

Phyllodes tumors of the breast: diagnosis, treatment and prognostic factors related to recurrence

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Abstract: Phyllodes tumors of the breast are rare tumor types that consist of 0.3–1.0% in all breast tumors. The naming and classification of breast phyllodes tumor have been debated for years. Based on the classification criteria modified by WHO in 2003, this review mainly introduced the clinicopathologic characteristics, pre-operational diagnosis and the treatment of breast phyllodes tumors, and also summarized the prognostic factors related to tumor recurrence.

Keywords: Phyllodes tumor of the breast (PTB); diagnosis; treatment; prognostic factors

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Introduction

Breast tumor is still a major health burden for women, especially in urban areas (1,2), phyllodes tumor of the breast (PTB) is a rare tumor type among all kinds of breast tumor, its incidence rate is 2% to 3% in all breast fibrous epithelial tumors, or 0.3% to 1.0% in all breast tumors (3,4). In 1838, Johannes Muller first reported and named this tumor cystosarcoma phyllodes (5), described as a huge neoplasia with a cystic lobulated section and rapid growth. Over the years there have been many disputes among investigators (4) regarding the nomenclature and classification of breast phyllodes tumors. In 2003, the WHO's international histological classification group suggested that it be named phyllodes tumor, and divided into three subtypes: benign, borderline and malignant (3). This proposal of nomenclature and classification gradually reached a consensus. The evolution of nomenclature reflects the increasing understanding of breast phyllodes tumors as a

rare tumor type.

The existing breast phyllodes tumor diagnostic method has a low diagnosis accuracy in general. Preoperative diagnosis uncertainty has hindered the rational development of surgical treatment options. High local recurrence is the most important prognostic feature of this condition, with an overall recurrence rate up to 40% of all histological types of breast phyllodes tumors (6). Borderline and malignant types have a different degree of malignancy. Without adequate treatment, there will be a tendency of rapid growth and metastasis. The modes of tumor metastasis are primarily via blood, rarely lymph nodes. Common clinical sites of metastasis include the lung, followed by soft tissue, bone, pleura, etc. (7). Borderline and malignant phyllodes tumor metastasis rate is about 25% to 31%, while the overall rate of all phyllodes tumor metastasis being 4% (8,9). Improving the accuracy of diagnostic methods for breast phyllodes tumor before surgery and reducing the local recurrence rate after surgery is essential for tumor control.

Table 1 Breast phyllodes tumor pathological diagnosis & grading criteria

Pathological characteristics	Histological type		
	Benign	Borderline	Malignant
Stromal cell atypia	Mild	Moderate	Severe
Interstitial cell hyperplasia	Mild	Moderate	Severe
Mitotic	<4/10 HPF	4–9/10 HPF	≥10/10 HPF
Tumor boundary	Clear	Clear or infiltration	Infiltration

HPF, high power field.

Clinical and pathological characteristics

Breast phyllodes tumors occur in women aged 35 to 55 years (10). Breast phyllodes tumor lesions are often unilateral, single, nodular, painless masses with an insidious onset and slow progression. Most patients have a history of masses that grow rapidly in the short term. The tumor activity is good, free to push on the chest wall. Tumor volume varies widely, as some studies have reported that the tumor size ranges from less than 1 cm to a maximum of 40 cm in diameter (11). The relationship between tumor size and prognosis is not clear. Some studies have presented that malignant phyllodes tumor has a larger diameter compared to benign and borderline ones, while other studies have failed to reach the same conclusion (9,12). Previous studies suggest that those with a diameter of 10 cm or more is defined as a huge lobulated tumor (9). About 20% patients have palpable axillary lymph nodes in clinical examination, but only 5% are pathologically confirmed with lymph node metastasis (13). Hines *et al.* (14) reported that the incidence of axillary lymph node metastasis of malignant phyllodes tumor was 15%. Patients with lymph node metastasis have poor prognosis.

Breast phyllodes tumor is mostly nodular on the surface, with a clear boundary and no true capsule. It is sometimes ill-defined because some lesions invade surrounding breast tissue. The tumor section is lobulated, solid and tough, in gray or gray-yellow color. Narrow gaps or cavities of different sizes are common, containing clear or bloody fluid or jelly-like substances. The solid part is braided, with a polypoid oppressing the cysts, visible focal hemorrhage, necrosis and cystic changes. Breast phyllodes tumor includes mesenchymal and epithelial components. Benign epithelial components often form ducts or liners overlying the cavity or fracture surface. Real tumor

components are hyperproliferative interstitial cells, namely fibroblasts. These cells have lost the normal arrangement, and are braided, mesh or spiral-shaped. Tumor cells can be uniformly dispersed, with unequal density in different regions and varying degrees of atypia and a variable number of mitotic figures. There may be mucoid degeneration and necrosis or hemorrhage. Epithelial components can be varying, but in general the worse the stroma differentiation, the fewer the epithelial component. Recurrent tumor histology is basically the same as primary tumor, or with a tendency to malignancy. Previous studies have shown that breast phyllodes tumor metastases contain only malignant mesenchymal components (15).

According to the diagnostic criteria established by WHO (3), benign, borderline and malignant phyllodes tumors are based on the tumor cell atypia, excessive growth, mitosis and tumor boundary (*Table 1*). Phyllodes tumors are sometimes observed with a fibroadenoma-like structure, where fibrocystic changes, adenosis, epithelial hyperplasia or atypical hyperplasia can occur. Invasive ductal carcinoma, lobular carcinoma and *in situ* carcinoma may also occur in phyllodes tumors, but they are very rare. Lobulated tumor fibroblasts can also differentiate in fat, cartilage, smooth muscle and striated muscle cells. All these components are likely to develop into a sarcoma. The presence of these components indicate poor prognosis (16).

Breast phyllodes tumor has rich biological characteristics and is difficult to predict, especially in borderline phyllodes tumor, which features two-way differentiation with obvious tendency to benign ones, clear boundary, less nuclear fission, and thus the prognosis is good. Sometimes malignant mitotic figures can be seen, and there may be bleeding, necrosis and multiple recurrence after surgery with poor prognosis. Therefore, the histological grade alone does not provide good guide for clinical treatment and prognosis.

Table 2 Comparison of pathological features on prognostic factors for local recurrence PTB

Author	Mitotic	Interstitial cells		Tumor necrosis	Residual tumor
		Hyperplasia	Atypia		
Gnerlich (17)	-	+	-	+	-
Sawalhi (18)	-	-	+	-	-
Tan (19)	-	+	+	-	-
Belkacémi (13)	-	-	-	-	+
Barrio (20)	+	+	-	+	-
Taira (21)	-	+	-	-	-
Fajdić (22)	+	-	+	-	-
Roa (23)	+	-	-	-	-
Ben (24)	+	-	-	+	-
Asoglu (25)	-	+	-	-	-
Chaney (9)	-	+	-	-	-

+, indicates relevance to prognosis; PTB, phyllodes tumor of the breast.

Many studies suggest that integrated histopathological prognostic indicators have more instructive significance (*Table 2*).

Preoperative diagnosis methods

The extensive clinical and pathological features of breast phyllodes tumors pose difficulties to the preoperative diagnosis. Imaging and cytology biopsy are the basis of preliminary judgment and classification before phyllodes tumor surgery. However, the existing breast diagnostic methods, whether it being breast ultrasound, MRI or X-ray imaging (26,27), is not characteristic of showing PTB, mostly showing the characteristics of fibroadenoma (28,29), making it difficult to distinguish them. Ultrasonography is convenient and non-invasive, so it is a preferred choice for the diagnosis of PTB (26). PTB shows on ultrasound as a bulky lobulated mass, with clear boundaries, internally mainly solid hypoechoic uneven echoes, potentially with scattered echo-free zones. Malignant phyllodes tumor does not follow the general rules of other types of breast cancer in terms of echo attenuation, and micro calcification is common. Breast X-ray findings are related to tumor size. Smaller tumors are nodules with more smooth edges, while the greater ones have more irregular lobulated yet clear borders, with higher density than normal glands. MRI can clearly show the tumor scope (27). Breast phyllodes tumor

is low signal-based on plain scan T1W1, and higher signal-based on T2W1. The dynamic contrast-enhanced lesion on time-signal intensity curve is increasing more and platform type, making it easy to be differentiated with fibroadenoma. Fine needle aspiration (FNA) and core needle biopsy (CNB) is the pathology basis for preoperative diagnosis. However, due to the location and coverage limits on the amount drawn, it is difficult to differentiate with epithelial neoplasms, or other type of fibroadenoma. Therefore, the diagnostic accuracy of phyllodes tumor is low. Most studies suggest that the diagnosis accuracy rate of FNA or CNB for breast phyllodes tumor is about 50% (*Table 3*). For breast phyllodes tumor patients, if clinicians rely solely on the low accuracy of the preoperative examination to determine the surgical approach, or rely on pathological histological classification to determine adjuvant therapy, prognosis and tumor progress are difficult to be followed. Looking for tumor specificity for different types of phyllodes tumors with high distinction, and it is associated with tumor recurrence and metastasis of immunological markers, which is worth exploring the direction (38). Considering clinical manifestations, imaging characteristics pre-biopsy and molecular markers comprehensive intraoperative judgment can effectively improve the breast phyllodes tumor preoperative diagnosis rate. The final diagnosis and tumor histological type depends on the postoperative pathological findings.

Table 3 Cytology diagnostic accuracy for PTB reported in literature

Author	Year	N	Biopsy	Cytology, N (%)		Postoperative pathological, N (%)		
				PT	Non-PT	Benign	Borderline	Malignant
Jang (30)	2012	129	CNB	74 (57.40)	55 (42.60)	90 (69.80)	30 (23.30)	9 (6.90)
Tsang (31)	2011	49	CNB	28 (57.00)	21 (43.00)	25 (51.00)	18 (36.70)	6 (12.30)
El Hag (32)	2010	15	FNA	6 (40.00)	9 (60.00)	8 (53.30)	6 (40.00)	1 (6.70)
Pătrașcu (33)	2009	17	FNA	0 (0)	17 (100.00)	11 (64.70)	4 (23.50)	2 (11.80)
Lee (34)	2007	36	CNB	5 (13.90)	31 (86.10)	18 (50.00)	12 (33.30)	6 (16.70)
Foxcroft (35)	2007	84	CNB	54 (64.30)	30 (35.70)	71 (84.50)	8 (9.50)	5 (6.00)
Komenaka (36)	2003	57	CNB	32 (56.10)	25 (43.90)	28 (43.90)	19 (33.30)	10 (22.80)
Jayaram (37)	2001	28	FNA	20 (71.40)	8 (28.60)	20 (71.40)	7 (25.00)	1 (3.60)

PTB, phyllodes tumor of the breast; CNB, core needle biopsy; FNA, fine needle aspiration.

Surgical treatment

Surgery is the preferred treatment for PTB. Preoperative CNB or excision biopsy diagnosis of breast phyllodes tumor patients requires additional wide excision, surgical margins ≥ 1 cm. Since there are very few of these lymph node metastasis, dissection of lymph nodes is not recommended under any surgical approach. For local recurrence mass, in the absence of metastases, repeat surgery is feasible, and postoperative radiotherapy can be considered. Metastases should be treated in accordance with principles of soft tissue sarcoma. However, many problems during lobular tumors are not provided with the solution in clinical guidelines. Now there are studies supporting that breast surgical methods and surgical margin status are important factors of recurrence (Table 4). Sotheran *et al.* (51), Haberer *et al.* (52) stressed the importance of breast tumor local extended resection (WLE excision) for the control of borderline and malignant phyllodes tumor in terms of recurrence. Bhargav *et al.* (53) believed that regardless of how the histological grade, wide local excision should be the first choice of surgical approach, but all patients with disease recurrence were required to undergo mastectomy. Ben Hassouna *et al.* (24) proposed mastectomy as the preferred surgical approach for malignant phyllodes tumor. However, Kapisir *et al.* (49) did not find in patients with malignant phyllodes tumor the statistical significance of expanded local resection and mastectomy, and suggested the importance of negative surgical margin to control malignant phyllodes tumor recurrence and distant metastasis,

consistent with the result of Moffat (50). Pandey *et al.* (48) found that all recurrent patients had positive surgical margins, suggesting that surgical margin was an independent risk factor for phyllodes tumor recurrence, thus improving disease-free survival (DFS) and reducing the possibility of local recurrence. Fou *et al.* (45) suggested that local resection of malignant phyllodes tumor circumstances to ensure negative margins can achieve a higher long-term survival. Mangi *et al.* (54) found that all relapse cases occurred in those with a surgical margin < 1 cm. Lenhard *et al.* (43) also studied the surgical margins and found no difference in recurrence group and non-recurrence group. Jang *et al.* (30) also found no benefits in positive surgical margins more than 1 cm versus less than 1 cm in control group.

Adjuvant therapy

The efficacy of postoperative adjuvant therapy for breast phyllodes tumor is not clear. In the study of Morales-Vásquez *et al.* (55), there was not statistically difference between postoperative adjuvant doxorubicin and dacarbazine treatment versus no treatment in terms of survival. In the 28 malignant phyllodes tumor, 17 patients received adjuvant chemotherapy, 7 patients received postoperative radiotherapy, and the 5-year relapse-free survival was 86% in the treated group versus 58% in the untreated group ($P=0.17$). The exact effect of adjuvant radiotherapy for local control of different histological types of phyllodes tumor recurrence has been focused on by many investigators, but the progress is still very small.

Table 4 Comparison of treatment approaches on prognostic factors for local recurrence PTB

Author	Histological grade	Surgical approach	Surgical margin	Adjuvant radiotherapy
Gnerlich (17)	-	-	+	+
Ramakant (39)	+	-	-	-
Sawalhi (18)	+	-	+	-
Teo (40)	+	-	-	-
Jang (30)	-	-	+	-
Tan (19)	+	-	+	-
Guillot (10)	-	-	+	-
Verma (41)	-	+	-	-
Barth (42)	-	-	-	+
Lenhard (43)	+	-	-	-
Belkacémi (13)	+	-	-	+
Pezner (44)	-	+	-	+
Barrio (20)	-	-	+	-
Taira (21)	-	+	+	-
Fajdić (22)	-	-	+	-
Fou (45)	-	-	+	-
Cheng (46)	-	-	-	-
Roa (23)	+	-	+	-
Ben (24)	+	+	+	-
Chen (47)	-	+	+	-
Pandey (48)	-	-	+	+
Kapiris (49)	-	-	+	-
Reinfuss (12)	+	-	-	-
Moffat (50)	-	+	+	-

+, indicates relevance to prognosis; PTB, phyllodes tumor of the breast.

Some studies reached the same view that in the clinical management of highly malignant phyllodes tumor cases, postoperative radiotherapy can significantly reduce the likelihood of recurrence. According to the Surveillance, Epidemiology and Results Program (SEER) Program, about 50% of patients with malignant phyllodes tumors first received breast-conserving surgery, of which only fewer than 5% received postoperative adjuvant radiotherapy (56). Pezner *et al.* (44) indicated that for patients undergoing local resection of tumor size >2 cm and mastectomy of tumor size >10 cm, the value of adjuvant radiotherapy

significantly increased. Pandey *et al.* (48) observed that PTB patients receiving adjuvant radiotherapy had a significantly longer 5-year DFS than those who did not receive radiation therapy (61% *vs.* 25%), but because of the small sample size, the study failed to show any significant difference ($P=0.16$) between the two groups. Belkacémi *et al.* (13) reported postoperative radiotherapy improved 10 years local control rate in borderline and malignant phyllodes tumor groups, but it did not affect overall survival. Other studies reported that regardless of breast-conserving surgery or mastectomy, local control rate of cases received

postoperative radiotherapy group was always higher than the control group (26,57). Barth *et al.* (42) revealed that adjuvant radiotherapy was an effective way to control local recurrence of borderline and malignant phyllodes tumors after control breast-conserving surgery, with significantly lower relapse rate in those with negative margins receiving adjuvant radiotherapy.

Conclusions

There are different reports regarding the histological grade, surgical options, surgery margin and pathological features of breast phyllodes tumor that are closely linked with the recurrence, so we recommend to develop reasonable surgical programs based on the clinical manifestations, imaging characteristics and biopsy results, and ensure negative surgical margins; and provide necessary postoperative adjuvant therapy according to histological grade, mitotic activity, stromal cell hyperplasia and atypia.

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Footnote

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