



# Accuracy and clinical implications of pre-operative breast core needle biopsy diagnoses of fibroepithelial neoplasms and sarcomatoid carcinomas

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## Abstract

**Purpose** Accurate classification of breast phyllodes tumors (PTs) on core biopsy can be challenging. The differential diagnosis of benign PT (BP) is fibroadenoma (FA), whereas the differential diagnosis of malignant PT (MP) is sarcomatoid (metaplastic) carcinoma (SC).

**Methods** Here, we compare the pre-excision core biopsy diagnosis and clinicopathologic features of histologically confirmed MP, borderline PT (BLP), BP, FA, and SC. Consecutive cases of 34 histologically confirmed PT (14 MP, 10 BLP, 10 BP), 13 SC, and 10 FA were identified.

**Results** A core biopsy diagnosis of SC was made only in SC (77%,  $p=0.003$ ). The diagnosis “malignant neoplasm” or “atypical spindle cell neoplasm” was made in 100% MP and 23% SC, but no other tumor ( $p=0.0001$ ). The diagnosis “phyllodes tumor” was made only in PT (44% BLP, 11% BP,  $p=0.06$ ). The diagnosis “fibroepithelial lesion” was made in 44% BLP, 67% BP, and 29% FA. The diagnosis “FA” was made most commonly in FA (57%) (versus 22% BP and no other tumor;  $p=0.002$ ). Neoadjuvant therapy was given only in SC (23%,  $p=0.03$ ); adjuvant therapy was given in 46% SC and 13% MP ( $p=0.04$ ).

**Conclusions** A pre-operative core biopsy diagnosis of “malignant spindle cell neoplasm” separates MP and SC from BLP, BP, and FA. However, MP and SC can have overlapping features on core biopsy. Thus, one must be careful not to overcall SC on core biopsy, as patients diagnosed with SC may receive neoadjuvant therapy. A core biopsy diagnosis of “phyllodes tumor” is specific for PT and can guide treatment planning of a wide local excision.

**Keywords** Phyllodes tumor · Malignant phyllodes tumor · Sarcomatoid carcinoma · Fibroepithelial lesion · Core biopsy

## Introduction

Phyllodes tumors (PTs) are rare fibroepithelial neoplasms of the breast. PTs are typically graded using a three-tiered system, with classifications of benign phyllodes (BP), borderline phyllodes (BLP), and malignant phyllodes (MP) tumors [1, 2]. Core needle biopsy is usually performed prior to excision, and core biopsy diagnosis may be challenging. The differential diagnosis of BP is fibroadenoma (FA) [3–8],

whereas the differential diagnosis for MP is sarcomatoid (metaplastic) carcinoma (SC) [7–10]. The recommended treatment for PT is complete local excision with a recommendation of at least 1 cm clear margins for MP [8, 11], whereas FA may be treated with enucleation. SCs are treated with wide local excision with or without sentinel lymph node sampling, chemotherapy, and/or radiotherapy [10, 12]. Here, we compare the pre-excision core biopsy diagnosis and clinicopathologic features of histologically confirmed MP, BLP, and BP with FA and SC to evaluate how the core biopsy diagnosis correlates with the final resection.

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## Materials and methods

This study was approved by the Institutional Review Board of the Johns Hopkins Medical Institutions. We previously searched the pathology archives for consecutive cases of PT,

SC, and FA with adequate archival tissue for future correlative studies [13–16]. Thirty-four histologically confirmed PTs consisting of 14 MP, 10 BLP, and 10 BP; 13 SC; and 10 FA were identified. The immunophenotypes of these cases have been previously evaluated and reported [13–16]. The PTs were classified on full-faced sections from resection specimens and on the basis of circumscription, the degree of stromal cellularity, the presence or absence of stromal overgrowth, the degree of stromal nuclear atypia and pleomorphism, and the presence of stromal mitosis using established criteria [1, 2].

Hematoxylin and eosin-stained whole sections of tumor slides and core biopsy slides were reviewed on all cases. Clinicopathologic features including pre-excision core biopsy diagnosis, patient age, race, tumor laterality, tumor size, tumor grade, surgical management, treatments received, and outcome were recorded. Statistical significance of the results was determined using the Fisher's exact test.

## Results

The results of pre-operative core biopsy diagnosis compared to excision diagnosis are summarized in Table 1. Side-by-side examples of each tumor type are depicted in Fig. 1, with paired histologic sections of a patient's core biopsy and subsequent resection. Pre-operative core needle biopsy slides were available to review for 43% MP, 90% BLP and BP, 70% FA, and 100% SC. Of these, a core biopsy diagnosis of "sarcomatoid (metaplastic) carcinoma" was made in 77% SC, but not in MP ( $p=0.003$ ) or any other tumor type. A core biopsy diagnosis of "malignant neoplasm" or "atypical spindle cell neoplasm" was made in 100% MP and 23% SC, but not in any other tumor type ( $p=0.0001$ ). A core biopsy diagnosis of "phyllodes tumor" was rendered only in PTs (44% BLP and 11% BP), but no other tumor type ( $p=0.06$ ).

A core biopsy diagnosis of "fibroepithelial lesion" not further specified was made in 44% BLP, 67% BP, and 29% FA. A core biopsy diagnosis of "fibroadenoma" was made more commonly in FA (57%) than other tumor types (seen only in 22% BP;  $p=0.002$ ). And finally, a core biopsy diagnosis of "benign breast tissue" was made in 12% BP and 14% FA.

The clinicopathologic characteristics are summarized in Table 2. Patients with MP were on average older (48 years) than patients with FA (26 years,  $p=0.0004$ ), and younger than patients with SC (65 years,  $p=0.004$ ). Mastectomies were performed in 43% MP and 62% SC, compared to no BLP, BP, or FA ( $p=0.0001$ ). Axillary sentinel lymph nodes were sampled in 14% MP compared to 77% of SC ( $p=0.002$ ), and lymph node metastases were detected only in 30% of the SC. The mean tumor size of MP (7.2 cm) was larger than the other tumor types (BLP 5.2 cm; BP 2.1 cm; FA 3.2 cm; and SC 4.7 cm) ( $p=0.003$ ). Concurrent conventional invasive ductal carcinoma was present in 38% SC but no PT or FA ( $p=0.0003$ ), although separate foci of ductal carcinoma in situ (DCIS) were present in 20% BLP. Follow-up data were available in 43% MP; 90% BLP, BP, and FA; and 100% SC. Neoadjuvant therapy was administered in 23% SC and no PT or FA ( $p=0.03$ ); adjuvant therapy was administered in 46% SC compared to 13% PT ( $p=0.04$ ). Metastases and death due to disease occurred in 50% MP, 23% SC, and no BLP, BP, or FA ( $p=0.003$ ).

## Discussion

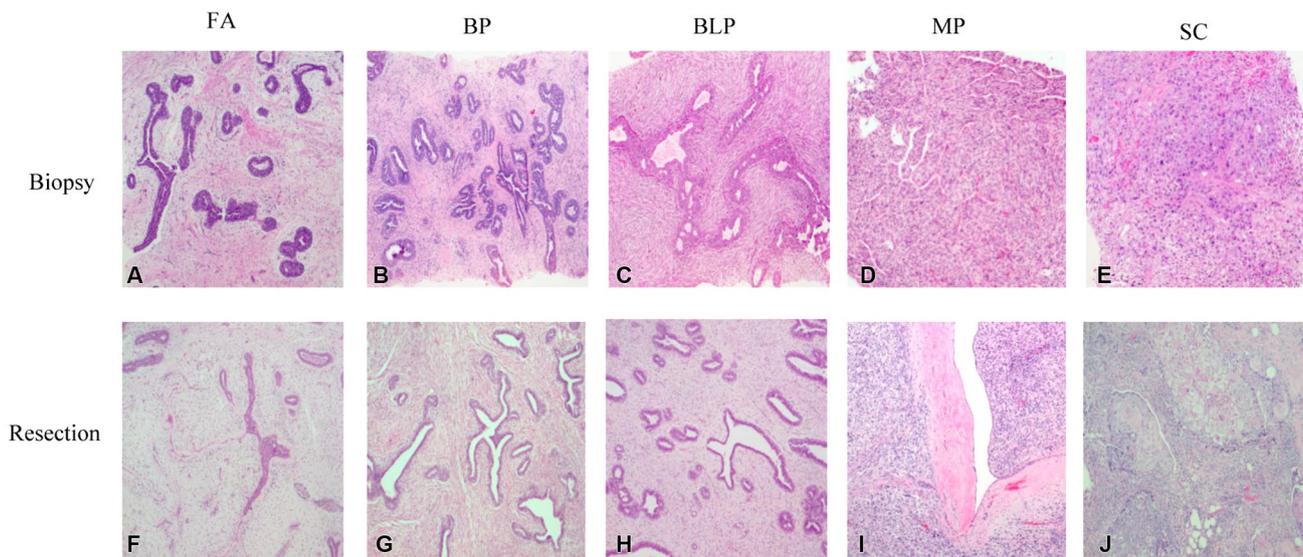
Breast PTs are fibroepithelial lesions that are divided into benign, borderline, and malignant subtypes [1, 2]. Depending on grade, PTs have local recurrence rates varying from <20% in BP to >25% in MP, and distant metastasis rates ranging from <5% in BP to 25% in MP [7, 8]. Tumors that are incompletely excised and have positive surgical

**Table 1** Pre-operative core needle biopsy diagnoses compared to the excision diagnoses in patients with breast fibroepithelial neoplasms and sarcomatoid (metaplastic) carcinoma

Resection diagnosis	<i>n</i> <sup>a</sup>	Pre-operative core needle biopsy diagnosis, <i>n</i> (%)					
		SC	Malignant or atypical spindle cell lesion	Phyllodes Tumor	Fibroepithelial lesion	FA	Benign breast tissue
MP	6	0	6 (100%)	0	0	0	0
BLP	9	0	0	4 (44%)	4 (44%)	0	1 (12%)
BP	9	0	0	1 (11%)	6 (67%)	2 (22%)	0
FA	17	0	0	0	2 (29%)	5 (57%)	1 (14%)
SC	13	10 (77%)	3 (23%)	0	0	0	0

BLP borderline phyllodes tumor, BP benign phyllodes tumor, FA fibroadenoma, MP malignant phyllodes tumor, *n* number, SC sarcomatoid (metaplastic) carcinoma

<sup>a</sup>The number of cases includes only those with slides available for histologic review for both the pre-operative core needle biopsy and subsequent resection specimen



**Fig. 1** Core needle biopsy samples (a–e) and paired resection specimens (f–j) in patients with breast fibroepithelial neoplasms and sarcomatoid (metaplastic) carcinoma. Sections from the core needle biopsies and subsequent resection specimens, respectively, from patients with fibroadenoma (FA; a, f), benign phyllodes tumor (BP; b, g), and borderline phyllodes tumor (BLP; c, h) demonstrate non-neoplastic glands with intracanalicular and pericanalicular patterns and increasing degrees of stromal cellularity. This constellation of histologic features enables classification on core biopsy of a fibroepithelial neoplasm. Sections from core needle biopsies of patients with malignant

phyllodes tumor (MP; d) and sarcomatoid (metaplastic) carcinoma (SC; e) contain sheets of atypical spindle and epithelioid cells with no overt lineage of differentiation. The core needle biopsy diagnosis of “malignant spindle cell neoplasm” is appropriate in this setting. In contrast, sections from the subsequent resection specimen of the patient with MP (i) demonstrate a focal benign epithelial component with leaf-like architecture, supporting definitive classification as a MP; sections from the subsequent resection specimen of the patient with SC (j) demonstrate overt malignant epithelial differentiation, supporting definitive classification as a SC

**Table 2** Clinicopathologic characteristics of patients with breast fibroepithelial neoplasms and sarcomatoid (metaplastic) phyllodes tumors

	<i>n</i>	Age (mean, range; year)	Mastectomy performed	Axillary SLNB	Tumor size (mean, range; cm)	NAT received	Adjuvant therapy received	Metastasis or death due to disease
MP	14	48 (30–67)	6 (43%)	2 (14%)	7.2 (2.5–20)	0	2 (13%)	7 (50%)
BLP	10	46 (20–70)	0	0	5.2 (1–12)	0	0	0
BP	10	38 (18–48)	0	0	2.1 (1–2.5)	0	0	0
FA	10	26 (13–51)	0	0	3.2 (1–6.3)	0	0	0
SC	13	65 (43–89)	8 (62%)	10 (77%)	4.7 (1.6–13)	3 (23%)	6 (46%)	3 (23%)

BLP borderline phyllodes tumor, BP benign phyllodes tumor, cm centimeter, FA fibroadenoma, MP malignant phyllodes tumor, *n* number, NAT neoadjuvant therapy, SC sarcomatoid (metaplastic) carcinoma, SLNB sentinel lymph node biopsy

resection margins are more likely to recur locally [7, 8, 17, 18]. While patients with BP and BLP typically have a favorable prognosis, up to 35% of patients with MP will die due to disease [19].

PTs may be difficult to diagnose on core needle biopsy [3, 4, 6, 8, 20, 21]. The differential diagnosis for BP on core biopsy includes FA [3–8], while the differential for MP includes SC [7–10]. High-grade SCs are rare breast tumors characterized by spindled or sarcomatoid areas in conjunction with heterologous elements such as chondrous, osseous, and/or squamous differentiation [10, 12, 22–25]. Conventional breast mammary carcinoma can also occur in

conjunction with SC [8, 26, 27]. Rarely, heterologous elements have been reported in MP [28, 29]. Both MP and SC contain atypical, pleomorphic spindled cells with a markedly increased mitotic rate. While PTs, including MP, are typically managed by wide local surgical excision, SCs may be treated with neoadjuvant therapy prior to surgery, which may include sentinel lymph node excision [25]. It is important to differentiate MP and SC on core needle biopsy to prevent unnecessary chemotherapy treatment and lymph node sampling.

Biopsy features such as fragments of stroma lined by epithelium, increased mitotic activity, increased stromal

cellularity, and stromal overgrowth suggest a diagnosis of PT [3, 30]. However, the distinction between MP and SC, which has important treatment implications, can be especially challenging. Several immunohistochemical and molecular modalities have been suggested to aid in the diagnosis of PT. PTs have an increased Ki-67 proliferation index compared to FA, with higher grade PT and SC having higher proliferation indices [5, 7, 13, 17, 19, 29–31]. MP may show strong and diffuse expression of p16, with or without loss of Rb [13], but RB loss and diffuse p16 positivity are also typically seen in ER/PR/HER2-negative breast carcinomas [32]. Sox-10 expression [14] can be seen in a subset of SCs but not in the MP studied to date, but GATA-3 labeling [15] has been observed in both. A broad panel of cytokeratin immunostains should be used to rule out SC, whereas stromal CD34 [9, 10] and bcl-2 immunoreactivity favor a diagnosis of PT [10]. P63 and p40, typically thought to favor SC, may also be seen in MP and should be used with caution [16]. We previously reported that the MP included in this current series display immunoreactivity for p63 (57%), p40 (29%), or cytokeratin (21%) [16]. In contrast, no FA, BP, or BLP displayed labeling for p63, p40, or cytokeratin; all SCs were immunoreactive for at least one cytokeratin labeling. Diffuse p53 positivity may be used to favor a diagnosis of MP over BP or BLP [5, 8, 17, 19, 31]. In addition, other genetic alterations in PTs have been described, including gains in chromosome 1q [8, 33, 34], *MED12* mutations [8, 35, 36], and *TERT* promoter hotspot mutations [35].

Despite the reported utility of immunohistochemical staining and ancillary testing in the diagnosis of PT, FA, and SC, histology is still the primary diagnostic tool due to the overlapping immunophenotypic features. However, our clinical experience reiterates that the histologic distinction between tumor types on biopsy may be difficult. We searched our pathology archives for cases of confirmed PT, FA, and SC with available core needle biopsy slides for comparison. We found that a pre-operative core biopsy diagnosis of “malignant spindle cell neoplasm” separates MP and SC from BLP, BP, and FA. However, we also found that MP and SC have overlapping features on core biopsy, and MP are rarely diagnosed outright as MP on core biopsy. In our experience, a core biopsy diagnosis of “PT” or “fibroepithelial neoplasm” is less likely to be malignant.

Like previous studies [11, 13, 17, 37], we found that patients with MP are on average older than those with FA and younger than those with SC. Patients with MP and SC often received more extensive surgical procedures, and a majority of patients with SC underwent sentinel lymph node sampling. Patients with MP typically do not undergo sentinel lymph node sampling [1, 8, 16, 37], however, two of six patients did in this study. The patients in this cohort with MP who underwent lymph node sampling both had a diagnosis of “malignant spindle cell neoplasm/tumor” on core biopsy;

one patient underwent a modified radical mastectomy, while the other underwent a lumpectomy. In our cohort, MP were larger than other tumor types. 38% of SC had concurrent conventional invasive ductal carcinoma, which was not found in any other tumor type. We also found that death due to disease was more likely in MP than in SC, and did not occur in BLP, BP, or FA.

The distinction between tumor types may become increasingly important in the future. Presently, the typical treatment for PT is complete local excision, with many institutions recommending a 1-cm margin clearance for MP [8]. Adequate tumor sampling is essential for an accurate diagnosis. BP rarely if ever metastasize and have low recurrence rates, typically related to positive surgical excision margins. In such cases, watchful waiting may be employed in lieu of surgical re-excision [37–39]. Metastases and death due to PTs are typically caused by MP, and negative surgical margins should be achieved in these cases [1, 8]. In addition to wide local excision, SCs may be treated with sentinel lymph node sampling and pre-surgical neoadjuvant chemotherapy [10, 12]. To avoid unnecessary or inadequate treatment, it is vital that MP are differentiated from SC on core biopsy.

In summary, accurate identification and classification of breast PT on core needle biopsy can be challenging. MP and SC have overlapping features on biopsy, but are more easily differentiated from BP, BLP, and FA. The distinction between MP and SC is vital and will guide treatment management. The distinction between BP and FA in difficult cases may not be as vital, and a core biopsy diagnosis of “fibroepithelial lesion” may be sufficient in such cases, with a note suggesting complete surgical excision. Our findings suggest differing biopsy and patient characteristics in PTs that can guide treatment planning.

## Compliance with ethical standards

**Conflict of interest** Dr. Cimino-Mathews receives research grants from Bristol-Myers Squibb and the HeritX foundation, unrelated to the work presented in this current study. Drs. Ware and Argani declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors. The study is approved by the Johns Hopkins Institutional Review Board to utilize de-identified, archival pathology specimens.

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