Phyllodes Tumors of the Breast: Natural History, Diagnosis, and Treatment

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Key Words
Phyllodes tumors, breast neoplasms, natural history, diagnosis, treatment

Abstract
Phyllodes tumors of the breast are unusual fibroepithelial tumors that exhibit a wide range of clinical behavior. These tumors are categorized as benign, borderline, or malignant based on a combination of histologic features. The prognosis of phyllodes tumors is favorable, with local recurrence occurring in approximately 15% of patients overall and distant recurrence in approximately 5% to 10% overall. Wide excision with a greater than 1 cm margin is definitive primary therapy. Adjuvant systemic therapy is of no proven value. Patients with locally recurrent disease should undergo wide excision of the recurrence with or without subsequent radiotherapy.

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Historical Overview
In 1838, Johannes Müller gave a detailed description of a large mammary tumor with a cystic appearance and leaf-like growth pattern which he named cystosarcoma phyllodes. In 1951, Treves and Sutherland suggested that benign, pre-malignant, and malignant forms of this disease existed. In 1960, Lomonaco proposed the name tumor phyllodes, thereby avoiding any implication of biologic behavior. The World Health Organization adopted the terminology phyllodes tumor in 1981, and this name has since gained widespread acceptance. Phyllodes tumors are unusual fibroepithelial lesions that account for less than 1% of all breast neoplasms. These tumors exhibit a wide range of clinical behavior and represent a spectrum of fibroepithelial neoplasms rather than a single disease entity.

Pathologic Features
Phyllodes tumors are characterized by the presence of both epithelial and stromal elements, but the distinguishing histologic features relate to the stroma. Microscopically, these tumors contain elongated ductal elements and papillary protrusions of connective tissue lined by epithelium that produce the leaf-like appearance. Marked stromal overgrowth and hypercellularity are important features that distinguish these lesions from the more common fibroadenomas. These lesions are categorized as benign, borderline, or malignant based on a combination of histologic features, including stromal cellular atypia, mitotic activity, stromal overgrowth, type of tumor margin (circumscribed vs. infiltrative), and tumor necrosis. Reported incidences of each subtype have varied widely in the literature. On average, more than 50% are categorized as benign and approximately 25% as malignant in most large series. Despite these classifications, histologic grade has been found to correlate poorly with biologic behavior.

The expression of estrogen and progesterone receptors is common in the epithelial component but uncommon in the stromal component of phyllodes tumors. In one series, epithelial estrogen receptor expression was seen in 58% and progesterone receptor expression in 75%. In this series, expression of hormone receptors was related to histologic grade, with estrogen and progesterone receptor expression present in 67% and 77% of benign, 43% and 84% of borderline, and 47% and 47% of...
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Table 1 Hormone Receptor Expression in Phyllodes Tumors

<table>
<thead>
<tr>
<th>Phyllodes Tumor Subgroup</th>
<th>Estrogen Receptor</th>
<th>Progesterone Receptor</th>
<th>Androgen Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Epithelial</td>
<td>Stromal</td>
<td>Epithelial</td>
</tr>
<tr>
<td>Benign</td>
<td>67%</td>
<td>3%</td>
<td>77%</td>
</tr>
<tr>
<td>Borderline</td>
<td>43%</td>
<td>0%</td>
<td>84%</td>
</tr>
<tr>
<td>Malignant</td>
<td>47%</td>
<td>5%</td>
<td>47%</td>
</tr>
</tbody>
</table>


malignant phyllodes tumors, respectively (Table 1). Expression of androgen receptors was low in all tumors.

The frequency of expression and role of the tumor suppressor gene p53 in phyllodes tumors is highly variable across series. In some but not all series, p53 expression increases across the spectrum of benign to malignant phyllodes tumors.15,16

Clonal analysis of phyllodes tumors documents that the epithelial component is polyclonal, whereas the stromal component is monoclonal, showing that the stroma represents the neoplastic component of phyllodes tumors.15,16

Clinical Presentation

The most common presentation of a phyllodes tumor is a palpable breast mass that may be rapidly growing. These tumors may exhibit biphasic growth and patients may present to medical attention only after noting rapid growth in a lesion that had been stable for years.19 Rarely, patients present with a mass detected on routine screening mammography.11 Phyllodes tumors can reach enormous proportions; tumors greater than 20 cm have been reported in multiple series.11,13,20 Many series have failed to show a correlation between tumor size and histologic subtype, because even benign phyllodes tumors can reach great size.19,20

On examination, most patients have a smooth, round, well-defined, firm mass that is mobile and painless. Large lesions may be associated with dilated veins visible over the skin, which may be stretched and attenuated. Nipple retraction,19,23 skin ulceration,19,21 invasion of the chest wall,19,21 and bloody nipple discharge21 have been reported but are rare. Palpable axillary lymphadenopathy can be identified in up to 20% of patients, but metastatic involvement of axillary lymph nodes is rare.19,24

Phyllodes tumors occur at a median age of 45 years,7 but cases in adolescents and the elderly have been well described.11,13,14,15,21,23 Recent Surveillance, Epidemiology, and End Result (SEER) data indicate that the mean age at diagnosis is 50 years among patients with malignant phyllodes tumors.20 Bilateral phyllodes tumors are reported to occur rarely,11,14,21,23 and a case of a phyllodes tumor arising in an accessory breast has been reported.21 Additionally, phyllodes tumors associated with gynecomastia have been reported in men,27 and a bilateral phyllodes tumor arising in ectopic axillary breast tissue has been described in a man.24

Diagnosis

Unfortunately, triple assessment using clinical, radiologic, and histologic examination results in low diagnostic accuracy in phyllodes tumors.8,29 The deficiencies of this approach relate to the fact that phyllodes tumors have overlapping characteristics with benign breast disease in all 3 categories. Because the surgical management of these lesions differs from that of a fibroadenoma, accurate preoperative diagnosis is optimal. Often, however, local excision of the mass is required for diagnosis, and patients then require further surgery to ensure adequate tumor-free margins.

Clinically, the diagnosis of a phyllodes tumor should be considered in the differential diagnosis of a large fibroadenoma. A history of rapid growth and attainment of large size can be suggestive, but these features cannot reliably differentiate phyllodes tumors from other benign breast disease. On mammogram, phyllodes tumors appear as well-defined oval, round, or lobulated masses that mimic the radiographic appearance of a fibroadenoma.10 Associated coarse microcalcifications are occasionally seen. On ultrasound, these lesions appear as solid, hypoechoic, well-circumscribed masses.11 The presence of a cystic area...
Local recurrence does not tend to have a very heterogeneous composition. Core biopsy, although subject to the same potential for sampling error, is associated with higher accuracy than FNA. In a recent article, Jacklin et al. concluded that core biopsy is potentially the most useful method of preoperatively diagnosing phyllodes tumor. To help clinicians select patients for core needle biopsy, they formulated a set of criteria that they refer to as the Paddington Clinicopathologic Suspicion Score (Table 2). The intraoperative diagnosis of phyllodes tumor using frozen section is often inaccurate, as is the case with intraoperative frozen section diagnosis of other breast masses. Chen et al. reported an accurate diagnosis using frozen section in only 41.6% of cases in their series of 172 patients with phyllodes tumor.

### Prognostic Factors

The clinical course of phyllodes tumors can be unpredictable, although in most patients the prognosis is favorable. Poor correlation exists between histologic features and biologic behavior. In most large series, approximately 25% of phyllodes tumors are categorized as malignant and more than 50% are characterized as benign. Benign lesions have the potential to recur locally and rarely at distant sites, and cases of benign tumors transforming into higher-grade lesions at recurrence have been reported. Despite having an increased risk for distant spread, malignant lesions follow an indolent clinical course in most patients with 15-year cause-specific survival rates of approximately 89%. Because of the unpredictable nature of these lesions, experts have suggested that all phyllodes tumors be regarded as having malignant potential.

Many studies have attempted to identify histologic and clinical prognostic factors implicated in the risk for local and distant recurrence. This is difficult because of the rarity of this tumor, differences in pathologic interpretation, and selection bias for the type of treatment provided in various series. Despite these impediments, several important observations have been made (Table 3). The literature does not suggest a correlation between tumor size and increased risk for local recurrence, although size has been implicated in the risk for developing distant disease. A positive surgical margin is the most powerful predictor of local recurrence. Local recurrence does not correlate with an increased risk for distant disease and does not seem to affect survival. The literature is divided on the relationship between histologic grade and risk for local recurrence. Some series suggest an increase in local recurrence among borderline and malignant lesions, but this has not been found in other large series. In contrast, the development of metastatic disease has been shown to correlate with grade, and experts have estimated that 20% of patients with malignant tumors will develop metastatic disease. Stromal overgrowth has been identified as

### Table 2 Paddington Clinicopathologic Suspicion Score

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>Prognostic Factor</th>
<th>Implicated in Risk for Local Recurrence</th>
<th>Implicated in Risk for Distant Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden increase in size in a long-standing breast lesion</td>
<td>Tumor size</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Apparent fibroadenoma &gt; 3 cm in diameter or in a patient &gt; 35 years</td>
<td>Histologic grade</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>Imaging Findings:</td>
<td>Positive margin</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Rounded borders/lobulated appearance at mammography</td>
<td>Stromal overgrowth</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Attenuation of cystic areas within a solid mass on ultrasonography</td>
<td>Prior local recurrence</td>
<td>NA</td>
<td>No</td>
</tr>
</tbody>
</table>

Any 2 features mandate core biopsy


### Table 3 Prognostic Factors Implicated in the Risk for Local and Distant Recurrence in Phyllodes Tumors

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Implicated in Risk for Local Recurrence</th>
<th>Implicated in Risk for Distant Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Histologic grade</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>Positive margin</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Stromal overgrowth</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Prior local recurrence</td>
<td>NA</td>
<td>No</td>
</tr>
</tbody>
</table>
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Primary Surgical Management

Local recurrence occurs in approximately 15% of patients with phyllodes tumors and is more frequent after inadequate excision.7 Distant failure occurs in approximately 5%–10% of cases overall and in approximately 20% of malignant lesions.7,12 Tumor biology seems to dictate metastatic potential, and this risk does not seem to be influenced by the choice of local treatment.13 Given these observations, the primary surgical objective is to attain definitive local control.

Wide local excision with margins of greater than 1 cm is the preferred primary treatment.13,19–21,34 Microscopic projections of tumor often extend into the pseudocapsule of normal compressed breast tissue that surround these lesions.15 Therefore, achieving a 1-cm microscopic margin frequently requires removing more tissue than would be expected based on gross inspection. Simple enucleation of the tumor, as is commonly used in the treatment of fibroadenoma, is inadequate treatment for phyllodes tumors.11,20,33 In a series of 101 patients, most of whom (99%) had pathologically negative margins after surgery, Chaney et al.20 reported a low actuarial 10-year rate of local recurrence (8%), suggesting that the risk for local recurrence can be significantly decreased but not eliminated when negative margins are obtained.

Historically, mastectomy was the standard surgical treatment for all phyllodes tumors.5 More recently, breast-conservative approaches have been increasingly used. In the series by Chaney et al.,20 approximately half the patients were treated with breast conservation and half with mastectomy. Only 4 local recurrences were seen, and these occurred equally in both groups. Other large series have shown similar findings.9,27 A recent analysis by Macdonald et al.26 used the SEER database to determine prognostic factors that predicted cause-specific survival among 821 patients with malignant phyllodes tumor. In this retrospective analysis, wide excision was associated with equivalent or improved cause-specific survival relative to mastectomy in a multivariate analysis. These data, similar to all retrospective series, are potentially confounded by physician selection bias regarding the type of surgery performed. However, given the overall low rate of local failure with breast-conserving surgery, breast conservation is the preferred primary therapy if negative margins can be obtained with an acceptable cosmetic result. In cases in which breast conservation is not possible because of large tumor size relative to breast volume, total mastectomy is appropriate.13,19,20

When phyllodes tumor is diagnosed only after narrow margin excision, re-excision to obtain margins of greater than 1 cm is indicated.13,34 Simple mastectomy may be required to achieve this. The primary mode of spread of phyllodes tumors is through hematogenous dissemination. Although axillary lymphadenopathy is present in approximately 20% of patients with phyllodes tumors, only approximately 5% of patients will have axillary metastases at lymph node dissection.15 The current literature supports the role of axillary lymph node staging only in cases where clinically pathologic nodes are found on examination.11,13

Role of Adjuvant Systemic Therapy

The adjuvant use of chemotherapy or hormonal therapy has no proven role in treating phyllodes tumors.
Chaney et al. proposed that adjuvant chemotherapy be considered for patients with histologic evidence of stromal overgrowth, particularly when the tumor size is greater than 5 cm, because these patients appear to have the greatest risk for developing distant disease. However, because systemic therapy has had limited value in patients with metastatic phyllodes tumors, it is not expected to be effective in the adjuvant setting, and no randomized data are available. Tse et al. suggested that the potential role of endocrine therapy in treating phyllodes tumors is limited because hormone receptors are primarily expressed on the epithelial component of the tumor, and the stromal component of phyllodes tumors is the component implicated in metastatic spread. Thus, there is no role for measuring hormone receptors in these tumors.

Role of Adjuvant Radiation Therapy

The role of adjuvant breast or chest wall radiotherapy is controversial. Most experience is based on case reports of patients with chest wall recurrences. Because of the important relationship between excision margin and the risk for local recurrence, some experts have suggested that adjuvant radiation at doses of 50 to 60 Gy be considered in patients for whom negative surgical margins cannot be attained. The use of adjuvant radiation in patients with a resection margin of 1 cm or larger is not recommended. However, no high-level evidence supports the role of adjuvant radiotherapy in phyllodes tumors.

In a series of 37 patients with malignant phyllodes tumors, Pandey et al. administered 45 to 50 Gy of radiation to 69% of patients, including all patients treated with wide excision alone and those experiencing recurrent phyllodes tumors after resection of the recurrent disease. In this study, the 5-year disease-free survival rate was 61.2% among patients who underwent adjuvant radiotherapy versus 51.4% among those who did not. Cox proportional hazard survival analysis, however, showed no statistically significant advantage to radiotherapy ($P = .47$). The recent analysis of SEER data found that the use of adjuvant radiotherapy predicted a worse cause-specific survival compared with surgery alone among 821 patients with malignant phyllodes tumors. In this series, however, only 9% of patients underwent radiotherapy, and patients selected for radiotherapy were probably those with larger tumors with narrow tumor-free or involved margins.

Management of Locally Recurrent Disease

In approximately 15% of cases of phyllodes tumor, the clinical course will be complicated by one or more local recurrences. General consensus is that these recurrences result from failure of primary surgical treatment, although the biologic behavior of the tumor may be an important determinant. de Roos et al. found that the development of one local recurrence seemed to predispose to further episodes of local recurrence regardless of the histologic subtype or type of initial surgery. Most tumors recur within 2 years of initial surgery, although tumors recurring as soon as 1 month and as late as 17 years after initial surgery have been reported. Some series have found that the time to local recurrence is shortest among patients with the malignant subtype compared with those with benign and borderline lesions. Generally, phyllodes tumors recur with the same histology as that of the initial disease, but cases of transformation to more aggressive tumors have been reported. In most patients, local recurrence is not associated with distant metastases.

Cases of successful treatment of patients with multiple recurrent tumors have been reported. However, some authors believe that mastectomy should be considered after the first recurrence of borderline or malignant lesions, whereas others believe that mastectomy should be considered after any second recurrence. Chaney et al. suggest that adjuvant radiotherapy may be appropriate after resection of recurrent disease. Mangi et al. reported a case of a patient with a high-grade tumor recurrence that could not be fully excised surgically. This patient was treated with radiotherapy to the chest wall and remained free of disease for 84 months after recurrence. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology support re-excision with wide margins for locally recurrent disease. Some members of the NCCN guidelines panel recommend local radiation therapy to the remaining breast or chest wall after resection of a local recurrence, but this recommendation is controversial.
Management of Metastatic Disease

Based on data from large cases series, it is estimated that approximately 5%–10% of patients with phyllodes tumors will develop distant disease, although the incidence of metastatic disease among patients with malignant tumors is estimated at approximately 20%. Metastatic lesions histologically contain only stromal elements and are devoid of epithelial elements. A metastatic phyllodes tumor carries a poor prognosis, with an average survival of less than 2 years. In a series of 170 patients, Reinfuss et al. found that among patients with metastatic disease, 93% developed metastases within 3 years and the median survival was 4 months. In this series, 3 patients initially diagnosed with benign tumors developed metastatic disease, and this phenomenon has been described in several other series. de Roos et al. reported a median survival of 17 months, ranging from 12 to 145 months. The most common sites of distant disease are the lung, bone, and abdominal viscera, although metastases have been reported in the brain, heart, soft tissues of the neck, thigh, pelvis, and oral cavity.

Clinical experience with chemotherapy for metastatic phyllodes tumors is limited. Multiple single-agent and combination regimens have been used with varying success. Responses, when they occur, are generally of short duration. Single-agent cyclophosphamide and ifosfamide have been associated with complete responses in a limited number of patients. A case report of doxorubicin and cisplatin documented a complete response and good palliation, whereas another report documented activity of etoposide and cisplatin. Among patients treated with ifosfamide, Hawkins et al. reported prolonged complete responses in 2 patients lasting 26 months (single-agent ifosfamide) and greater than 61 months (ifosfamide and doxorubicin). Burton et al. found that hormonal therapy was ineffective in a small number of patients with hormone receptor–positive disease. The NCCN recommends that treatment of metastatic disease follow the algorithm outlined in the NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (the most recent version is available online at http://www.nccn.org).

In addition to chemotherapy, radiation can be useful to palliate sites of painful disease. Buchanan et al. recommend considering limited resection of solitary sites of metastatic disease, because isolated reports of long-term survival have been described.

Summary

Phyllodes tumors of the breast are rare tumors that present as rapidly growing breast masses and are often misdiagnosed as fibroadenomas. These tumors have both an epithelial and stromal component and may be benign, borderline, or malignant in histology. They have a propensity for local recurrence, but systemic metastasis occurs in only approximately 5% to 10% of patients overall and approximately 20% of those with the malignant subtype. Long-term cause-specific survival among patients with the malignant subtype is approximately 90%. Local excision with a 1-cm or larger tumor-free margin is definitive therapy after initial diagnosis. Local radiation therapy after breast-conserving therapy or mastectomy may be considered when adequate excision margins cannot be attained. Adjuvant systemic therapy has no proven value.

Patients experiencing local recurrences after initial therapy should undergo wide excision of the recurrence with or without subsequent local radiation therapy. Patients with metastatic disease should be managed, as appropriate, following treatment guidelines for patients with metastatic soft tissue sarcoma.

References

Telli et al.


