Jakate K, et al. Phyllodes tumour of the breast and margins: How much is enough? *Can J Surg* 2019;62:E19-E21. <https://doi.org/10.1503/cjcs.005718>
- Veneti S, Manek S. Benign phyllodes tumour vs fibroadenoma: FNA cytological differentiation. *Cytopathology* 2001;12:321-328. <https://doi.org/10.1046/j.1365-2303.2001.00334.x>
- Cohn-Cedermark G, Rutqvist LE, Rosendahl I, et al. Prognostic factors in cystosarcoma phyllodes: a clinicopathologic study of 77 patients. *Cancer* 1991;68:2017-2022. [https://doi.org/10.1002/1097-0142\(19911101\)68:9<2017::aid-cnrc2820680929>3.0.co;2-v](https://doi.org/10.1002/1097-0142(19911101)68:9<2017::aid-cnrc2820680929>3.0.co;2-v)
- Spitaleri G, Toesca A, Botteri E, et al. Breast phyllodes tumor: a review of literature and a single center retrospective series analysis. *Crit Rev Oncol Hematol* 2013;88:427-436. <https://doi.org/10.1016/j.critrevonc.2013.06.005>
- Wei J, Tan YT, Cai YC, et al. Predictive factors for the local recurrence and distant metastasis of phyllodes tumors of the breast: a retrospective analysis of 192 cases at a single center. *Chin J Cancer* 2014;33:492-500. <https://doi.org/10.5732/cjc.014.10048>
- Tan BY, Acs G, Apple SK, et al. Phyllodes tumours of the breast: a consensus review. *Histopathology* 2016;68:5-21. <https://doi.org/10.1111/his.12876>
- Holthouse DJ, Smith PA, Naunton-Morgan R, et al. Cystosarcoma phyllodes: the Western Australian experience. *Aust N Z J Surg* 1999;69:635-638. <https://doi.org/10.1046/j.1440-1622.1999.01654.x>
- El Hag IA, Aodah A, Kollur SM, et al. Cytological clues in the distinction between phyllodes tumor and fibroadenoma. *Cancer Cytopathol* 2010;118:33-40. <https://doi.org/10.1002/cncy.20057>
- Bhattarai S, Kapila K, Verma K, et al. Phyllodes tumor of the breast. A cytohistological study of 80 cases. *Acta Cytol* 2000; 44: 790-796. <https://doi.org/10.1159/000328563>
- Shimizu K, Korematsu M. Phyllodes tumor of the breast. A cytomorphologic approach based on evaluation of epithelial cluster architecture *Acta Cytol* 2002;46:332. <https://doi.org/10.1159/000326730>
- Maritz RM, Michelow PM. Cytological Criteria to Distinguish Phyllodes Tumour of the Breast from Fibroadenoma. *Acta Cytol* 2017;61:418-424. <https://doi.org/10.1159/000477573>
- Jacklin RK, Ridgway PF, Ziprin P, et al. Optimising preoperative diagnosis in phyllodes tumour of the breast *J Clin Pathol* 2006;59:454-459. <https://doi.org/10.1136/jcp.2005.025866>
- Komenaka IK, El-Tamar M, Pile-Spellman E, et al. Core needle biopsy as a diagnostic tool to differentiate phyllodes tumor from fibroadenoma. *Arch Surg* 2003;138:987-990. <https://doi.org/10.1001/archsurg.138.9.987>
- Parker SJ, Harries SA. Phyllodes tumours. *Postgrad Med J* 2001;77:428-435. <https://doi.org/10.1136/pmj.77.909.428>

- 32 Choi J, Koo JS. Comparative study of histological features between core needle biopsy and surgical excision in phyllodes tumor. *Pathol Int* 2012;62:120-126.
- 33 Leibl S, Gogg-Kammerer M, Sommersacher A et al. Metaplastic breast carcinomas: are they of myoepithelial differentiation?: immunohistochemical profile of the sarcomatoid subtype using novel myoepithelial markers *Am J Surg Pathol* 2005;29:347-353. <https://doi.org/10.1097/01.pas.0000152133.60278.d2>
- 34 Suzuki-Uematsu S, Shiraishi K, Ito T, et al. Malignant phyllodes tumor composed almost exclusively of a fibrosarcomatous component: a case report and review of malignant phyllodes tumors with metastases. *Breast Cancer* 2010;17:218-224. <https://doi.org/10.1007/s12282-009-0099-7>
- 35 Abdelkrim SB, Trabelsi A, Bouzrara M, et al. Phyllodes tumors of the breast: A review of 26 cases. *World J Oncol* 2010;1:129-134. <https://doi.org/10.4021/wjon2010.06.220w>
- 36 Mitus J, Reinfuss M, Mitus JW, et al. Malignant phyllodes tumor of the breast: treatment and prognosis. *Breast J* 2014;20: 639-644. <https://doi.org/10.1111/tbj.12333>
- 37 Liu M, Yang S, Liu B et al. Giant malignant phyllodes tumor of the breast: a rare case report and literature review. *Oncology Lett* 2016;12:121-124. <https://doi.org/10.3892/ol.2016.4583>
- 38 Pornchai S, Chirappapha P, Pipatsakulroj W et al. Malignant transformation of phyllodes tumor: a case report and review of literature. *Clin Case Reports* 2018;6:678-685. <https://doi.org/10.1002/ccr3.1428>
- 39 Stamatakos M, Tsaknaki S, Kontzoglou K et al. Phyllodes tumor of the breast: A rare neoplasm, though not that innocent. *Internat Sem Surg Oncol* 2009;6:6-11. <https://doi.org/10.1186/1477-7800-6-6>
- 40 Krishnamurthy S, Ashfaq R, Shin HJ, et al. Distinction of phyllodes tumor from fibroadenoma: a reappraisal of an old problem. *Cancer* 2000;90:342-349.
- 41 Lawton TJ, Acs G, Argani P et al. Interobserver variability by pathologist in the distinction between cellular fibroadenomas and phyllode tumors. *Int J Surg Pathol* 2014;22:695-698. <https://doi.org/10.1177/1066896914548763>
- 42 Mylvaganam S, Toro C, Frank L, et al. Phyllodes tumors of the breast: best practice for follow-up. *Updates Surg* 2015;67:91-95 <https://doi.org/10.1007/s13304-015-0278-3>.
- 43 Chen WH. Surgical treatment of phyllodes tumors of the breast: retrospective review of 172 cases. *J Surg Oncol* 2005;91:185-194. <https://doi.org/10.1002/jso.20334>
- 44 August DA, Kearney T. Cystosarcoma phyllodes: mastectomy, lumpectomy, or lumpectomy plus irradiation. *Surg Oncol* 2000;9:49-52. [https://doi.org/10.1016/s0960-7404\(00\)00022-0](https://doi.org/10.1016/s0960-7404(00)00022-0)
- 45 Chao, X., Chen, K., Zeng, J. et al. Adjuvant radiotherapy and chemotherapy for patients with breast phyllodes tumors: a systematic review and meta-analysis. *BMC Cancer* 2019;19:372.
- 46 Gradishar WJ, Anderson BO, Balassanian R, et al. NCCN Guidelines Insights: breast Cancer, Version 1.2017. *J Natl Compr Canc Netw* 2017;15:433-451. <https://doi.org/10.6004/jnccn.2017.0044>
- 47 Cimino-Mathews A, Argani P, Sharma, R, et al. A subset of malignant phyllodes tumors express p63 and p40: a diagnostic pitfall in breast core needle biopsies 2014;38:1689-1696. <https://doi.org/10.1097/PAS.0000000000000301>
- 48 Chia Y, Thike A, Cheok PY, et al. Stromal keratin expression in phyllodes tumours of the breast: a comparison with other spindle cell breast lesions *J Clin Pathol* 2012;65:339-347. <https://doi.org/10.1136/jclinpath-2011-200377>
- 49 Sawyer EJ, HanbyAM, Rowan AJ, et al. The Wnt pathway, epithelial-stromal interactions, and malignant progression in phyllodes tumours. *J Pathol* 2002;196:437-444. <https://doi.org/10.1002/path.1067>
- 50 Sawyer EJ, HanbyAM, Poulosom R, et al. Beta-catenin abnormalities and associated insulin-like growth factor overexpression are important in phyllodes tumours and fibroadenomas of the breast. *J Pathol* 2003;200:627632. <https://doi.org/10.1002/path.1391>
- 51 NoronhaY, RazaA, Hutchins B, et al. CD34, CD117, and Ki-67 expression in phyllodes tumor of the breast: an immunohistochemical study of 33 cases. *Int J Surg Pathol* 2011;19:152-158. <https://doi.org/10.1177/1066896910382009>
- 52 Tan PH, Jayabaskar T, Yip G, et al. p53 and c-kit (CD117) protein expression as prognostic indicators in breast phyllodes tumors: a tissue microarray study. *Mod Pathol* 2005;18:1527-1534. <https://doi.org/10.1038/modpathol.3800488>
- 53 Tse GM, Lui PC, Vong JS, et al. Increased epidermal growth factor receptor (EGFR) expression in malignant mammary phyllodes tumors. *Breast Cancer Res Treat* 2009;114:441-448. <https://doi.org/10.1007/s10549-008-0030-5>
- 54 Karim RZ, Gerega SK, Yang YH, et al. p16 and pRb immunohistochemical expression increases with increasing tumour grade in mammary phyllodes tumours. *Histopathology* 2010;56:868-875. <https://doi.org/10.1111/j.1365-2559.2010.03562.x>
- 55 Tse GM, LuiPC, Lee CS, et al. Stromal expression of vascular endothelial growth factor correlates with tumor grade and microvessel density in mammary phyllodes tumors: a multicenter study of 185 cases. *Hum Pathol* 2004;35:1053-1057. <https://doi.org/10.1016/j.humpath.2004.01.023>
- 56 Tariq MU, Haroon S, Kayani N. Role of CD10 immunohistochemical expression in predicting aggressive behavior of phyllodes tumors. *Asian Pac J cancer Prevention* 2015;16:3147-3152. <https://doi.org/10.7314/apjcp.2015.16.8.3147>.
- 57 Laé M, La Rosa P, Mandel J, et al. Whole-genome profiling helps to classify phyllodes tumours of the breast. *J Clin Pathol* 2016;69:1081-1087. <https://doi.org/10.1136/jclinpath-2016-203684>
- 58 Lv S, Niu Y, Wei L, et al. Chromosomal aberrations and genetic relations in benign, borderline and malignant phyllodes tumors of the breast: a comparative genomic hybridization study. *Breast Cancer Res Treat* 2008;112:411-418. <https://doi.org/10.1007/s10549-007-9876-1>
- 59 Lu YJ, Birdsall S, Osin P, et al. Phyllodes tumors of the breast analyzed by comparative genomic hybridization and association of increased 1q copy number with stromal overgrowth and recurrence. *Genes Chromosomes Cancer* 1997;20:275-281.
- 60 Tan WJ, Lai JC, Thike AA, et al. Novel genetic aberrations in breast phyllodes tumours: comparison between prognostically distinct groups. *Breast Cancer Res Treat* 2014;145:635-645. <https://doi.org/10.1007/s10549-014-2982-y>
- 61 Chang HY, Koh VCY, Md Nasir ND, et al. MED12, TERT and RARA in fibroepithelial tumours of the breast. *J Clin Pathol* 2020;73:51-56. <https://doi.org/10.1136/jclinpath-2019-206208>
- 62 Lien HC, Huang CS, Yang YW, et al. Mutational analysis of MED12 exon 2 in a spectrum of fibroepithelial tumours of the breast: implications for pathogenesis and histogenesis. *Histopathology* 2016;68:433-441. <https://doi.org/10.1111/his.12764>
- 63 Md Nasir ND, Ng CCY, Rajasegaran J et al. Genomic characterisation of breast fibroepithelial lesions in an international cohort. *J Pathol* 2019;249:447-460. <https://doi.org/10.1002/path.5333>
- 64 Loke BN, Md Nasir ND, Thike AA, et al. Genetics and genomics of breast fibroadenomas. *J Clin Pathol* 2018;71:381-387.
- 65 Kim JY, Yu JH, Nam SJ, et al. Genetic and clinical characteristics of phyllodes tumors of the breast. *Transl Oncol* 2018;11:18-23. <https://doi.org/10.1016/j.tranon.2017.10.002>
- 66 Geyer FC, Burke KA, Piscuoglio S, et al. Genetic analysis of uterine adenocarcinomas and phyllodes tumors of the breast. *Mol Oncol* 2017;11:913-926. <https://doi.org/10.1002/1878-0261.12049>

- ⁶⁷ Sim Y, Ng GXP, Ng CCY, et al. A novel genomic panel as an adjunctive diagnostic tool for the characterization and profiling of breast Fibroepithelial lesions. *BMC Med Genomics* 2019;12:142. <https://doi.org/10.1186/s12920-019-0588-2>
- ⁶⁸ Ng CCY, Md Nasir ND, Loke BN, et al. Genetic differences between benign phyllodes tumors and fibroadenomas revealed through targeted next generation sequencing. *Mod Pathol* 2021;34:1320-1332. <https://doi.org/10.1038/s41379-021-00787-w>
- ⁶⁹ Kersting C, Kuijper A, Schmidt H, et al. Amplifications of the epidermal growth factor receptor gene (egfr) are common in phyllodes tumors of the breast and are associated with tumor progression. *Lab Invest* 2006;86:54-61. <https://doi.org/10.1038/labinvest.3700358>
- ⁷⁰ Suo Z, Nesland JM. Phyllodes tumor of the breast: EGFR family expression and relation to clinicopathological features. *Ultrastruct Pathol* 2000;24:371-381. <https://doi.org/10.1080/019131200750060032>
- ⁷¹ Mohd Ali NA, Nasaruddin AF, Mohamed SS, et al. Ki67 and P53 Expression in relation to clinicopathological features in phyllodes tumour of the breast. *Asian Pac J Cancer Prev* 2020;21:2653-2659. <https://doi.org/10.31557/APJCP.2020.21.9.2653>
- ⁷² Vorotnikov IK, Vysotskaya IV, Denchik DA, et al. Prognostic molecular and biological characteristics of phyllodes tumors of the breast. *Bull Exp Biol Med* 2020;169:806-810. <https://doi.org/10.1007/s10517-020-04985-5>
- ⁷³ Confavreux C, Lurkin A, Mitton N, et al. Sarcomas and malignant phyllodes tumors of the breast-a retrospective study. *Europ J Cancer* 2006;42:2715-2721. <https://doi.org/10.1016/j.ejca.2006.05.040>
- ⁷⁴ Kraemer B, Hoffmann J, Roehm C, et al. Cystosarcoma phyllodes of the breast: A rare diagnosis: case studies and review of literature. *Arch Gynecol Obstet* 2007;276:649-653. <https://doi.org/10.1007/s00404-007-0393-6>
- ⁷⁵ Gnerlich JL, Williams RT, Yao K, Jaskowiak N, et al. Utilization of radiotherapy for malignant phyllodes tumors: analysis of the National Cancer Data Base, 1998-2009. *Ann Surg Oncol* 2014;21:1222-1230. <https://doi.org/10.1245/s10434-013-3395-6>
- ⁷⁶ Kapisir I, Nasiri N, A'Hern R, et al. Outcome and predictive factors of local recurrence and distant metastases following primary surgical treatment of high-grade malignant phyllodes tumours of the breast. *Eur J Surg Oncol* 2001;27:723-730. <https://doi.org/10.1053/ejso.2001.1207>
- ⁷⁷ Singh G, Sharma RK. Immediate breast reconstruction for phyllodes tumors. *Breast* 2008;17:296-301. <https://doi.org/10.1016/j.breast.2007.11.005>
- ⁷⁸ Farias-Eisner GT, Small K, Swistel A, et al. Immediate implant breast reconstruction with acellular dermal matrix for treatment of a large recurrent malignant phyllodes tumor. *Aesthetic Plastic Surgery* 2014;38:373-378. <https://doi.org/10.1007/s00266-014-0283-9>