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Phyllodes Tumors (Cystosarcoma Phyllodes): A Diagnostic and Therapeutic Challenge

Vargas-Hernandez VM[1] and Aguilar VMV[2]*

[1]Department of Gynecology and Obstetrics, Hospital Juarez de México, Mexico

[2]Department of Gynecology and Obstetrics, Tlaxcala Women's Specialties Hospital, Mexico

Abstract

Phyllodes tumors were first reported in 1774 and in 1838, Johannes Müller defined this tumor as cystosarcoma phyllodes. Phyllodes tumors represent less than 0.5% of all malignant breast tumors; an average annual incidence rate of 2.1 per million women is phyllodes tumor occur almost exclusively in women, most occur at the average age 42 to 45 years of age (ranging from 10 to 82 years), classification Precise and reproducible is a challenge, due to the need to evaluate multiple histopathological parameters, which hinder its interpretation; but, they are classified pathologically as benign, borderline and malignant according to the number of mitosis. They are presented as smooth, multinodular, asymptomatic mass and are suspected for their rapid tumor growth, or typical appearance in breast imaging. The treatment is surgical and wide local excision is recommended, with surgical margin >1 cm.

Conclusion: The Phyllodes tumor presents related challenges on histopathological diagnostic criteria, clinical behavior, preoperative diagnosis and correct management is important to avoid recurrences.

Keywords: Phyllodes tumor; Benign tumor; Malignant tumor; Lumpectomy; Mastectomy; Survival

Correspondence:

Vargas-Hernandez VM, Department of Gynecology and Obstetrics, Hospital Juarez de México, National Polytechnic Institute 5160, Magdalena de las Salinas, Gustavo A. Madero, 07760 Ciudad de México, CDMX, Mexico; Tel: 5557477503;

E-mail: vvargashernandez@yahoo.com.mx

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Introduction

Phyllodes tumors are rare fibroepithelial lesions that comprise 2% to 3% of all fibroepithelial tumors and 0.3% to 0.5% of all breast tumors in women. Detected at any age, they are rare in adolescents and postmenopausal; and the peak age is around 45 to 49 years; the incidence is low with a rate of 2.1/1,000,000 [1-3]. The tumor size was 6 cm (1 cm to 13 cm). Histopathologically, 55% are benign, 25% borderline and 20% malignant; they are morphologically similar to intracanalicular fibroadenomas at the benign end of the spectrum, but with greater stromal cellularity and a similar architecture [4-11].

Phyllodes tumors are classified into categories of benign, borderline and malignant grade based on histopathological parameters, that is, the degree of cellularity and atypia of the stroma, mitotic count, excessive stromal growth and surgical margins [1]. Since each microscopic parameter has two or three levels of stratification, there are significant challenges for its precise and reproducible categorization [3]. Phyllodes tumors have different forms of biological behavior; the least aggressive, is similar in behavior to benign fibroadenomas, although with a tendency to resort locally after excision without wide negative margins. At the other end of the spectrum are tumors that give distant metastases, sometimes with histopathologically sarcomatous degeneration without epithelial component [1,2,12]. Phyllodes tumors were first defined as a type of giant fibroadenoma in 1774. In 1838, Johannes Müller defined this tumor as "cystosarcoma phyllodes"; Cooper and Ackerman stated that biologically there is a malignant potential in these tumors in 1943, 64% of these tumors are benign and 25% malignant (Table 1) [1-3].

The classification criteria: Some suggest that these histopathologically defined categories do not reliably predict clinical behavior. The terminology of phyllodes tumors has evolved; sometimes they have cystic components, and because of their cellular origin or biological behavior they are not true sarcomas. The term phyllodes, similar to leaves, describes typical papillary projections that are observed on the histopathological examination; Since its original description, more than 60 synonyms have been applied to this entity and phyllodes tumors have been adopted by the World Health Organization (WHO) [3,4].

Table 1: Classification of filioid tumors.

Benign: The 0-4 mitosis/10 × magnification area, minimal stromal hypercellularity and atypia, minimal or moderate stromal growth and negative surgical margins.
Limit: The 5-9 mitosis/10 × magnification area, moderate stromal hypercellularity, atypia and stromal overgrowth, negative or permeable surgical margins.
Malignant: >10 mitosis/10 × magnification area, moderate or marked stromal hypercellularity, atypia and stromal overgrowth, permeable surgical margins.

Epidemiology

Phyllodes tumors represent less than 0.5% of all malignant breast tumors with greater incidence in white Latin women, compared to non-white Latinas, Asians and African Americans most present at the average age 42 years to 45 years of age (ranging from 10 years to 82 years), the tumor grade increases with the average age at diagnosis [3,13-17]. Some cases of these tumors occur in men, usually in association with gynecomastia [3].

There are no etiological or predisposing factors associated with phyllodes tumors, with the exception of Li-Fraumeni syndrome, an autosomal dominant rare disease characterized by the development of multiple tumors; it is suggested that phyllodes tumors arise from benign epithelial fibroadenomas due to their histopathological and molecular similarity, but it is still controversial [1-3,18,19].

Classification of Phyllodes Tumors

The diagnostic criteria and their classification the World Health Organization (WHO) recommends that they be diagnosed when the fibroepithelial architecture shows an exaggerated intracanalicular pattern with leaf branches protruding cystic dilated spaces accompanied by stromal hypercellularity [1-10]. A benign phyllodes tumor shows a slightly increased stromal cellularity compared to a fibroadenoma, and has minimal nuclear atypia, causing edges and mitosis of ≤ 4/10 High Potency Fields (HPFs). Stromal overgrowth is not present (defined as the stromal presence without epithelium in at least one observed low power field x4). The key feature to distinguish it from fibroadenoma is an exaggerated intracanalicular growth pattern with the presence of increased stromal cellularity. In the absence of well-developed stromal branches, presence of elongated, branched ducts and grooves that undulate through the cell stroma, are histopathological clues for diagnosis. At the other end of the spectrum, the malignant phyllodes tumor shows marked stromal cellularity and atypia has infiltrable margins, with mitotic activity of at least 10/10 HPFs. Stromal overgrowth is easily identified. Phyllodes tumors with intermediate or borderline characteristics, including the nature of the border of the tumor, stromal overgrowth, mitotic activity and cellular atypia.

There are no objective criteria to separate the minimum/mild levels of moderate and marked stromal hypercellularity and atypia, confusing classification attempts. The evaluation of stromal cellularity focuses on more cellular areas of the lesion, the mild hypercellularity characterized by a slight increase in stromal cells compared to normal perilobular stroma, with uniformly spaced nuclei that do not touch or hide. Marked stromal cellularity shows confluent areas of densely overlapping nuclei, while moderate stromal cellularity has intermediate findings, with some stromal nuclei overlapping (Figure 1). Mild stromal atypia shows nuclei with little variation in size, with mild nuclear contours. Moderate atypia shows variation in nuclear size, with contracted nuclear membranes, an extension that exceeds in mild atypia but less than the marked atypia. The marked atypia shows marked variation in nuclear size, thick chromatin and irregular nuclear membranes with confusing nucleoli, (Figure 1 and 2) [3,20].

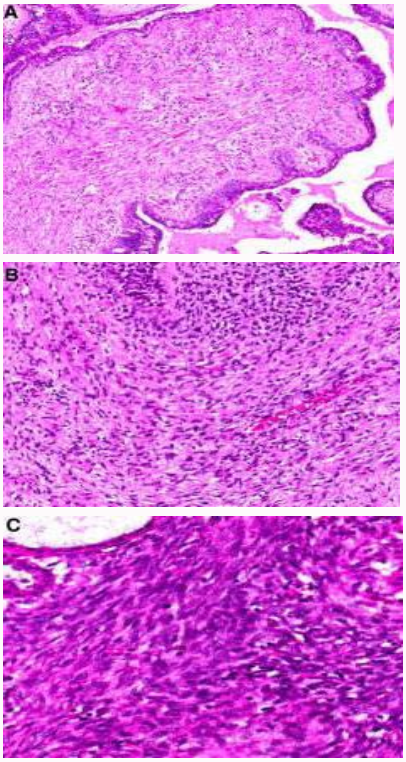

Figure 1: Evaluation of stromal cellularity in phyllodes tumors. (A) Mild hypercellularity with slight increase in cellularity, where the stromal nuclei do not overlap. (B) Moderate hypercellularity with some superimposed stromal nuclei. (C) Hypercellularity marked with many superimposed stromal nuclei.

The importance of the classification of phyllodes tumors is to predict their clinical behavior: the benign ones have the potential to recur locally; borderline tumors recur locally with a lower risk of metastasis; the malignant ones have a higher risk of metastatic behavior, which can be fatal, but it is generally accepted that they are rare for all forms of phyllodes tumors when complete local excision is performed.

The criteria are simple, but ambiguous; the way in which the subdivisions of each microscopic parameter interact constitutes the subjective final qualification. It is also not uncommon for phyllodes tumors to show intratumoral heterogeneity and benign characteristics in some areas and borderline or malignant in other foci, some pathologists consider a phyllodes tumor with marked stromal atypia and acute mitotic activity, but without permeable margins or excessive stromal growth, as a limit, others as malignant due to different characteristics, the atypical stromal prevailing (Figure 3). A phyllodes tumor is classified as malignant when it shows all the histopathological changes of malignancy and limit when not all the malignant characteristics are present. Malignant heterologous such as liposarcoma, chondrosarcoma or osteosarcoma is malignant regardless of whether other histopathological parameters (stromal hypercellularity, atypia, mitotic rate, excessive growth and nature of tumor borders) show characteristic changes of malignant phyllodes

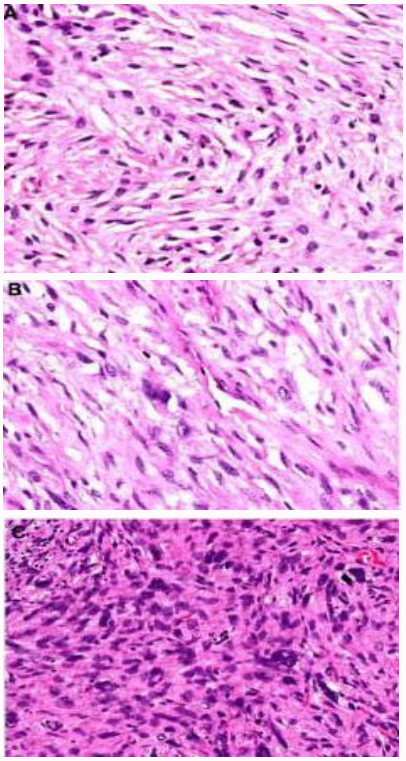

Figure 2: Evaluation of stromal atypia in phyloid tumors. (A) Mild nuclear atypia shows minimal variation in nuclear size with uniform chromatin and smooth nuclear contours. (B) Moderate nuclear atypia with more variation in nuclear size and irregular nuclear membranes. (C) Nuclear atypia marked with marked nuclear pleomorphism, hyperchromasia and irregular nuclear contours.

Table 2: Factors associated with local recurrence in Phyllodes tumors of the breast (NAMMOSS).

1. Tumor necrosis (N)
2. Age (A)
3. Positive resection margin or resection within 1 cm (M)
4. Increased mitotic index (M)
5. Stromal overgrowth (O)
6. Stromal atypia (S)
7. Large tumor size (S)
8. Stromal atypia (S)

tumor; stromal atypia, mitosis, overgrowth and surgical margins are independent predictors of clinical behavior and the most important surgical margin (Table 2). The surgical approach and the tumor border are independent prognostic factors of recurrence-free or postoperative Recurrence-Free Survival (RFS) in Patients with Breast Phyllodes Tumors (PTBs), a clinical management approach based on the histopathological type is recommended, border tumor, residual tumor, mitotic activity degree of stromal cell hyperplasia and atypia. This predictive nomogram based on clinic pathological and surgical characteristics is applied for its management [20].

Biological behavior and metastatic potential of phyllodes tumors

The recurrence rates reported were and 23% to 30% for benign, borderline and malignant tumors [11,15,18], respectively with distant metastases in 9% of malignant tumors [1]; Asian patients have a higher recurrence rate than those of non-Asian origin [14].

Table 3: Metastasis in philoid tumors according to the grade.

Authors	Tumor Grade,% (no.)		
(2000-2015)	Benign	Limitrofe	Malignant
Total	0.13 (2/1524)	1.62 (7/431)	16.71 (66/395)

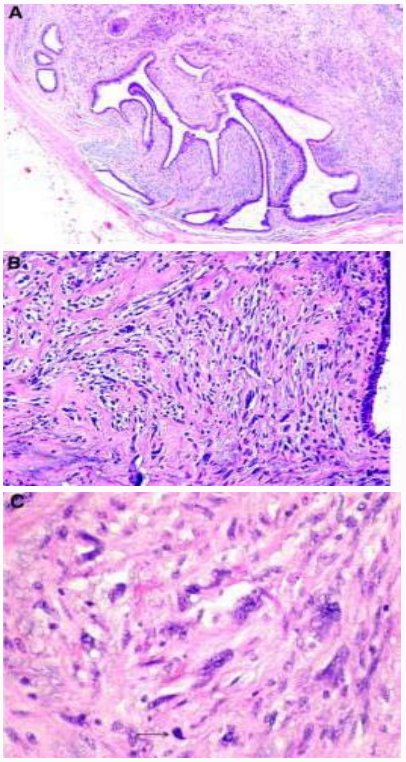

Figure 3: Phylloid tumor classified as a limit, since they do not meet all the malignancy criteria. (A) Rounded thrust contour of the tumor. (B) Stromal hypercellularity of moderate degree, accompanied by focally marked nuclear atypia. (C) The highest enlargement of atypical stromal cells showed hyperchromatic nuclei, prominent nucleoli and occasional mitosis (arrow).

Progression of grade during local recurrence; it occurs due to lack of representative sampling of the initial tumor, tumor heterogeneity with the presence of stromal subclones and the loss of stromal-epithelial interdependence [15,16]. The metastases and death of phyllodes tumors are preceded by a primary malignant diagnosis [17], which must be recognized for proper and effective clinical management. The metastases are of poor prognosis and fatal [19]. They occur mainly in lung and skeleton, although, all sites are affected (Figure 4). Histopathologically, metastases include malignant stromal elements without an accompanying epithelium [17,19]. Two exceptional cases of metastatic phyllodes tumors that house an epithelial component, primary and metastatic tumors, showed liposarcomatous differentiation. The metastatic epithelial component doubled the immunoreactivity of the Estrogen Receptor (ER), Progesterone Receptor (RP) and cystic disease cystic protein observed in the epithelium of the primary tumor [19].

Metastases rarely occur in benign phyllodes tumors, but they should be adequately studied for intratumoral heterogeneity, metastatic behavior, risk in malignant phyllodes tumors, although rare, and accurate histopathological diagnosis (Table 3).

Relationship between fibroadenoma and phyllodes tumor

Phyllodes tumors are generally considered de novo lesions derived from periductal and specialized lobular stroma. The initiation

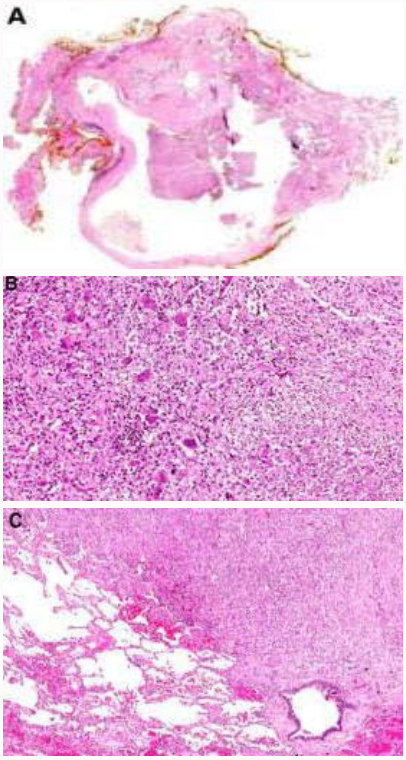

Figure 4: Malignant phyllodes tumor with lung metastases. (A) Low enlargement of the primary tumor with cystic space projected by the stromal branches. Part of the tumor showed fibroadenoma-like appearance, the remaining parts were more cellular. (B) The highest enlargement of the stromal cell areas showed thick swollen cell sheets with enlarged vesicular nuclei with distinct nucleoli and scattered mitoses. Several giant osteoclastic cells were dispersed among the spun cells. (C) Lung metastasis 1 year later showed clefts with scattered osteoclastic giant cells. There was no epithelial component present in metastasis.

of tumor genesis depends on epithelial-stroma interactions, the histopathological overlap between fibroadenoma and phyllodes tumor have pathogenetic kinship [12,21-28]. Epithelial and stromal cells were polyclonal in all 10 fibroadenomas, while stromal cells were monoclonal in all five phyllodes tumors, the same allele of the androgen receptor gene was inactivated in fibroadenomas and phyllodes tumors in each of the three patients with both tumors, 5% (1/20) of "complex" fibroadenomas and 1% (1/25) of "simple" fibroadenomas showed stromal monoclonality. 'Simple' fibroadenoma coexisted with a phyllodes tumor component, which showed a similar stromal monoclonality; the areas of 'stromal expansion' in three of the 25 fibroadenomas were monoclonal. In addition, nine of the 12 phyllodes tumors showed stromal monoclonality, Phyllodes tumors harbored a subset of Loss of Heterozygosity (LOH), which were absent in fibroadenomas. Primary and recurrent phyllodes tumors shared common regions of LOH. A single laser microdissected fibroadenoma and the phyllodes (synchronous) tumor showed similar allelic loss (D7S522) in both components, while the phyllodes component showed additional losses in TP53 and D22S264. The 11 of the 36 cases of malignant phyllodes tumors were associated with previous diagnoses of fibroadenomas, benign Phyllodes tumors that developed in a mother, and her daughter raised the possibility of a genetic predisposition for phyllodes tumor development. Recurrent somatic mutations in exon 2 of MED12 were discovered in 59% of 98 fibroadenomas in exome sequencing, with 71% of mutations occurring in codon 44. MED12 mutations were found in phyllodes

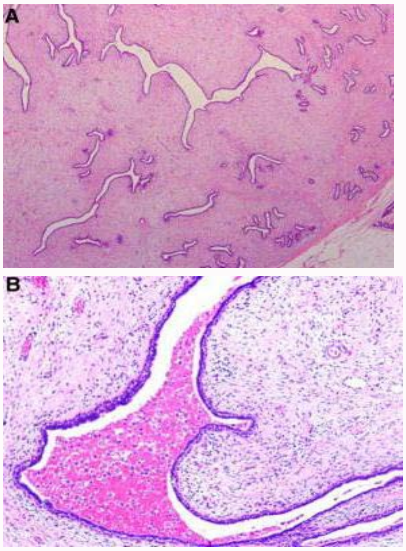

Figure 5: Cellular fibroepithelial neoplasia; the differential diagnosis of cellular fibroadenoma against a benign phyloid tumor. (A) The low increase showed some elongated grooves aligned epithelium with stromal clusters. Mild stromal hypercellularity was observed. (B) Higher increase of a stromal frond pushing the cleft space that contained blood and hemosiderophages, with accentuation of the stromal nuclei in the peri-epithelial area.

tumors of all grades histological in the next generation of sequencing. Other mutations in p53, RB1 and NF1, as well as high-level alterations in copy number, such as amplifications in EGFR and IGF1R, were characteristic of malignant tumors; all grades of phyllodes tumors showed MED12 mutations. The microdissection analysis confirmed MED12 mutations to be stroma confined in fibroadenomas and phyllodes tumors, malignant phyllodes tumors were significantly less likely to harbor MED12 mutations than fibroadenomas, and benign tumors and borderline phyllodes; MED12 mutations were found in 67% of fibroadenomas (6/9) and in 45% of phyllodes tumors (5/11); 60% of all fibroepithelial breast lesions (fibroadenomas and phyllodes tumors) showed MED12 mutations. Intracanalicular fibroadenomas showed the highest frequency of mutations (82%), while malignant phyllodes tumors were less likely to contain mutations (20%); 62.5% (70/112) of phyllodes tumors showed MED12 mutations. Tumors with MED12 mutations were associated with longer disease-free survival, while the absence of MED12 mutations was correlated with a higher chance of recurrence [28-30].

Cellular fibroepithelial lesions evaluated by different breast pathologists using the WHO criteria, in few cases a uniform agreement was reached as to whether the lesion represented a cellular fibroadenoma or a phyllodes tumor, the problematic lesions were over diagnosed When the fibroadenomas Cellular and benign phyllodes tumors were combined and compared with borderline and malignant tumors; improved considerably, with complete agreement in 53% of cases [30-32]. It is a challenge to separate cellular fibroadenomas from benign phyllodes tumor at one end of the spectrum, and the difficulty of achieving a consensus on the classification of phyllodes tumors (Figure 5). Fibroadenomas in pediatric age tend to have an increased stromal cellularity, which should not be over-interpreted, apart from the increase in stromal cellularity in pediatric fibroepithelial tumors, mitotic activity, up to 7 mitoses/10 HPF can be found, an evaluation of mitotic and cellular activity in pediatric fibroepithelial lesions and diagnosis are needed Phyllodes tumor is based on the findings of well-developed stromal leaves accompanied by increased stromal

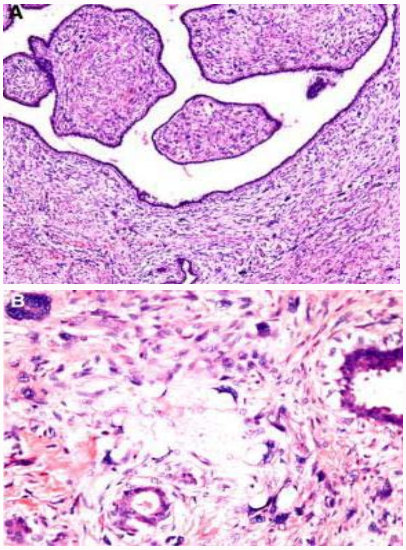

Figure 6: Malignant phyloid tumor with liposarcoma. (A) The stromal branches contained cells with marked nuclear pleomorphism with few foreign cells. (B) Among the abnormal stromal cells were scattered lipoblasts with hyperchromatic nuclei terminated with vacuolated cytoplasm, indicating a liposarcomatous component.

Figure 7: Clinical appearance of the phyloid tumor as an asymmetric breast and vascular network presence (a and b). Visual palpation findings: palpation revealed a 10-cm hard, elastic, non-movable mass in the medial left breast (a).

hypercellularity [33-36].

The 60% concordance rate between thick needle biopsies and the surgical specimen, the larger tumor size correlates significantly with the results [37]. Clinical-radiological evaluation as size and density contribute to clinical decision making, the histomorphological assessment of the lesion removed is the standard diagnostic reference; for classification [38], the presence of foliar architecture and increased stromal cellularity typically used as a discriminant between cellular fibroadenoma and benign phyllodes tumor. Fibroadenomas containing multinucleated giant stromal cells also confuse with phyllodes tumors and Ki67 proliferation activity as an aid WHO has proposed that the term "benign fibroepithelial neoplasia" be used in equivocal cases [3], in order to avoid over-treating, should be used sparingly, it does not represent a new category of diagnosis, it was claimed that the "recurrences" of fibroadenomas were undoubtedly presentations of multicentric lesions; which contrasts with the 10.9% recurrence rate of benign phyllodes tumors that typically occurs at the site of previous surgery [4]. The recurrence rate 3.4% in benign phyllodes tumors, with all benign recurrent cases 74, without any association with the surgical margin, malignant phyllodes tumors are associated with a recurrence rate of 29.6%, metastases and Death in 22%, require complete surgical eradication [1,4].

At the other end of the histopathological spectrum, a high-grade breast fusiform cell neoplasm invokes different diagnostic considerations, namely malignant phyllodes tumor with sarcomatous overgrowth, metaplastic fusiform cell carcinoma and primary or secondary breast sarcoma. The architectural seal of foliar foliage crowned by benign glandular epithelium serves to delineate the phyllodes tumor of its simulators. In some malignant phyllodes tumors, the greater stromal growth may be so prominent that epithelial elements are difficult to find, requiring extensive sampling with many cuts for identification. The stroma of a malignant phyllodes tumor sometimes shows heterologous sarcomatous differentiation, most often liposarcoma, or myosarcoma, angiosarcoma, chondrosarcoma and osteosarcoma (Figure 6) [33].

A spindle cell metaplastic breast carcinoma contains varying proportions of malignant epithelial component, squamous, glandular or adenosquamous type. Metaplastic carcinomas are also completely devoid of frank epithelial elements or, show heterologous mesenchymal differentiation; liposarcomatous elements are almost not seen. The presence of ductal carcinoma in situ adjacent to a malignant tumor of mammary fusiform cells favors the diagnosis of metaplastic carcinoma. Primary breast sarcomas are rare and metastatic breast sarcomas are exceptionally rare, with no histopathological features other than the phyllodes tumor or metaplastic breast carcinoma and histopathologically common to sarcomas anywhere. The history of previous or metastatic sarcoma, image and clinical correlation is useful [10,18,22,30].

In limited samples with thick needle biopsies, the precise diagnosis of high-grade malignant breast malignant cell lesions is excessively difficult, especially when an epithelial element is elusive. The demonstration of diffuse cytokeratin or p63 immunoreactivity in malignant bone cells supports a diagnosis of metaplastic carcinoma, although interpretation should be moderated in cases of focal keratin or p63 expression, such reactivity's have been described in stromal tumor cells phyllodes [34]. The usefulness of p40 in the diagnosis of this investigation; it is more specific but less sensitive than p63 [35,36], like p63, p40 if it stains the stromal cells of phyllodes tumors in some cases; the reactivity of CD34, described in the stromal cells of phyllodes tumors, is inversely related to adverse histopathological characteristics [13,14]; and will be considered of diagnostic utility to differentiate high-grade lesions from spindle cell lesions of the breast, as malignant phyllodes tumors are less likely to express CD34. Other markers, including bcl-286, which is expressed more frequently in phyllodes tumors, CD117, shows greater expression in phyllodes tumors of higher grade and cytogenetic alterations specific to sarcoma are possible diagnostic complements. Although aberrant nuclear β-catenin is routinely used in the diagnosis of fibromatosis, it is expressed in the stroma of phyllodes tumors, as well as in metaplastic carcinomas. The use of β-catenin as a solitary marker in the evaluation of spindle cell lesions breast should be warned. The appropriate sample, at least one centimeter of tumor size, with heterogeneous areas and morphological evaluation, is the standard reference for diagnosis, supported by clinical, radiological and immunohistochemical correlation [1-14].

Epithelial-stromal interactions in phyllodes tumors

In stromal mitotic activity occurs near the epithelial compartment in fibroepithelial lesions, and stromal growth depends on the

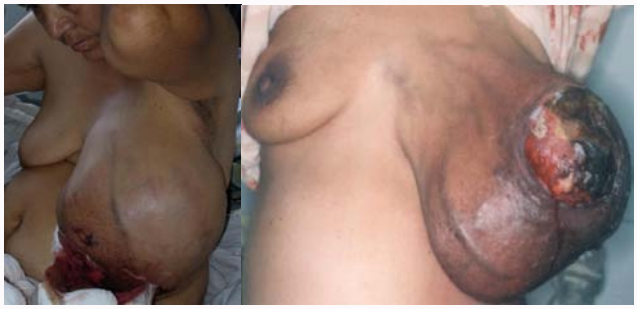

Figure 8: Clinical appearance of the Phyllodes tumor as an asymmetric breast and presence of vascular and ulcerated network.

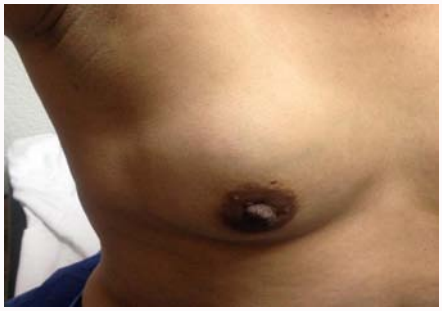

Figure 9: Clinical appearance of the Phyllodes tumor in an adolescent with the presence of bulging tumor in the right breast.

epithelial component; the increase in malignancy correlates with the loss of stromal dependence in the epithelium. Allelic balances were demonstrated on chromosomes 3p and 1q on both epithelial and stromal elements of the phyllodes tumor 96; Stromal proliferation is observed in benign phyllodes tumors dependent on anomalies in the Wnt pathway resulting from Wnt5a epithelial component expression, with malignant progression, linked to the independence of the latter. E-cadherin is a known epithelial differentiation marker that it is affected by the Wnt signaling pathway, and its expression in the epithelium of phyllodes tumors was correlated with the shorter recurrence and specific survival, the (PDGF)/copropolity of the PDGF-β stromal receptor that correlated with the disease-related death in 43% of phyllodes tumors 98. Clonal abnormalities have been detected in both epithelial and stromal components of phyllodes tumors. The expression of biomarkers in epithelial and stromal elements gives greater credibility to their interactions, the level of CXCR4, an epithelial-stromal interaction related to the molecular interaction, is encoded he noted that it increased in the stromal component of higher grade phyllodes tumors [13,14].

The expression of hormonal receptors and the reactivity of HER2/c-erbB-2 in phyllodes tumors, the expression of RE-α was limited to the epithelial compartment, without stromal positivity, demonstrating an inverse correlation with grade. The expression of RE-β, is observed in stromal cells of the tumor Phyllodes; but, its role is limited, MED12 mutations are related to aberrantly activated estrogen signaling [2,14,38-43].

Clinical presentation and diagnosis

Phyllodes tumors are usually identified for the first time as a breast mass or abnormal mammographic finding. On clinical breast examination, most patients have a firm, well-defined multinodular smooth mass that is mobile and painless [1-8]. The size of the tumor is variable, from 1 cm and 41 cm (on average from 4 cm to 7 cm); the skin is bright, stretched, and diminished that the inspection is seen to cover the tumor. There is rarely a nipple retraction, ulceration, chest wall fixation, or bilateral disease (Figures 7-9) [1-13].

Tumors can be slow or fast growing, or exhibit a biphasic growth pattern. As they grow, phyllodes tumors distort the breast or cause superficial ulceration through pressure necrosis. The mass is visible on inspection, mainly when it expands rapidly: the clinical lymph node involvement of the palpable axillary is identified in 20%; but, positive or metastatic lymph nodes are rare [4-13]. The typical appearance of a phyllodes tumor on Mammography (MMG) is a smooth, polylobulated mass similar to a fibroadenoma; 20% of phyllodes tumors present as a palpable mass identified in the screening MMG. Suspicion of phyllodes tumor instead of fibroadenoma is based on the presentation of large and rapidly growing tumor size [1,13]. Patients with suspicious lesion of phyllodes tumors in the MMG should have an ultrasound; where mainly they are reported as solid, hypoechoic and well circumscribed; Occasionally cystic areas are present within the mass that increases the suspicion of phyllodes tumors (Figures 10-13) [13,42].

The role of Magnetic Resonance Imaging (MRI) in the diagnosis and management of phyllodes tumors is unclear; in malignant phyllodes tumors are well circumscribed tumors with irregular walls, high signal intensity in T1 weighted images and low signal intensity in T2 weighted images, with cystic changes. Rapid growth is most often observed in benign and non-malignant phyllodes tumors, which is the opposite of what was observed in breast adenocarcinoma. When the diagnosis of phyllodes tumor is made in a thick needle biopsy, MRI is useful to determine the extent of the disease and facilitate pre-surgical management; although, it is controversial [1-8].

The main challenge facing doctors in emerging countries is the availability of resources to properly distinguish between fibroadenoma and phyllodes tumor, to reach their classification for surgery improves their prognosis if it is malignant [3]. Fine needle aspiration biopsy is associated with false negative results with high or low overall accuracy for diagnosis, the three main diagnostic cytological features are: fibromixoid stromal fragments with fusiform nuclei, fibroblast layers and cells fusiform thick needle biopsy is the preferred method of making a diagnosis [1-13]. There are some useful features to distinguish phyllodes tumors and fibroadenomas in the thick needle biopsy sample. These include increased cellularity, mitosis, excessive stromal growth, and fragmentation (stroma with

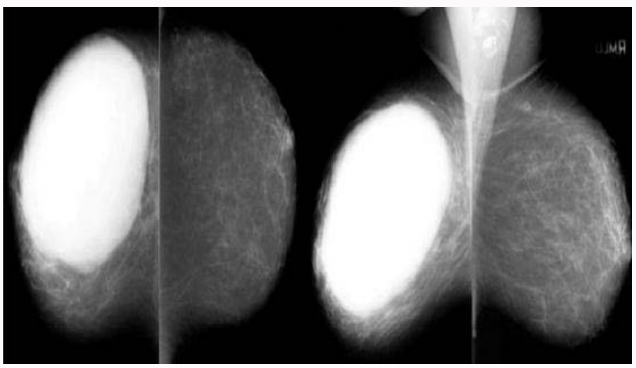

Figure 10: Mammography demonstrating a well-circumscribed lobed mass with rounded edges. Radio transparent halo around the lesion due to compression.

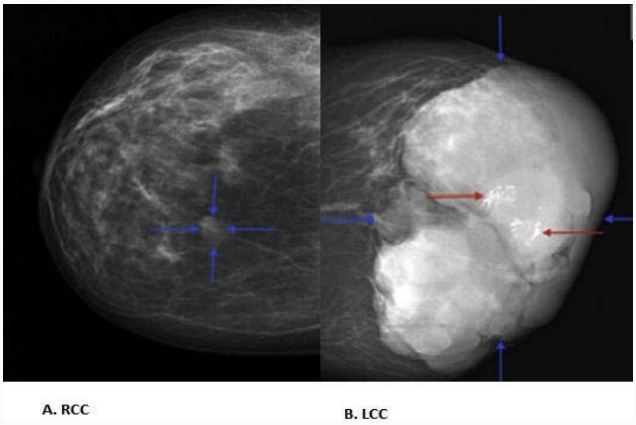

Figure 11: Mammographic image of the left breast. A). The right craniocaudal view showing heterogeneously dense breast tissue with a rather well defined spherical opacity in the upper right inner quadrant (blue arrows). YES). The left craniocaudal view shows a large mass of 13 cm (AP) × 13 cm (TS) with lobed margins that replace most of the left mammary parenchyma (blue arrows). There are some scattered foci of thick, punctate and plaque-shaped calcifications within the mass centrally (red arrows).

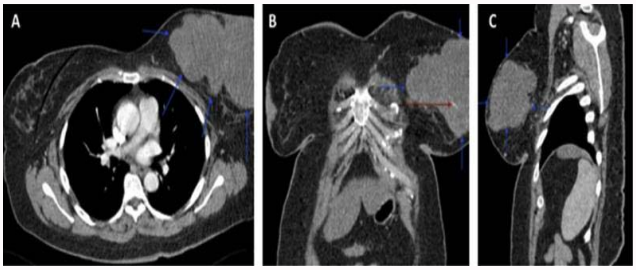

Figure 12: Images of a CT scan of the chest after IV contrast in the arterial phase and in the soft tissue window without significant improvement after administration of IV contrast. A). Axial view A large mass of lobulated soft tissue density in the left breast corresponding to the mammographic mass seen above (blue arrows) is partially seen in the field of vision. The displayed portion measures 9 cm (AP) × 12 cm (TS). No enlarged axillary or internal mammary lymph nodes are observed. YES). Coronal Image A large mass of lobulated soft tissue density in the left breast corresponding to the mammographic mass seen above (blue arrows) is partially seen in the field of vision. Few central calcifications were observed (red arrow). The displayed portion measures 12 cm (TS) × 12 cm (Skull-Flow, CC). C) Parasagittal image. A large mass of lobulated soft tissue density in the left breast corresponding to the mammographic mass seen above (blue arrows) is partially seen in the field of vision. The portion displayed is 9 cm (AP) × 12 cm (CC).

epithelium at one or both ends of the fragment); the false negative rate is 25% to 30%; if in a solid mass the biopsy with thick acute is benign, which subsequently exhibits rapid growth or shows symptoms, the excisional biopsy is performed [1,13].

Macroscopically, phyllodes tumors are round or oval multinodular masses with a gray-white appearance that resemble the head of a cauliflower; indistinguishable from fibroadenomas, (Figure 15) [1,14]. Phyllodes tumors grow radially create a pseudocapsule through which they project protruding from the stroma and grow into adjacent breast tissue; Necrosis and hemorrhage occur in large tumors [13,14]. Microscopically, the aspects cover the entire spectrum from a benign fibroadenoma to a high-grade sarcoma. The characteristic architecture of the leaves, such as the combination of similar elongated cleft spaces that contain papillary projections of the epithelial stroma enriched with varying degrees of hyperplasia

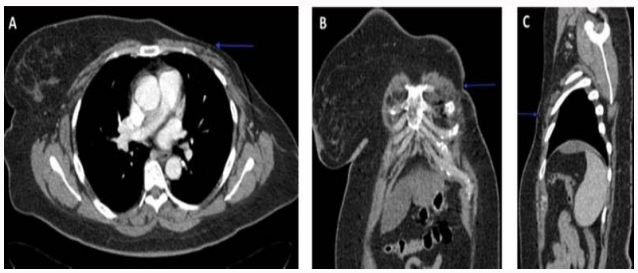

Figure 13: Selected images of a chest CT after IV contrast in the arterial phase and in the soft tissue window. A). Axial view (B). Coronal view (C). Sagittal view showing observed postsurgical changes (left mastectomy) without recurrent/residual masses (blue arrow).

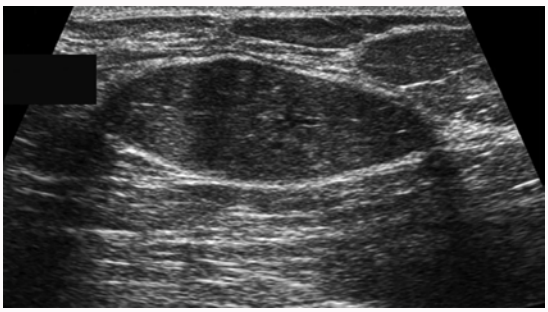

Figure 14: Transverse ultrasound shows well-circumscribed hypoechoic oval mass with parallel orientation.

and atypia [13,14]. Stromal elements are a key component in the differentiation of phyllodes fibroadenomas tumors and to distinguish a benign malignant phyllodes tumor. Histopathologically, phyllodes tumors are classified as benign, borderline or malignant. The most commonly accepted criteria used for the classification of benign compared to malignant tumors are the following; degree of stromal cell atypia, mitotic activity, infiltration compared to circumscribed margins of the tumor, presence or absence of stromal overgrowth (i.e., the presence of pure stroma devoid of epithelium). In most, more than 50% of phyllodes tumors are classified as benign; 25% are malignant [1-14].

When strict adherence to well-established histopathological criteria is used, benign phyllodes and borderline tumors rarely recur after extensive local excision. Patients with benign tumors improve local control and Disease-Free Period (DFS) compared to borderline or malignant lesions; that are associated with stromal overgrowth or aggressive behavior (or metastasis); clinically in the majority of malignant metastatic phyllodes tumors excessive growth of one or several sarcomatous elements is reported; including liposarcoma, undifferentiated/unclassified sarcoma (previously included under the terms "Malignant Fibrous Histiocytoma (MFH) and Undifferentiated Pleomorphic Sarcoma (UPS), and now in the category of soft tissue sarcoma independent of the undifferentiated pleomorphic variant, rhabdomyosarcoma and Chondrosarcoma Stromal examination is necessary because the sarcomatous component is present in only a small portion of the phyllodes tumor [13,14].

The evaluation of tumor markers, p53, Ki-67, epidermal growth factor receptors, c-kit, platelet-derived growth factor and others in phyllodes tumors do not predict the results; only the expression of Estrogen (RE) and Progesterone (RP) Receptors is common in the epithelial component but uncommon in the stromal component

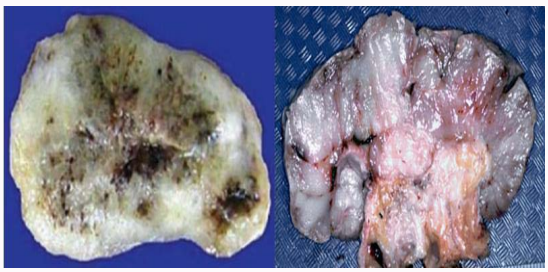

Figure 15: Macroscopically, Phyllodes tumors are round or oval multinodular masses with a gray-white appearance that resemble the head of a cauliflower; indistinguishable from fibroadenomas.

of phyllodes tumors. On a molecular level, intratumoral genetic heterogeneity, the number of aberrations coincides with an increase in malignant potential [14,36-41]. Characteristics of a malignant tumor include the following; recurrent malignant tumors are more aggressive than the original tumor. The lungs are the most common metastatic site, followed by the skeleton, heart and liver; symptoms of metastatic involvement arise from a few months to 12 years after initial treatment; most patients with metastases die within 3 years of initial treatment; there is no cure for systemic metastases.

We observe three different patterns of somatic mutation. First, we frequently observe MED12 and RARA mutations in both fibroadenomas and phyllodes tumors, highlighting the importance of these mutations in fibroepithelial tumorigenesis. Second, phyllodes tumors exhibited mutations in FLNA, SETD2 and KMT2D, suggesting a role in the development of phyllodes tumor. Third, borderline and malignant phyllodes tumors harbored additional mutations in cancer-associated genes. RARA mutations exhibited clustering in the portion of the gene that encodes the ligand binding domain, functionally suppressed RARA-mediated transcriptional activation and improved RARA interactions with transcriptional corepressors [44]. Phyllodes tumors are rare and those with a coexisting carcinoma are even less frequent. The treatment plan changes with the diagnosis of carcinoma and the treatment should be guided by the stage of the carcinoma detected [45].

Therapeutic management

The therapeutic principles are mainly based on retrospective series and clinical cases. Due to their clinical behavior and prognosis, phyllodes tumors are treated as primary breast sarcomas instead of infiltrating ductal carcinomas. Excision with such wide margins is not required, in large tumors this can make the conservation of the breast impracticable [1-14,50-67].

There are few data that support a tumor-free surgical margin associated with reduced tumor recurrence; the greater amount of normal tissue gives greater confidence in the excision (but with poor cosmetic results), a single layer of cells between the tumor and the surgical plane constitutes, a clear margin, without taking into account other factors of its accuracy, including the tumor irregularity, multifocality, ink filtration, sampling and technical aspects of sectioning, among others; in borderline and malignant phyllodes tumors, it was reported that surgical excision size had no impact on the Disease-Free Period (DFS), without significant local control advantage with wide margins (at least 10 mm) over narrower margins, nor relationship between the width of the surgical margin and recurrence, although many institutions offer additional surgical treatment for narrow margins; post-excision recurrences were limited to cases with positive margins or margins <10 mm; the benefit of a second split after an "inappropriate" initial margin (<10 mm); tumor size and mitotic activity have independent prognoses of local recurrence, while margin status and surgical procedure were not; It was proposed that wide margins, if necessary by re-excision, for the treatment of small tumors (<50 mm) with high mitotic activity (>10 mitosis/10 HPF), in these tumors the local recurrence rate is significant (55.6%). For an appropriate surgical margin should be considered as positive, if the tumor is in the ink, or is <1 mm; but, a conservative approach is performed for benign phyllodes tumors that have been initially removed without margins and excision with negative margins for recurrent and malignant phyllodes tumors should be achieved; without recommending routine axillary dissection [13,14,32-46]. Surgery is the standard phyllodes tumor treatment, with negative histopathological margins for malignant cells, a histopathological margin of 1 cm, local excision often, without paying attention to the margins is performed, and mainly in phyllodes tumors are often misdiagnosed as fibroadenomas before surgery. Recurrence rates are unacceptably high after excision or enucleation without negative margins, a positive surgical margin is associated with four times greater risk (local recurrence, distant metastasis) risk ratio or Hazard Ratio (HR) 3.9, 95% CI 1.1 to 14.3). Conservative breast surgery is appropriate for non-malignant fillid tumors, as well as malignant lesions, provided adequate margins are achieved. The re-split is indicated when necessary to ensure acceptable margins. Wide excision produces local recurrence rates of 8% of benign phyllodes tumors and 21% to 36% of borderline and malignant tumors, and recurrence rates are higher without appropriate margins. In women with high-grade malignant phyllodes tumors, local excision (margins <1 cm), excision (margins ≥ 1 cm) and mastectomy. The average size was 7 cm to 8 cm and the median follow-up was 9 years. Recurrence rates were 60% for those treated with single local resection compared with 28% with excision with adequate margins. Local recurrence and cancer-specific survival is related to tumor size, excision and margins. Even large tumors are effectively treated with breast preservation without risk for cancer-specific survival. In malignant phyllodes tumors, management with mastectomy and excision is reported in 52% and 48%, respectively. Wide excision was associated with similar or better survival than with mastectomy, regardless of tumor size; in general, axillary dissection is not required; Axillary lymph node involvement is rare, even in malignant tumors, only 6.2% have lymphatic positive axillary nodes [13,14,51,55-62].

Adjuvant Radiotherapy (Rt) has been offered to patients with malignant phyllodes tumors individually, although it is controversial; there is an increase in the use of Rt from 9.5% to 19.5% without associated less local recurrence, or impact on global survival or DFS [13,14,55,57-63]. Adjuvant Rt for borderline and malignant tumors decreases local recurrence without benefit in survival. The role of adjuvant chemotherapy in phyllodes malignant tumors is considered on a case-by-case basis [55,59-63].

Radiation therapy (Rt) is unnecessary for benign phyllodes tumors that are widely removed. Adjuvant Rt decreases local recurrences after conservative breast surgery with negative margins for borderline or malignant phyllodes tumors [22,23,54,64-68]. The benefit of adjuvant Rt; in malignant phyllodes tumors treated with surgical resection alone, the five-year control rates are lower (79% with excision and 91% with mastectomy) [13,14]. Malignant phyllodes tumors, in particular larger than 2 cm in diameter and treated with excision, adjuvant Rt should be considered; Rt was

associated with a local control rate greater than 10 years, from 59% to 86% for borderline or malignant phyllodes tumors. In malignant or borderline tumors, resection with histopathological negative margins and adjuvant Rt was performed, no local recurrence development after a follow-up of 56 months and 2 patients with malignant phyllodes tumor died of metastatic disease. For some tumors, a 1 cm margin is not possible even with total mastectomy. In these patients, Rt is indicated even after mastectomy. The role of adjuvant Rt when wide margins ≥ 1 cm are obtained, Rt reduces recurrence, the use of adjuvant Rt seems to be modest; patients with malignant phyllodes tumor, 14% received adjuvant Rt in women 50 to 59 years of age, with tumors >10 cm, or axillary Lymphadenectomy (LDN), adjuvant Rt reduces local recurrence, without impact on the Disease-Free Period (DFS) or average overall survival during a follow-up of 53 months [13,14,54,63-68].

The benefit of adjuvant Chemotherapy (Qt) is controversial; patients with malignant phyllodes tumors treated with adjuvant doxorubicin plus dacarbazine or observation alone after surgical resection [24]. There were no differences in DFS, without using ifosfamide in combination with doxorubicin (which is superior to dacarbazine plus doxorubicin in other soft tissue sarcomas); Qt is chosen in more aggressive disease, while those with favorable disease, observation is chosen, adjuvant Qt should be administered only the minority of patients at high risk, tumor size (>5 cm) or recurrent malignant tumors, assessing the risks and benefits of Qt and in benign or doubtful phyllodes tumors is not indicated.

Hormonal therapy is not effective for phyllodes tumors despite the presence of positive hormone receptors in the epithelial component of some of these tumors [13,14,23,25]. The stromal component is the principle of the neoplastic cell population responsible for the metastatic behavior in these tumors and expresses the estrogen beta receptor mainly in opposition to the alpha receptor expressed in breast adenocarcinoma [27,28].

Prognostic

Most patients with benign phyllodes tumors and borderline are cured with surgery. The survival rate for malignant phyllodes tumors is 60% to 80% at 5 years [12]. The impact of histopathology on the survival of primary breast sarcomas and treated phyllodes tumors, the three-year survival rate in benign and borderline tumors combined was 100%; in malignant 54%, similar to primary angiosarcomas or non-breast sarcomas (60%), the overall survival of patients with benign and borderline tumors combined was 91% at 5 years; for malignant 82%. Eight developed distant metastases (7 had been classified as histopathologically malignant and benign); they all had stromal overgrowth and 6 were ≥ 5 cm in size. Of the patients with phyllodes tumors, few developed disease at a distance, in those who had positive surgical margins, with marked cellularity and stromal overgrowth, high mitotic count and necrosis with tumors ≥ 7 cm in size; in few benign phyllodes tumors the recurrence was local as in the malignant ones; the ability of benign tumors to malignant transformation indicates that there are no absolute predictive factors for these rare tumors; Although, most meet the established histopathological classification criteria and adequate surgical margins are obtained, benign and borderline rarely recur [13,14,51-60].

Advanced or recurrent disease

When tumors recur, it is usually locally within two years after the initial excision; the time to local recurrence is shorter in patients with malignant phyllodes tumors compared to benign and borderline phyllodes tumors. Locally recurrent disease is treated with new excision with wide margins or mastectomy followed by Rt to help avoid the morbidity of another recurrence and additional radical surgery; in patients with locally unresectable tumors, it is managed only with palliative Rt; High-grade tumor recurrences that cannot be removed, Rt controls locally for 84 months after recurrence, there is still no better treatment for recurrent phyllodes tumors [61]. A favorable outcome is reported in patients treated with surgery with or without adjuvant Rt; no recurrence; But, its benefit is still uncertain [55].

The reported metastatic disease is 13% to 40% of patients [13,14,54,64-67], after its development, the general average survival is 30 months and more often in the lungs its resection is indicated when it is technically feasible; if it is not resectable, Qt is based on treatment guidelines for soft tissue sarcoma [28]. The regimen typically consists of doxorubicin and/or ifosfamide, or a combination of gemcitabine and docetaxel, or dacarbazine. Ifosfamide appears to be an especially active agent, 50% complete response was achieved. Others suggest the benefit with cisplatin plus etoposide or doxorubicin [13,14,25,28,54,55,57-68]. Metastases occurs significantly more often in patients with the malignant form; it is difficult to predict the clinical course of a phyllodes tumor. Metastatic lesions are most often located in the lungs (66% to 84.5%) and bones (28% to 39%), more rarely in the liver and brain. They can also occur in the nasal cavity, oral cavity, larynx, salivary glands, thyroid glands, heart, pleura, adrenal glands, kidneys, spleen, pancreas, stomach, small intestine, large intestine, ovary, vulva and skin; distant metastases can appear without coexisting local recurrence. The appearance of metastases is an unfavorable prognosis [62]. In patients with a single metastatic focus, surgical resection is a feasible approach to prolong survival [63].

Surveillance

There are no evidence-based recommendations for post-treatment surveillance for malignant phyllodes tumors of the breast and these adapt to the follow-up of soft tissue sarcomas. Most recurrences occur in the first two years after treatment more frequently in the lungs. Isolated metastases limited to the lung are often asymptomatic and susceptible to resection, close monitoring for two years; with interrogation, physical examination and chest X-ray every six months for two years and then annually. They are useful for evaluation when suspicious findings are found in the clinical examination of MAM, MMG with ultrasound and/or Magnetic Resonance of the breast. Patients who underwent breast conservation surgery should resume annual surveillance with annual MMG. Patients who are at greater risk of metastatic disease (for example, tumors >5 cm), surveillance can be carried out more frequently. Follow-up should be carried out according to the NCCN guidelines for soft tissue sarcomas by chest radiographs and/or chest CT [13,14,64].

Discussion

Phyllodes tumors are rare fibroepithelial lesions; rare in men, and is associated with gynecomastia [1,13,14]. Clinically, they appear as a benign mass of rapidly growing breast, the local recurrence rate was 14%, they are usually identified for the first time as a breast mass or an abnormal MMG; as a smooth and polylobulated mass reported as BIRADS [3,11]. Image-guided biopsy for histopathological study is diagnostic; recurrence rates generally 8% to 19%, with

distant metastases from 2.4% to 7.5%. The number of patients who relapsed was relatively small. The tumor, the patients and the treatment characteristics were not significantly different between the relapsed and non-recurrent groups. The previous diagnosis decides the appropriate surgical management [1,13,14,37-41]. Stromal hypercellularity, cellular stromal atypia, mitotic rate and the relative relationship of the stroma with the epithelium help to make the diagnosis the four stromal characteristics are detected (cellularity, nuclear atypia, mitotic rate and relative stromal ratio to epithelium) excisional biopsy is recommended for definitive, and therapeutic diagnosis. The risk of malignancy increases with the increase in tumor size, degree of mitosis, surgical margin, stromal cellularity and atypia [13-19].

The primary treatment of the phyllodes tumor is surgery regardless of the nature of the tumor. Removal or mastectomy. Local recurrence and 5 year survival vary from 4% to 96%. Tumor size, surgical margin <1 cm, and stromal overgrowth are factors that increase the local recurrence rate [13,14,48-57]. Nodal metastases occur in less than 1% does not require axillary dissection. Remote metastases are detected in 10% of patients, and 25% of malignant ones. Most of these distant metastases occur in the absence of local recurrence. Distant metastases are more frequent in lungs (66%), bone (28%), brain (9%), followed by the liver and heart and exceptional in the larynx.

The prognosis of the phyllodes tumor is poor, and fatal; the role of adjuvant Rt is controversial, chemotherapy (anthracyclines, ifosfamide, cisplatin, etoposide, dacarbazine, doxorubicin) has been used, with no survival benefit. Mainly for patients who had a high mitotic index, large tumor size and marked increase in vascularization. The overall 5 years survival rates in patients with benign and malignant phyllodes tumors were 91% and 82%, respectively [1-14,37-51,57].

Conclusion

Phyllodes tumors are rare mesenchymal and epithelial breast tumors; they present with different clinical forms, so they can be confused with other diseases of the breast, mainly fibroadenomas. Due to their higher rate of local recurrence and malignant potential, preoperative diagnosis and diligent management are significant. Early diagnosis and resection before the development of distant metastases are crucial. However, due to its rare incidence and lack of specific clinical or imaging properties that may help in the diagnosis, the decision to proceed with follow-up or surgery is based on the accumulation of more detailed information. Adjuvant Qt reduces the rate of local recurrence and increases overall survival in patients with high mitotic index, high nuclear pleomorphism, large tumor size and marked increase in vascularization.

References

1. Acar T, Tarcan E, Haciyanli M, Kamer E, Peskersoy M, Yigit S, et al. How to approach phyllodes tumors of the breast? Ulus Cerrahi Derg. 2015;31(4):197-201.
2. Demian GA, Fayaz S, El-Sayed Eissa H, Nazmy N, Samir S, George T, et al. Phyllodes tumors of the breast: Analysis of 35 cases from a single institution. J Egypt Natl Canc Inst. 2016;28(4):243-8.
3. Tan BY, Acs G, Apple SK, Badve S, Bleiweiss IJ, Brogi E, et al. Phyllodes tumours of the breast: a consensus review. Histopathology. 2016;68(1):5-21.
4. Hayati F, Lian HH, Azizan N, Ali AA, Abidin ZZ, Suhaili MA. Approaches to phyllodes tumour of the breast: a review article. Int Surg J. 2017;4(3):841-5.
5. Toh YF, Cheah PL, Looi LM, Teoh KH, Tan PH. Phyllodes tumours of the breast: retrospective análisis of a University Hospital's experience. Malays J Pathol. 2016;38(1):19-24.
6. Zhang Y, Kleer CG. Phyllodes tumor of the breast: histopathologic features, differential diagnosis, and molecular/genetic updates. Arch Pathol Lab Med. 2016;140(7):665-71.
7. Lannin DR, Konstantakos AK, Raaf JH, Geibel J, Daley BJ, Grosso MA, et al. Phyllodes Tumor (Cystosarcoma Phyllodes). Medscape. 2019.
8. Rodrigues MF, Truong PT, McKevitt EC, Weir LM, Knowling MA, Wai ES. Phyllodes tumors of the breast: The British Columbia Cancer Agency experience. Cancer Radiother. 2018;22(2):112-9.
9. Lavoué V, Fritel X, Antoine M, Beltjens F, Bendifallah S, Boisserie-Lacroix M, et al. Clinical practice guidelines from the French College of Gynecologists and Obstetricians (CNGOF): Benign breast tumors - short text. Eur J Obstet Gynecol Reprod Biol. 2016;200:16-23.
10. Bendifallah S, Canlorbe G. Common benign breast tumors including fibroadenoma, phyllodes tumors, and papillary lesions: Guidelines. J Gynecol Obstet Biol Reprod (Paris). 2015.44(10):1017-29.
11. Tan J, Ong CK, Lim WK, Ng CC, Thike AA, Ng LM, et al. Genomic landscapes of breast fibroepithelial tumors. Nat Genet. 2015;47(11):1341-5.
12. Wang H, Wang X, Wang CF. Comparison of clinical characteristics between benign borderline and malignant phyllodes tumors of the breast. Asian Pac J Cancer Prev. 2014;15(24):10791-5.
13. Hernández VM, Moriceau Y, López A. Benign breast diseases. Diagnosis and treatment. In: Vargas-Hernández VM, editor. Cancer in women. 1st ed. Mexico. 2011;1053-77.
14. Grau AM, Chakravarthy AB, Chugh R. Phyllodes tumors of the breast: Literature review current through. 2016.
15. Acar T, Tarcan E, Haciyanli M, Kamer E, Peskersoy M, Yigit, et al. How to approach phyllodes tumors of the breast? Ulus Cerrahi Derg. 2015;31(4):197-201.
16. Tsang JY, Ni YB, Ng EK, Shin VY, Mak KF, Go EM, et al. MicroRNAs are differentially deregulated in mammary malignant phyllodes tumour. Histopathology. 2015;67:294-305.
17. Vilela MH, de Almeida FM, de Paula GM, Ribeiro NB, Cirqueira MB, Silva AL, et al. Utility of Ki- 67, CD10, CD34, p53, CD117, and mast cell content in the differential diagnosis of cellular fibroadenomas and in the classification of phyllodes tumors of the breast. Int J Surg Pathol. 2014;22(6):485-91.
18. Tan WJ, Thike AA, Bay BH, Tan PH. Immunohistochemical expression of homeoproteins Six1 and Pax3 in breast phyllodes tumours correlates with histological grade and clinical outcome. Histopathology. 2014;64(6):807-17.
19. Goh CH, Lim YP, Su JW, Khoo KS, Thomas A, Sittampalam K, et al. Cardiopulmonary thromboembolism of epithelioid angiosarcoma arising from malignant phyllodes tumour of the breast. J Clin Pathol. 2014;67(5):450-4.
20. Zhou ZR, Wang CC, Sun XJ, Yang ZZ, Chen XX, Shao ZM, et al. Prognostic factors in breast phyllodes tumors: a nomogram based on a retrospective cohort study of 404 patients. Cancer Med. 2018;7(4):1030-42.
21. Bumpers HL, Tadros T, Gabram-Mendola S, Rizzo M, Martin M, Zaremba N, et al. Phyllodes tumors in African American women. Am J Surg. 2015;210:74-9.
22. Lim WK, Ong CK, Tan J, Thike AA, Ng CC, Rajasegaran V, et al. Exome sequencing identifies highly recurrent MED12 somatic mutations in breast fibroadenoma. Nat Genet. 2014;46:877-80.
23. Cani AK, Hovelson DH, McDaniel AS, Sadis S, Haller MJ, Yadati V, et al. Next-gen sequencing exposes frequent MED12 mutations and actionable

therapeutic targets in phyllodes tumors. Mol Cancer Res. 2015;13(4):613-19.

24. Yoshida M, Sekine S, Ogawa R, Yoshida H, Maeshima A, Kanai Y, et al. Frequent MED12 mutations in phyllodes tumours of the breast. Br J Cancer. 2015;112(10):1703-8.

25. Piscuoglio S, Murray M, Fusco N, Marchiò C, Loo FL, Martelotto LG, et al. MED12 somatic mutations in fibroadenomas and phyllodes tumours of the breast. Histopathology. 2015;67:529-37.

26. Nagasawa S, Maeda I, Fukuda T, Wu W, Hayami R, Kojima Y, et al. MED12 exon 2 mutations in phyllodes tumors of the breast. Cancer Med. 2015;4(7):1117-21.

27. Pfarr N, Kriegsmann M, Sinn P, Klauschen F, Endris V, Herpel E, et al. Distribution of MED12 mutations in fibroadenomas and phyllodes tumors of the breast-implications for tumor biology and pathological diagnosis. Genes Chromosom Cancer. 2015;54(7):444-52.

28. Ng CC, Tan J, Ong CK, Lim WK, Rajasegaran V, Nasir ND, et al. MED12 is frequently mutated in breast phyllodes tumours: a study of 112 cases. J Clin Pathol. 2015;68(9):685-91.

29. Croce S, Chibon F. MED12 and uterine smooth muscle oncogenesis: State of the art and perspectives. Eur J Cancer. 2015;51(12):1603-10.

30. Lawton TJ, Acs G, Argani P, Farshid G, Gilcrease M, Goldstein N, et al. Interobserver variability by pathologists in the distinction between cellular fibroadenomas and phyllodes tumors. Int J Surg Pathol. 2014;22:695-8.

31. Tay TKY, Chang KTE, Thike AA, Tan PH. Paediatric fibroepithelial lesions revisited: pathological insights. J Clin Pathol. 2015;68(8):633-41.

32. Yasir S, Gamez R, Jenkins S, Visscher DW, Nassar A. Significant histologic features differentiating cellular fibroadenoma from phyllodes tumor on core needle biopsy specimens. Am J Clin Pathol. 2014;142:362-9.

33. Yang X, Kandil D, Cosar EF, Khan A. Fibroepithelial tumors of the breast: pathologic and immunohistochemical features and molecular mechanisms. Arch Pathol Lab Med. 2014;138(1):25-36.

34. Piscuoglio S, Ng CK, Murray M, Burke KA, Edelweiss M, Geyer FC, et al. Massively parallel sequencing of phyllodes tumours of the breast reveals actionable mutations and TERT promoter hotspot mutations and TERT gene amplification as likely drivers of progression. J Pathol. 2016;238(4):508-18.

35. Cimino-Mathews A, Sharma R, Illei PB, Vang R, Argani P. A subset of malignant phyllodes tumors express p63 and p40: A diagnostic pitfall in breast core needle biopsies. Am J Surg Pathol. 2014;38:1689-96.

36. Kim SK, Jung WH, Koo JS. p40 (ΔNp63) expression in breast disease and its correlation with p63 immunohistochemistry. Int J Clin Exp Pathol. 2014;7(3):1032-41.

37. D'Alfonso TM, Ross DS, Liu YF, Shin SJ. Expression of p40 and laminin 332 in metaplastic spindle cell carcinoma of the breast compared with other malignant spindle cell tumours. J Clin Pathol. 2015;68(7):516-21.

38. Bellezza G, Prosperi E, Del Sordo R, Colella R, Rulli A, Sidoni A. IMP3 Is Strongly Expressed in Malignant Phyllodes Tumors of the Breast: An Immunohistochemical Study. Int J Surg Pathol. 2016;24(1):37-42.

39. Tan BY, Acs G, Apple SK, Badve S, Bleiweiss IJ, Brogi E, et al. Phyllodes tumours of the breast: a consensus review. Histopathology. 2016;68(1):5-21.

40. Hayati F, Lian HH, Azizan N, Ali AA, Zainal Abidin ZA, Suhaili MA. Approaches to phyllodes tumour of the breast: a review article. Int Surg J. 2017;4(3):841-5.

41. Toh YF, Cheah PL, Looi LM, Teoh KH, Tan PH. Phyllodes tumours of the breast: retrospective analysis of a University Hospital's experience. Malays J Pathol. 2016;38(1):19-24.

42. Munawer NH, Md Ali SA, Md Zin R, Muhammad R. The co-expression of estrogen receptor beta (ERß) and smooth muscle actin in phyllodes tumour of breast: a tissue microarray study. Sains Malaysiana. 2014;43(2):233-40.

43. Zeng S, Zhang X, Yang D, Wang X, Ren G. Effects of adjuvant radiotherapy on borderline and malignant phyllodes tumors: a systematic review and metaanalysis. Mol Clin Oncol. 2015;3(3):663-71.

44. Kalambo M, Adrada BE, Adeyefa MM, Krishnamurthy S, Hess K, Carkaci S, et al. Whitman Phyllodes Tumor of the Breast: Ultrasound-Pathology Correlation. Am J Roentgenol. 2018;210(4):W173-9.

45. Piscuoglio S, Geyer FC, Burke KA, Murray MP, Ng CK, Mota A, et al. Massively parallel sequencing analysis of synchronous fibroepithelial lesions supports the concept of progression from fibroadenoma to phyllodes tumor. NPJ Breast Cancer. 2016;2:16035.

46. Sun L, Zhu R, Ginter P, Malik M, Sung KJ, Hughes JM, et al. Coexisting DCIS and phyllodes breast tumors in Young Chinese women: Case series. Int J Surg Case Rep. 2019;56:13-6.

47. Lannin DR, Konstantakos AK, Raaf JH, Geibel J, Daley BJ, Grosso MA, et al. Phyllodes Tumor (Cystosarcoma Phyllodes) Medscape. 2019.

48. Rodrigues MF, Truong PT, McKevitt EC, Weir LM, Knowling MA, Wai ES. Phyllodes tumors of the breast: The British Columbia Cancer Agency experience. Cancer Radiother. 2018;22(2):112-9.

49. Bendifallah S, Canlorbe G. [Common benign breast tumors including fibroadenoma, phyllodes tumors, and papillary lesions: Guidelines]. J Gynecol Obstet Biol Reprod (Paris). 2015;44(10):1017-29.

50. Demian GA, Fayaz S, El-Sayed Eissa H, Nazmy N, Samir S, George T, et al. Phyllodes tumors of the breast: Analysis of 35 cases from a single institution. J Egyp Nat Cancer Inst. 2016;28(4):243-8.

51. Mallick S, Joshi NP, Roy S, Gandhi AK, Pandit S, Sharma D, et al. Malignant and borderline phyllodes tumor of breast treated with a multi-modality approach in a tertiary cancer care centre in North India. South Asian J Cancer. 2016:5(1);1-3.

52. Onkendi EO, Jimenez RE, Spears GM, Harmsen WS, Ballman KV, Hieken TJ. Surgical treatment of borderline and malignant phyllodes tumors: the effect of the extent of resection and tumor characteristics on patient outcome. Ann Surg Oncol. 2014;21(10):3304-9.

53. Chao X, Chen K, Zeng J, Bi Z, Guo M, Chen Y, et al. Adjuvant radiotherapy and chemotherapy for patients with breast phyllodes tumors: A systematic review and meta-analysis. BMC Cancer. 2019;19(1):372.

54. Gnerlich JL, Williams RT, Yao K, Jaskowiak N, Kulkarni SA. Utilization of radiotherapy for malignant phyllodes tumors: analysis of the National Cancer Data Base, 1998-2009. Ann Surg Oncol. 2014;21(4):1222-30.

55. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology (NCCN Guidelines). Soft Tissue Sarcoma. Version 1.2013.

56. Mylvaganam S, Toro C, Frank L, Vestey S, Thrush S. Phylloides tumours of the breast: Best practice for follow-up. Updates Surg. 2015;67(1):91-5.

57. Zeng S, Zhang X, Yang D, Wang X, Ren G. Effects of adjuvant radiotherapy on borderline and malignant phyllodes tumors: A systematic review and meta-analysis. Mol Clin Oncol. 2015;3(3):663-71.

58. Tan J, Ong CK, Lim WK, Ng CC, Thike AA, Ng LM, et al. Genomic landscapes of breast fibroepithelial tumors. Nat Genet. 2015;47(11):1341-5.

59. Park HJ, Ryu HS, Kim K, Shin KH, Han W, Noh DY. Risk Factors for Recurrence of Malignant Phyllodes Tumors of the Breast. *In Vivo*. 2019;33(1):263-9.

60. Karczmarek-Borowska B, Bukala A, Syrek-Kaplita K, Ksiazek M, Filipowska J, Gradalska-Lampart M.. A Rare Case of Breast Malignant Phyllodes Tumor With Metastases to the Kidney: Case Report. Medicine (Baltimore). 2015;94(33):E1312.

61. Wei J, Tan YT, Cai YC, Yuan ZY, Yang D, Wang SS, 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(10):492-500.

62. Pareja F, Geyer FC, Kumar R, Selenica P, Piscuoglio S, Charlotte KY Ng, et al. Phyllodes tumors with and without fibroadenoma-like areas display distinct genomic features and may evolve through distinct pathways. Breast Cancer. 2017;3:40.

63. Onkendi EO, Jimenez RE, Spears GM, Harmsen WS, Ballman KV, Hieken TJ. Surgical treatment of borderline and malignant phyllodes tumors: The effect of the extent of resection and tumor characteristics on patient outcome. Ann Surg Oncol. 2014;21:3304-9.

64. Wei J, Tan YT, Cai YC, Yuan ZY, Yang D, Wang SS, 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(10):492-500.

65. Jung YY, Lee YK, Koo JS. Expression of lipid metabolism-related proteins in breast phyllodes tumors. Neoplasma. 2016;63(2):254-62.

66. Mituś J, Reinfuss M, Mituś JW, Jakubowicz J, Blecharz P, Wysocki WM, et al. Malignant phyllodes tumor of the breast: treatment and prognosis. Breast J. 2014;20:639-44.

67. Yom CK, Han W, Kim S-W, Park SY, Park IA, Noh D-Y. Reappraisal of conventional risk stratification for local recurrence based on clinical outcomes in 285 resected phyllodes tumors of the breast. Ann Surg Oncol. 2015;22:2912-8.

68. Tomohiro Sera, Kashiwagi S, Takashima T, Asano Y, Wataru Goto, Iimori N, Noda S, et al. Multiple metastatic malignant phyllodes tumor of the breast with tonsillar metastasis: A case report. BMC Res Notes. 2017;10:55.