



Diagnosis and management of phyllodes tumors of the breast

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Abstract: Phyllodes tumors are very uncommon and represent less than 1% of breast lesions. They may appear histologically and radiographically similar to fibroadenomas making definitive diagnosis challenging on core needle biopsy. Often the diagnosis of phyllodes may not be determined until surgical excision. Phyllodes tumors are characterized as benign, borderline, or malignant based on histologic criteria set forth by the World Health Organization. Surgical excision is the mainstay of treatment for all subtypes. When core needle biopsy is inconclusive, fibroepithelial lesions should be surgically excised though a wide margin is not necessary until a definitive diagnosis has been made. Wide local excision with 1cm margins has been advocated, though narrow margins with close observation may suffice for benign tumors. Positive margins are associated with greater recurrence risk and should be excised if feasible. Recurrence is common and may be treated with wide local excision. Radiation has been increasingly used for treatment in borderline and malignant phyllodes with improvement in local control though no improvement in overall survival. Malignant phyllodes tumors behave histologically similar to sarcomas with lung metastasis being most common. Nodal involvement is very uncommon given the propensity for hematogenous spread and routine nodal evaluation is not recommended. No trials have demonstrated a survival benefit to systemic therapy and most individuals presenting with metastatic disease have a poor prognosis.

Keywords: Benign phyllodes; borderline phyllodes; malignant phyllodes; recurrence; margins

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Introduction

Phyllodes tumors are fibroepithelial lesions of the breast representing less than 1% of all breast tumors (1). Histologically, they can resemble fibroadenomas and are differentiated by stromal hyper cellularity and a characteristic “leaf-like” architecture (2). Phyllodes tumors are classified as benign, borderline, or malignant based on histologic grading of tumor border, stromal cellularity, mitotic figures, the presence of atypia, and stromal overgrowth (3). Categorizing these tumors is somewhat subjective with variance in classification among pathologists. Phyllodes tumors often present in younger women and are often described as firm, palpable masses demonstrating rapid growth. The mainstay

of treatment for phyllodes tumors is surgical excision with some debate on the appropriate margin. In the setting of malignant phyllodes tumors, the benefit of adjuvant therapy is not well established and is recommended on a case by case basis. In this paper we aim to present an overview of the diagnosis and management of benign as well as malignant phyllodes tumors.

Presentation and diagnosis

Phyllodes tumors are a rare subtype of fibroepithelial lesions which may be difficult to distinguish from fibroadenomas (4). Presentation is typically in women in their forties compared to younger women who are

Table 1 WHO Classification of phyllodes tumors

Criteria	Benign	Borderline	Malignant
Tumor border	Well-defined	Well-defined; may be focally infiltrative	Infiltrative
Stromal cellularity	Cellular, usually mild	Cellular, usually moderate	Cellular, usually marked and diffuse
Stromal cell atypia	None to mild	Mild or moderate	Marked
Mitotic activity	<5 per HPF	5–9 per HPF	>10 per HPF
Stromal overgrowth	Absent	Absent or very focal	Often present
Malignant heterologous elements	Absent	Absent	May be present

Tan PH, Tse G, Lee A, *et al.* Fibroepithelial tumours. In: Lakhani SR, Ellis IO, Schnitt SJ, *et al.* editors. WHO Classification of Tumours of the Breast. Lyon: IARC Press, 2012:142-7. HPF, high power field.

diagnosed with fibroadenomas (5). Phyllodes tumors are more common in Asian women, and may present earlier in age (6). Patients with a TP53 mutation (Li Fraumeni syndrome) have increased risk for developing phyllodes tumors (7). The work up of a phyllodes tumor includes mammography and ultrasound. Phyllodes tumors can be difficult to distinguish from fibroadenomas radiographically, although certain features such as larger size, hyper dense appearance on mammography, heterogeneous echo, the presence of round cysts within the mass and internal clefts on ultrasound may be suggestive, but not pathognomonic for phyllodes tumors (8). A core needle biopsy is necessary to aide in distinguishing fibroadenomas from phyllodes tumors but may still possess some uncertainty histologically due to overlapping features and tumor heterogeneity (9). In this instance, lesions may be classified as a fibroepithelial lesion with recommendations for complete surgical excision for definitive diagnosis.

The World Health Organization (WHO) criteria for classifying phyllodes tumors evaluates tumor border, stromal cellularity, stromal atypia, mitotic activity, and stromal overgrowth to categorize tumors as benign, borderline or malignant (3) (*Table 1*). Phyllodes tumors may present with features from more than one category making classification somewhat difficult and subjective.

Benign phyllodes tumors (BPTs) are the most common (60–75%) are typically well defined with mild stromal cellularity, no to mild atypia, few mitoses, with no stromal overgrowth. Borderline phyllodes tumors may demonstrate moderate stromal cellularity, mild to moderate atypia and more frequent mitotic figures, 5–9 per high power field (HPF). Malignant phyllodes tumors demonstrate infiltrative borders, diffuse stromal cellularity, marked atypia and >10 mitoses per HPF. A phyllodes tumor presenting with

malignant heterologous elements is sufficient for the diagnosis of a malignant phyllodes even in the absence of other malignant features (3).

Surgical management

Once a diagnosis of phyllodes tumor is confirmed or suspected, the mainstay of treatment is surgical excision. A mass with increased stromal cellularity suspicious for a phyllodes tumor should also be excised, though surgical excision may be more conservative with the understanding re-excision with wider margins may be necessary if final pathology is consistent with a phyllodes tumor. It is important to clearly denote the prior resection cavity with clips or identify the resection cavity with ultrasound in the event re-excision is necessary. Breast conservation is an appropriate treatment for phyllodes tumors if good aesthetic and oncologic outcomes are feasible (10). Despite the demonstrated equivalence with breast conservation, mastectomy is still performed in nearly 50% of cases due to large tumor size and recommendations for wide local excision (11). The majority of tumors larger than 5cm will undergo mastectomy though advanced oncoplastic techniques are also an option. Regardless of surgical intervention, nodal evaluation is not recommended though still performed in as many as 25% of phyllodes cases (11). Hematogenous spread of these tumors makes axillary nodal sampling unnecessary even in the setting of malignant phyllodes unless there is clinical evidence of nodal involvement (11,12).

Prior recommendations mandating wide, 1 cm margins for BPTs have recently come under scrutiny. Multiple studies performed have investigated the potential for recurrence based on less than 1cm margins and have concluded the only prognostic indicator for recurrence is a positive margin

Table 2 Studies evaluating margins for phyllodes tumors

Author	Year	Findings/recommendations
Wen (13)	2020	No difference in recurrence with narrow vs. wide margin 3% recurrence in benign PT with positive margins Positive margins in BPT can be observed rather than re-excised
Li (27)	2019	Involved margins associated with LR Negative margins sufficient. No benefit to wide margins
Lu (26)	2019	Positive margins associated with LR in malignant PT but not in borderline or BPT Narrow or focally positive margins for BPT may not require re-excision
Ogunbiyi (15)	2018	BPT or borderline tumors with positive margins can be treated with re-excision or close surveillance Patients with positive margin and malignant PT should have further surgery to achieve negative margins
Qian (16)	2018	No correlation between margin status and recurrence for BPT Wide local excision is not a requirement for BPT
Moo (19)	2017	No association in recurrence for re-excision for focally positive/close margin vs. observation in BPT
Shaaban (18)	2017	No significant difference in recurrence in narrow vs. wide margin for BPT Counsel patients on observation vs. re-excision for positive margins for BPT
Cowan (17)	2016	Extent of positive margin does not predict recurrence for BPT No difference in recurrence in BPT for positive vs. negative margins
Borhani-Khomani (20)	2016	Recurrence 6.2% BPT and 9% borderline No correlation in margin size and recurrence for borderline or BPT Wide local excision may not be mandatory to prevent LR
Yom (21)	2015	65% of patients with positive margins with no re-excision Margins <0.1 mm not associated with increased LR All BPT recurrences were benign
Tan (28)	2012	Margin status (positive/negative) significantly affected recurrence free survival. 2% of BPT recurrences were malignant
Jang (22)	2012	Positive margin is a risk factor for LR Recurrence is not influenced by margin width
Gulliot (23)	2011	26% benign PT had <10 mm margins. No difference in recurrence in benign PT for re-excision vs. observation

BPT, benign phyllodes tumor; LR, local recurrence.

and recurrence does not improve with wider margins (13-27) (Table 2). For this reason, a 1cm margin is no longer deemed the standard in effectively managing BPTs. In fact, approximately 87% of patients with BPTs and a focally positive margin will not experience recurrence (18). For patients with a BPT and a positive margin either re-excision or surveillance are acceptable options for management. The most recent National Comprehensive

Care Network (NCCN) recommendations still recommend wide excision for borderline and malignant phyllodes tumors but note the inability to achieve a 1-cm margin with breast conservation is not an absolute indication for mastectomy (29). Adjuvant radiation has been shown to decrease local recurrence and may be indicated when a recurrence would cause significant morbidity (27,29,30).

Recurrence

Historical data site recurrence as a relatively common phenomenon occurring in up to 21% of cases (12,31,32) while more contemporary data cite recurrence of 8–10% for benign, 13–14% for borderline and 18% for malignant phyllodes tumors (26,28).

An externally validated nomogram has been developed to predict likelihood of recurrence based on stromal atypia, mitosis, overgrowth and surgical margins (AMOS) (24,28,33,34). This provides a predictable manner to assess the likelihood for reoccurrence compared to tumor grading alone. This nomogram may be used to help guided decision making in initial treatment as well as the decision to re-excite versus for close surveillance in the setting of a positive margin.

Involved surgical margins is a well-documented independent prognostic factor in local recurrence (25,27,28). In the setting of distant metastasis, histologic factors such as high tumor grade, mitotic count, pleomorphism, overgrowth, infiltrative border and necrosis are more important than margin status (27). Though positive margins are a risk factor for local and distant recurrence, margin width has not been shown to impact recurrence rates (27,28). Additionally, genomic assays have demonstrated mutations present in borderline and malignant phyllodes tumors in proto oncogenes NF1, RB1, TP53, PIK3CA, ERBB4 and EGFR which may play a role in their higher rates of recurrence (35).

A meta-analysis assessing recurrence found 26% of BPTs and 21% of borderline tumors upgraded at recurrence noting the importance of close surveillance even in benign and borderline cases (26). It is important to note there was no pathology review as part of this meta-analysis and some cases were misclassified at initial presentation and falsely upgraded at recurrence. Time to recurrence varies with several studies but is generally within 3 years (17,26). After recurrence, efforts should be made for repeat excision to negative margins. Radiation is used with increasing frequency in borderline and malignant phyllodes with reports of improved local control (36).

Malignant phyllodes

Malignant phyllodes are extremely rare and no randomized trials exist in the treatment of phyllodes tumors. The NCCN recommendation for treatment of malignant phyllodes tumors is wide local excision with the intention of

achieving 1 cm margins (29). Malignant phyllodes tumors behave histologically similar to sarcomas. Metastasis can be seen in up to 22% of patients with malignant phyllodes at presentation with the most common site being lung followed by bone, heart and liver (37). Once a diagnosis of malignant phyllodes is made, staging computed topography (CT) of the chest is prudent to rule out pulmonary metastasis. Additional imaging may be warranted pending patient symptoms. Patients with metastasis have an overall poor prognosis, many dying within 3 years regardless of systemic therapy regimen (37). There is no survival benefit to surgical excision of the breast primary in the setting of metastatic disease; however, palliative surgery could be performed on an individualized basis for local control if feasible. Once metastasis has been excluded, surgical excision of the malignant tumor is recommended with wide 1 cm margins. Routine axillary nodal staging is not recommended for the effective treatment of phyllodes given low propensity for nodal spread (11,12,37).

Radiation is increasingly utilized for treatment of both borderline and malignant phyllodes tumors. Radiation has been effective in decreasing loco-regional recurrence with no change in overall survival (25,30). A meta-analysis has demonstrated improved local control in patients with breast conservation surgery and radiation regardless of margin status (38). Despite documented lower recurrence rates, radiation with breast conservation has not demonstrated improved cancer specific survival (CSS) (36). The data is scarce for mastectomy and radiation. Prior studies have demonstrated inferior outcomes in this patient population but this is likely due to selection bias with patients in these studies having more advanced tumors with poor prognostic features (36). Newer studies have demonstrated inferior, but not statistically significant, outcomes with mastectomy and radiation suggesting larger studies may further reduce the impact of selection bias (36). Overall, findings would suggest improved local control but overall no improvement in CSS with the use of adjuvant radiation (36–38).

The use of chemotherapy is uncertain given the high likelihood for recurrence and poor prognosis in metastatic disease. Doxorubicin with Dacarbazine compared to no medical therapy has been studied with no benefit in relapse free survival (39). For this reason, chemotherapy is not routinely recommended but may be considered on an individualized basis for large tumors or those with chest wall involvement. Chemo embolization has also been described in the literature for large, bulky tumors but lacks data for recommended routine use (40).

Conclusions

Phyllodes tumors are rare fibroepithelial lesions which can resemble benign fibroadenomas. The mainstay of treatment is complete surgical excision. BPTs with narrow or focally positive margins may be closely observed as opposed to routine margin re-excision (Table 2). Recurrence can be managed with wide local excision and radiation may be considered to improve local control for borderline and malignant subtypes. Data on systemic therapy for malignant phyllodes tumors is sparse and it is not routinely recommended.

Clinical scenario 1: fibroepithelial lesion

A 40-year-old female presents with an enlarged mass in the right breast. She has no prior imaging. A diagnostic mammogram and targeted ultrasound of the breast reveal a 4-cm lobulated breast mass. A core needle biopsy is performed which demonstrates a fibroepithelial lesion with increased stromal cellularity.

Question: What are the next steps in management?

Answer: This lesion have overlapping features of a cellular fibroadenoma and a phyllodes tumor. Surgical excision is the next step in management. Given the uncertainty of diagnosis, surgical excision should be performed similar to a fibroadenoma where the lesion is enucleated from the surrounding breast tissue.

The patient has the lesion surgically excised. The final pathology is consistent with a BPT measuring 4 cm in size. Multiple margins are positive on final pathology.

Question: What are the next steps in management?

Answer: The diagnosis of a phyllodes tumor was made after surgical excision. Positive margins are common after enucleation but may not reflect a true positive margin as the specimen surface may become damaged during surgery or in during pathology processing. This is supported in low recurrence rates and no residual tumor with re-excision in the setting of a “positive” margin (41). It may not be mandatory to re-excise an enucleated phyllodes tumor with benign morphology.

Clinical scenario 2: BPT

A 40-year-old female presents with a rapidly enlarged mass in the right breast. She has no prior breast imaging. She underwent diagnostic mammogram and targeted ultrasound of the right breast revealing a lobulated mass measuring

5 cm. A core needle biopsy was performed. Biopsy results demonstrate a fibroepithelial lesion, favor benign phyllodes.

Question: What are next steps for management?

Answer: Surgical excision is the mainstay of treatment. Depending on the size of the tumor relative to the volume of breast tissue, breast conservation with or without oncoplastic reduction would be the best management of this benign lesion. Surgical pathology reveals a BPT. The posterior margin is locally positive and all remaining margins are negative.

Question: What are the next steps in management?

Answer: A focally positive margin does not necessitate re-excision. Patient can be offered re-excision if feasible or close surveillance. If the patient develops a recurrence, excision is recommended.

Clinical scenario 3: malignant phyllodes tumor

A 40-year-old patient presents with a rapidly enlarging right breast mass. She has no prior imaging. A diagnostic mammogram and targeted ultrasound of the breast reveal a lobulated mass with internal clefts. A core needle biopsy was performed. Biopsy results demonstrate a fibroepithelial lesion suspicious for malignant phyllodes tumor.

Question: What are the next steps in management?

Answer: The patient has a malignant phyllodes tumor. A thorough history and physical to identify any symptoms that may suggest metastatic disease should be performed. A chest CT as well additional appropriate imaging guided by H&P should be performed to rule out metastatic disease. The H&P was unremarkable and CT of the chest is negative for metastatic disease.

Question: What are the next steps in management?

Answer: Wide local excision of the tumor is recommended. Breast conservation with oncoplastic reduction or mastectomy can be performed depending on tumor size and breast volume. Inability to achieve 1cm margins with breast conservation does not mandate a mastectomy. A sentinel lymph node biopsy is not recommended.

Wide local excision of the tumor with oncoplastic reduction is performed. The surgical margins are negative but less than 1 cm.

Question: What are the next steps in management?

Answer: Closure surveillance is recommended to assess for recurrence. Referral to radiation oncology is appropriate to discuss the benefits of adjuvant radiation therapy. There are no standard recommendations for adjuvant

chemotherapy in the setting of malignant phyllodes tumors. This tumor has been excised to negative margins and is not invading the chest wall therefore there is no benefit to adjuvant chemotherapy.

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