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A Survey of Recurrent Diagnostic Challenges in Breast Phyllodes Tumours

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Abstract

Background: Breast phyllodes tumours (PTs) are graded as benign, borderline, or malignant by analysis of multiple histological features. PT grading is often inconsistent, likely due to variation in weighting of grading criteria by pathologists.

Design: The hierarchy of use of diagnostic criteria was identified using a 20-question survey.

Results: 213 pathologists from 29 countries responded. 54% reported 10-50 PT cases per year. Criteria considered key to PT diagnosis were: increased stromal cellularity (84.3%), stromal overgrowth (76.6%), increased stromal mitoses (67.8%), stromal atypia (61.5%), stromal fronding (59.0%), periductal stromal condensation (58.0%), irregular tumour borders (46.3%), lesional heterogeneity (33.7%). Importance of grading parameters were: mitotic activity (55.5%), stromal overgrowth (54.0%), stromal atypia (51.9%), increased stromal cellularity (41.7%), nature of the tumour border (38.9%). 49% would diagnose malignant PT without a full array of adverse features. 89% used the term "cellular fibroepithelial lesion (FEL)" for difficult cases. 45% would diagnose a FEL with stromal fronding (but lacking other PT features) as FA, 35% FEL, and 17% PT. 59% deemed clinic-radiological findings diagnostically significant. 68% considered age (⩾40 years) important in determining if a FEL was a FA or PT. In juvenile FELs, increased stromal cellularity (83%), fronding (52%), and mitoses (41%) were more common. 34% regarded differentiating cellular FA from PT as a specific challenge. 54% had issues assigning a borderline PT grade.

Conclusion: Criteria for grading PT lie on a spectrum, leading to interpretive variability. The survey highlights the criteria most used by pathologists, which do not completely align with WHO recommendations.

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Background

Breast phyllodes tumours (PTs) are graded as benign, borderline, or malignant by an integrative evaluation of multiple histological parameters[1]. Despite the wide availability of published guidelines, practical difficulties are often encountered in PT diagnosis and grade assignment, on core biopsy as well as excisional material. There is a pressing need to identify recurrent diagnostic challenges to guide future work in classification.

Design

In order to identify areas of diagnostic difficulty and the hierarchy of use of diagnostic criteria, a survey in English, containing 20 open- and closed-ended questions, was disseminated via email to practicing pathologists. Some questions allowed more than one response. Respondents were free to answer as many questions as they wished, and additional comments permitted. Answers were entered on an online form. The survey was open for a month from June to July 2021.

Results

Demographics

213 pathologists from 29 countries participated in the survey. Approximately half (53%) of respondents were in their first 10 years of post-graduate practice. 197 (93%) practiced in hospital or academic settings. 35 (16%) reported breast specimens exclusively in their practice, while another 35 (16%) subspecialized in breast pathology in addition to other organ system(s); the majority (67%) of respondents were not subspecialized breast pathologists.

45% of respondents handled ≤100 cases of breast core biopsies in their practice per year, while 55% reported more than 100 cases. 43% reported ≤100 breast excisional cases annually, while 57% reported more than 100 breast excisions.

Frequency of PT Diagnosis

Most institutions (54%) encountered 10 to 50 cases of PT per year (inclusive of in-house and referral cases), while 35% reported fewer than 10 cases each year. Individually, the vast majority (73%) of respondents reported ≤10 cases of PT annually.

Diagnosis and Grading

Ranked by respondents in order of diagnostic importance, the histologic features considered key to the diagnosis of PT were: increased stromal cellularity (84.4%), stromal overgrowth (76.6%), increased stromal mitoses (67.8%), stromal atypia (61.5%), stromal fronding (59.0%), periductal stromal condensation (58.0%), irregular tumour borders (46.3%) and lesional heterogeneity (33.7%) [Table 1].

Most (67%) respondents did not consider tumour size to be an important criterion in PT diagnosis. Of the 33% who were influenced by size, 22% used 1cm to <5cm, 39% used 5cm to <10cm, and 39% used 10cm or more as the significant cut-off dimension.

Of conventionally assessed parameters, the following were ranked by respondents in order of importance in formulating a PT grade: mitotic activity (55.5%), stromal overgrowth (54.0%), stromal atypia (51.9%), increased stromal cellularity (41.7%), and nature of tumour border (circumscribed vs. permeative) (38.9%) [Table 2].

Notably, among the three established grades of PT, most (54%) considered the borderline grade to be the most challenging to diagnose, while 41% indicated that a benign PT posed the most difficulty. Only 5% encountered issues in diagnosing malignant PTs.

43% had experience of diagnosing epithelial malignancies (in-situ and invasive carcinomas) within PT [Table 3], although this was an uncommon occurrence, with most (70%) respondents stating that these lesions comprised at most 5% of all PTs they had reported.

Malignant PT

Nearly half (49%) of respondents did not require all the histological parameters for PT grading to be on the malignant end of the spectrum (as recommended by the WHO[1]) before diagnosing malignant PT. Of these respondents, stromal overgrowth, atypia, and increased mitoses were the three most cited histologic features considered crucial to formulating a malignant diagnosis.

Within malignant PTs, the most frequently encountered heterologous elements were: liposarcoma (31.2%), chondrosarcoma (28.8%), osteosarcoma (18.2%) and rhabdomyosarcoma (10.0%) [Table 4]. A third of respondents (31%) were not aware that the presence of liposarcoma within a PT, in the absence of other adverse features, was not diagnostic of a malignant grade according to current guidelines. Interestingly, half (50%) of respondents had observed benign adipose tissue within all grades of PT, albeit infrequently (up to 30% of cases; 71%).

Over a third (35%) had encountered metastatic PT in their practice, with the majority (80%) of metastases in the form of spindle cell sarcoma. 15% of metastatic PT comprised mixed epithelial-stromal elements, while the remaining were composed solely of malignant heterologous elements (e.g., rhabdomyosarcoma).

Ancillary Tests

Most respondents (52%) did not routinely utilize immunohistochemistry in the diagnosis of PT. The most used immunohistochemical markers were: CD34 (22.4%), Ki67 (22%), p63 (20.1%), and other epithelial markers (16.2%). Respondents were ambivalent on the role of molecular tools in diagnosis, with 55% considering them unhelpful - lesional heterogeneity, inexperience in interpreting such tests, and cost were commonly cited concerns.

Equivocal Lesions

The vast majority (89%) employed a term such as "cellular fibroepithelial lesion (FEL)" or "fibroepithelial neoplasm" for cases that were difficult to classify, with most (73%) restricting

the use of these terms to core biopsy specimens. 68% of respondents considered older age (more than 40 years) an important factor in determining if a FEL was a fibroadenoma (FA) or PT.

In FELs from young patients, the following features were encountered more frequently: increased stromal cellularity (83%), increased stromal fronding (52%), and increased stromal mitoses (41%). In these lesions, the degree of increased stromal cellularity observed was most frequently moderate (52%), followed by mild (44%) and marked (4%). Most FELs in young patients demonstrated ≤5 mitoses/10hpf (74%), with 22% showing 6-10 mitoses/10hpf, and only 4% disclosing more than 10 mitoses/10hpf. One respondent commented that in the absence of other features suggestive of PT, mitotic activity in a juvenile FEL was "ignored" by the pathologists at that institution.

In a hypothetical scenario of an FEL with increased stromal fronding, but lacking other features of PT, 45% of respondents would diagnose the lesion as FA, 35% as FEL, and 17% as benign PT. In free text responses, some elaborated that the extent of fronding was an important factor – architectural fronding in excess of a third of the tissue would lead them to categorize the lesion as a benign PT, while lesser degrees of fronding were compatible with an FA diagnosis.

Many (34%) called attention to the distinction of cellular FA from benign PT to be a specific area of difficulty. 59% considered clinical and radiological findings to be important contributing factors to diagnostic categorization, while 35% would be influenced in their diagnosis by a prior history of PT. Only 3% considered ethnicity significant.

54% of respondents encountered issues in assigning a borderline grade to PT; concerns included the seemingly subjective and imperfectly reproducible criteria, apart from mitotic count, that separate benign from borderline PT.

Discussion

Breast FELs, which comprise FAs and PTs, are biphasic breast neoplasms characterized by proliferation of both epithelial and stromal elements. FAs are common benign lesions. PTs, which are graded as benign, borderline or malignant, are rare, comprising 0.3%-1% of primary breast tumours and 2.5% of all FELs[1]. PTs appear to be more frequent in Asian populations, with reported incidences of up to 6.9%[2,3]. Malignant PTs have been more frequently reported in Hispanic populations in central and South America[3,4].

In distinction to an FA, which shows a "balanced" growth of epithelium and stroma with intermingled pericanalicular and intracanalicular patterns, a fibroepithelial lesion is diagnosed as a PT when it possesses an exaggerated intracanalicular pattern of stromal growth, which usually imparts a characteristic "frond-like" architecture. The stroma of PT is usually more cellular than that of FA, with accentuation in the immediate peri- or subepithelial region. Intralesional heterogeneity is typical of PTs[5]; the characteristic growth pattern, therefore, may be present only focally within some tumours, necessitating adequate sampling.

PT grading, as recommended by the WHO[1], is performed by a histological evaluation of multiple microscopic parameters in a semi-quantitative manner, namely, an assessment of the degree of stromal cellularity, stromal mitotic activity, stromal atypia, presence or absence of stromal

overgrowth, nature of lesional borders, and the presence or absence of malignant heterologous stromal elements. PT grade correlates with outcome[6]; reported rates of local recurrence are 10-17%, 14-25%, and 23-30% respectively for benign, borderline and malignant PTs[1]. Recurrences may be of a higher grade than the original tumour in up to 31.5% of cases[7]. Metastases are seen almost exclusively in malignant PTs, with the pulmonary and skeletal systems being especially common metastatic sites[8].

A benign PT is well-circumscribed, shows variable, usually mildly increased stromal cellularity, and displays at most mild stromal atypia. Stromal mitotic counts number fewer than 5/10 high power field (hpfs). No stromal overgrowth or malignant heterologous stromal element should be present. Focal bizarre multinucleated giant cells are compatible with a benign PT diagnosis[9,10].

Malignant PTs show infiltrative tumour borders, with marked stromal hypercellularity and pronounced stromal atypia. Stromal overgrowth is present, as well as brisk stromal mitotic activity (≥10/10hpf). The presence of any malignant heterologous stromal element, even in the absence of other adverse histological features, classifies a tumour as a malignant PT [Figure 1]. The exception to the rule is well-differentiated liposarcoma [Figure 2]; such elements pose a low metastatic risk and lack the characteristic *MDM2/CDK4* amplification present in extra-mammary tumours[11–13]. Rare pleomorphic liposarcomas within PT may have more adverse outcomes[11,14]. Intra-lesional benign adipocytic elements do not affect grading[15,16].

A borderline PT [Figures 3 and 4] displays some, but not all, of the adverse histologic features that may be seen in malignant PT, with the caveat of malignant heterologous stromal elements as detailed above.

Despite guidelines, significant interobserver variability exists in the interpretation and application of the criteria, even among experienced pathologists[17,18]. In addition, differentiation from other entities occasionally pose diagnostic issues.

At the benign end of the spectrum, distinction of cellular FA from a benign PT can be challenging, even on an excisional specimen [Figure 5]. Both lesions may display mitotic activity and variably prominent areas of stromal cellularity. Useful features in the diagnosis of a benign PT are the presence of stromal fronds, a higher degree of stromal cellularity, which usually exceeds that seen in FA, and periductal stromal accentuation. Lerwill et al enumerated the features that are helpful in distinguishing a fibroadenoma from a benign phyllodes tumour[19]. In a truly equivocal case, a term such as "benign fibroepithelial neoplasm" may be used to convey the diagnostic difficulty as well as benign nature of the lesion, so that overtreatment can be avoided.

A breast lesion consisting of high-grade malignant spindle cells may represent a metaplastic spindle cell carcinoma, a malignant PT, or (rarely) a primary breast sarcoma. A broad panel of appropriate immunohistochemical stains (including broad-spectrum cytokeratins, high molecular weight cytokeratins, p63 and p40) may be used to differentiate the former two entities; however, patchy cytokeratin, p63 and p40 expression has been reported in malignant PTs[20,21], necessitating caution in interpretation, especially on a limited biopsy specimen. In such cases, diagnosis may be best deferred to adequate examination of an excisional specimen, with sampling of (at least)

one block per centimetre of maximum tumour dimension, including grossly heterogeneous foci [Figure 6]. On the other hand, distinction of a primary breast sarcoma from a malignant PT may not be as crucial, given overlapping biologic and genomic features[22,23]. Diagnosis of a morphologically typical PT does not usually call for the use of immunohistochemical stains.

PTs are treated by surgical excision in the first instance, although opinions differ on what constitutes an adequate margin[24]. Evidence suggests that benign PTs may not require "clear" margins, with low recurrence rates following enucleation[25–30]. On the other hand, malignant and recurrent PTs should be completely excised. A systematic review found a relationship between the width of surgical margins and local recurrence as well as distant metastatic rates[31]. Using a threshold of 10mm (margins <10mm and ≥10mm), the 5-year incidence rates per 100 person-years of local recurrence were 5.22 vs. 3.63 for benign PT, 9.60 vs. 7.33 for borderline PT, and 28.58 vs. 21.84 for malignant PT respectively; distant metastatic rates were 0.88 vs. 0.86 for benign PT, 1.61 vs. 1.74 for borderline PT, and 4.80 vs 5.18 for malignant PT. The rare case reports that described metastatic benign PT require cautious evaluation, with regard to the accuracy of initial diagnosis and adequacy of tumour sampling[24]. National Comprehensive Cancer Network (NCCN) guidelines[32] (version 2.2022) advocate consideration of post-operative radiotherapy for recurrent tumours without distant metastases in settings where additional recurrence would cause significant morbidity. There is currently no role for routine chemotherapy in PT management[33]; however, for recurrent tumours with metastatic disease, the patient is usually managed following therapeutic principles for soft tissue sarcoma[34]. NCCN guidelines also recommend wide excision (with a margin of ≥10mm) for borderline PTs.

MED12 (MEDiator complex subunit 12) mutations, first described in uterine leiomyomas[35], were discovered in FAs and subsequently reported in PTs[36–41]. *MED12*-dependent and *MED12* wild-type progression pathways have been postulated for PTs[42]. *MED12* mutation has been reported to be associated with longer disease-free survival in PT[43]. In distinction to FAs, PTs more frequently harbour *TERT* promoter mutations[44,45].

Recurrent Challenges

Current WHO recommendations assign equal weight to each of the listed histologic criteria used in PT grading[1]. However, as reflected in this survey, many pathologists may differentially weigh criteria when assigning a PT grade, disregard certain parameters, and/ or include others in their personal diagnostic algorithms. A retrospective single-institution study of 213 FELs in 178 patients, which included 133 PTs (63 benign, 42 borderline, and 29 malignant), found age > 50, stromal overgrowth, diffuse marked atypia, necrosis, and mitoses ≥10 per 10hpf to be predictive of distant metastases[46]. An infiltrative border was observed in all grades of FELs (including some FAs), although widely infiltrative borders (>2 foci of infiltration into adjacent breast stroma) were more frequent in borderline PT (17%) and malignant PT (35%). Interestingly, the authors stated that infiltrative borders were not observed in about 40% of tumours diagnosed as malignant PT at that institution, and that when present such infiltration was often only focal (1-2 foci of infiltration). The same authors proposed including necrosis as an additional criterion to diagnose malignant PT. A meta-analysis of 9234 PT cases[47] found tumour necrosis, mitoses (≥10/10hpf), an infiltrative tumour border, moderate/ severe stromal cellularity, severe stromal

atypia, stromal overgrowth, type of surgery (breast conservation surgery for malignant PTs), and positive surgical margin status to be predictors of local recurrence. Tumour size (≤5 and >5cm) and age (<40 and ≥40) were not significant factors. Another study of 241 PT cases found PT grade, increased mitoses, necrosis, infiltrative margins, stromal atypia, and heterologous components to be correlated with adverse outcomes[48]. A single-institution study of 605 PTs found stromal atypia, mitotic activity, stromal overgrowth and surgical margins ("AMOS" criteria) to be predictive of PT recurrence[7]; based on the data, a validated nomogram[49–52] (accessible online at: https://mobile.sgh.com.sg/ptrra/) was formulated to predict the risk of recurrence post-excision.

A borderline PT should, according to guidelines, be diagnosed when a lesion falls short of a definitive benign or malignant diagnosis; however, this grade category appears to pose a challenge to many pathologists. While this may be partly attributed to lack of familiarity in dealing with a relatively rare entity, it could be difficult, even for an experienced pathologist, to refrain from labelling a large, infiltrative, mitotically active tumour with necrosis as anything but malignant, despite it lacking stromal overgrowth. Conversely, a mildly cellular PT that has well-circumscribed margins, few mitoses, barely discernible atypia, and no stromal overgrowth, but a very focally infiltrative border, may on occasion render a degree of diagnostic hesitation. A recent study on methylation and copy number analysis of FELs found that the methylation profiles of PT and FA converge in a distinct cluster, while the copy number profiles of these FELs suggest that they may be separated into benign (flat copy number profiles/ few copy number variants (CNVs)) and malignant (high CNVs) categories, the implication being that borderline PTs may separate into benign and malignant forms based on such analysis, thus potentially obviating the need for a discrete "borderline" grade[53].

Johannes Müller, in 1838, conferred the appellation "cystosarcoma phyllodes"[54] (from the Greek: *kystis* [pouch, bladder], *sarkoma* [fleshy tumour] and *phyllon* [leaf]), accompanied by a "complete and comprehensive" description[55]. The term that now stands, "phyllodes tumour (*Tumore Filloide*)", was devised by Lomonaco in 1960[56]. Despite the emphasis on leaf-like fronds, their presence alone is neither pathognomonic nor sufficient for a PT diagnosis. A cellular FEL that lacks fronds but exhibits other features of PT should be diagnosed as such, while an otherwise typical FA should not be labelled a PT despite focal frond-like architecture.

The distinction of cellular FA from a benign PT can be challenging. Even with exhaustive sampling, a FEL may show overlapping features. Fronds, when observed in FA, tend to be less cellular than those of a PT, usually lack periductal stromal condensation, and often fit together like a "jigsaw" as opposed to the bulbous projections into irregularly dilated epithelial spaces of a PT[57]. In a well-resourced academic setting, molecular analysis may be helpful in elucidating reported alterations of PT such as *TERT* promoter mutation. Practically, when faced with an equivocal case, a useful descriptive diagnosis (such as "benign fibroepithelial neoplasm") could be made, in conjunction with close communication with the managing clinician, the key being to avoid overtreatment while maintaining appropriate follow-up for the patient.

The periductal stromal tumour (PST) which features cellular and variably atypical stroma hugging ducts and lobules, without circumscription or stromal fronds, is now regarded as a subtype of PT[1,58–60].

Diagnostic issues in core biopsies may arise when a PT with morphologically heterogeneous areas (including FA-like foci) is sampled. Mitotic activity (≥2/10hpf), marked stromal hypercellularity, stromal overgrowth, adipose tissue infiltration, ill-defined lesional borders, lesional heterogeneity, subepithelial condensation, stromal nuclear atypia, tissue (core) fragmentation, large lesion size, and older age group, are features reported to be predictive of a PT (as opposed to FA) diagnosis[61–67]. In one multi-centre study[68], digital point counting of stromal cellularity and expansion did not aid in classification of equivocal FELs on core biopsies. A recent study using artificial intelligence modelling on core biopsy images of FELs attained an overall diagnostic accuracy of 87.5%, with 80% and 95% accuracy rates for FAs and PTs respectively[69], pointing to a potential future role of computer-aided diagnosis in challenging cases. To distinguish PT from FA on core biopsies, a 16-gene panel target sequencing study[70] was tested on an international cohort of 303 (38%) FAs and 493 (62%) PTs contributed by the International Fibroepithelial Consortium[71]. Molecular alterations in *MED12*, *TERT* promoter, *RARA*, *FLNA*, *SETD2*, *TP53*, *RB1*, *EGFR*, and *IGF1R* were more frequently detected in PTs compared to FAs. In particular, *TERT* promoter mutations were far more frequently observed in PT (32%, 61%, and 46% of benign, borderline, and malignant PTs, respectively) in comparison to FAs (6%). Practically, reliable distinction between FA and PT may not be achieved on a limited core biopsy specimen that lacks higher-grade PT features, and a recommendation for excision for definitive categorization could be offered. In addition, worrisome clinical or radiological features, such as rapid lesional growth, large tumour size, or suspicious imaging features, should also prompt consideration of lesional excision[72].

In paediatric patients, FAs may demonstrate increased stromal cellularity, frequent mitoses (up to 7 mitoses/10hpf), and focal, small stromal fronds[73–75]. Up to moderate stromal atypia was found in a study of 68 fibroepithelial lesions from a paediatric cohort; no stromal overgrowth was identified in any of these lesions[73]. In a study including 23 juvenile FAs, none demonstrated stromal overgrowth or significant stromal atypia[76]. While recurrent *MED12* mutations were elucidated in FAs and benign PTs in adolescents and young adults, no *TERT* promoter mutations were found[77]. A judicious approach to diagnosis should be taken in the young, with a firm diagnosis of PT made only in the presence of unequivocal histologic findings.

Many survey respondents appear to deviate from standard recommendations for PT grading – possible reasons include unfamiliarity (including access issues due to resource limitation), institutional practice, personal diagnostic preferences informed by prior experience, or a recognition of currently contentious aspects of grading.

Despite the correlation of PT grade with outcomes, the relative importance of each histologic parameter may merit further clarification. The relevance of prospective histologic grading criteria, for instance the presence of tumour necrosis[47,48,78], can be addressed in further studies. The borderline PT grade appears to pose a diagnostic challenge, particularly at the benign and malignant ends of the spectrum. Although a quasi-quantitative approach towards grading, such as

assigning a numerical value to each category of a histologic criterion, with an overall summative value conveying the adverse biologic potential of a tumour, may appear to represent a low-cost, systematic way of risk stratification, such a "total histological score" had been shown to be inferior to the nomogram in conveying recurrence risk[7], suggesting that the biologic impact of each criterion is more complex than may be communicated by a simple additive linear scale.

Conclusion

Established criteria for PT grading lie on a histologic spectrum, leading to interobserver variability in their interpretation and application. PTs often exhibit intralesional morphologic heterogeneity, contributing to challenges in classification. Cellular FELs and FELs in young patients commonly contain features that place them in diagnostic "grey zones". Core biopsies represent an additional area of diagnostic difficulty. The precise clinico-biologic importance of each histological criterion in diagnosis and grading warrants further study. These recurrent challenges, underscored by this cross-sectional survey, can serve as a framework for future work on classification. Published guidelines may benefit from outreach efforts for timely and equitable access by pathologists in wide-ranging geographical and socioeconomic settings.

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References

1. *WHO Classification of Tumours Editorial Board. Breast Tumours.* 5th ed. International Agency for Research on Cancer; 2019; 2019. https://publications.iarc.fr/581
2. Chua CL, Thomas A, Ng BK. Cystosarcoma phyllodes--Asian variations. *Aust N Z J Surg*. 1988;58(4):301-305. Accessed August 24, 2015. http://www.ncbi.nlm.nih.gov/pubmed/2855393
3. Bernstein L, Deapen D, Ross RK. The descriptive epidemiology of malignant cystosarcoma phyllodes tumors of the breast. *Cancer*. 1993;71(10):3020-3024. Accessed April 12, 2017. http://www.ncbi.nlm.nih.gov/pubmed/8387873
4. Pimiento JM, Gadgil P v., Santillan AA, et al. Phyllodes Tumors: Race-Related Differences. *J Am Coll Surg*. 2011;213(4):537-542. doi:10.1016/j.jamcollsurg.2011.07.012
5. Tan BY, Md Nasir ND, Chang HY, et al. Morphologic and genetic heterogeneity in breast fibroepithelial lesions-a comprehensive mapping study. *Mod Pathol*. 2020;33(9):1732-1745. doi:10.1038/S41379-020-0533-0
6. Cheo FF, Tan YB, Tan PH. An update on the classification of phyllodes tumours of the breast. *Diagnostic Histopathology*. 2022;28(3):119-125. doi:10.1016/J.MPDHP.2021.12.001
7. Tan PH, Thike AA, Tan WJ, et al. Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. *J Clin Pathol*. 2012;65(1):69-76. doi:10.1136/jclinpath-2011-200368
8. Schwentner L, Kurzeder C, Kreienberg R, Wöckel A. Focus on haematogenous dissemination of the malignant cystosarcoma phylloides: institutional experience. *Arch Gynecol Obstet*. 2011;283(3):591-596. doi:10.1007/S00404-010-1746-0
9. Powell CM, Cranor ML, Rosen PP. Multinucleated stromal giant cells in mammary fibroepithelial neoplasms. A study of 11 patients. *Arch Pathol Lab Med*. 1994;118(9):912-916. Accessed April 1, 2017. http://www.ncbi.nlm.nih.gov/pubmed/8080361
10. Tse GMK, Law BKB, Chan KF, Ma TKF. Multinucleated stromal giant cells in mammary phyllodes tumours. *Pathology*. 2001;33(2):153-156. doi:10.1080/00313020123549
11. Bacchi CE, Wludarski SC, Lamovec J, et al. Lipophyllodes of the breast. A reappraisal of fat-rich tumors of the breast based on 22 cases integrated by immunohistochemical study, molecular pathology insights, and clinical follow-up. *Ann Diagn Pathol*. 2016;21:1-6. doi:10.1016/J.ANNDIAGPATH.2015.12.001
12. Inyang A, Thomas DG, Jorns J. Heterologous Liposarcomatous Differentiation in Malignant Phyllodes Tumor is Histologically Similar but Immunohistochemically and Molecularly Distinct from Well-differentiated Liposarcoma of Soft Tissue. *Breast J*. 2016;22(3):282-286. doi:10.1111/TBJ.12567

13. Lyle PL, Bridge JA, Simpson JF, Cates JM, Sanders ME. Liposarcomatous differentiation in malignant phyllodes tumours is unassociated with MDM2 or CDK4 amplification. *Histopathology*. 2016;68(7):1040-1045. doi:10.1111/HIS.12898

14. Sancheti SM, Sawaimoon SK, Ahmed R. Pleomorphic liposarcoma arising in a malignant phyllodes tumor of breast: A rare occurrence. *Journal of Cancer Research and Therapeutics*. 2015;11(4):1032. doi:10.4103/0973-1482.154013

15. Rowe JJ, Cheah AL, Calhoun BC. Lipomatous tumors of the breast: A contemporary review. *Semin Diagn Pathol*. 2017;34(5):453-461. doi:10.1053/J.SEMDP.2017.05.008

16. Powell CM, Rosen PP. Adipose differentiation in cystosarcoma phyllodes. A study of 14 cases. *Am J Surg Pathol*. 1994;18(7):720-727. doi:10.1097/00000478-199407000-00008

17. Tan PH. Fibroepithelial lesions revisited: implications for diagnosis and management. *Modern Pathology*. 2021;34:15-37. doi:10.1038/s41379-020-0583-3

18. Tan BY, Tan PH. A Diagnostic Approach to Fibroepithelial Breast Lesions. *Surgical Pathology Clinics*. 2018;11(1):17-42. doi:10.1016/J.PATH.2017.09.003

19. Lerwill MF, Lee AHS, Tan PH. Fibroepithelial tumours of the breast-a review. *Virchows Arch*. 2022;480(1). doi:10.1007/S00428-021-03175-6

20. Chia Y, Thike AA, Cheok PY, Yong-Zheng Chong L, Man-Kit Tse G, Tan PH. Stromal keratin expression in phyllodes tumours of the breast: a comparison with other spindle cell breast lesions. *J Clin Pathol*. 2012;65(4):339-347. doi:10.1136/jclinpath-2011-200377

21. 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(12):1689-1696. doi:10.1097/PAS.0000000000000301

22. Lim SZ, Selvarajan S, Thike AA, et al. Breast sarcomas and malignant phyllodes tumours: comparison of clinicopathological features, treatment strategies, prognostic factors and outcomes. *Breast Cancer Res Treat*. 2016;159(2):229-244. doi:10.1007/S10549-016-3946-1

23. Lim SZ, Ng CCY, Rajasegaran V, et al. Genomic profile of breast sarcomas: a comparison with malignant phyllodes tumours. *Breast Cancer Res Treat*. 2019;174(2):365-373. doi:10.1007/S10549-018-5067-5

24. Tan BY, Acs G, Apple SK, et al. Phyllodes tumours of the breast: a consensus review. *Histopathology*. 2016;68(1):5-21. doi:10.1111/his.12876

25. Genco IS, Purohit V, Hackman K, Ferreira L, Tugertimur B, Hajiyeva S. Benign and borderline phyllodes tumors of the breast: Clinicopathologic analysis of 205 cases with emphasis on the surgical margin status and local recurrence rate. *Ann Diagn Pathol*. 2021;51. doi:10.1016/J.ANNDIAGPATH.2021.151708

26. Sevinç Aİ, Aksoy SÖ, Güray Durak M, Balci P. Is the extent of surgical resection important in patient outcome in benign and borderline phyllodes tumors of the breast? *Turk J Med Sci*. 2018;48(1):28-33. doi:10.3906/SAG-1704-47

27. Moo TA, Alabdulkareem H, Tam A, et al. Association Between Recurrence and Re-Excision for Close and Positive Margins Versus Observation in Patients with Benign Phyllodes Tumors. *Ann Surg Oncol*. 2017;24(10):3088-3092. doi:10.1245/S10434-017-5955-7

28. Cowan ML, Argani P, Cimino-Mathews A. Benign and low-grade fibroepithelial neoplasms of the breast have low recurrence rate after positive surgical margins. *Mod Pathol*. 2016;29(3):259-265. doi:10.1038/MODPATHOL.2015.157

29. Borhani-Khomani K, Talman MLM, Kroman N, Tvedskov TF. Risk of Local Recurrence of Benign and Borderline Phyllodes Tumors: A Danish Population-Based Retrospective Study. *Ann Surg Oncol*. 2016;23(5):1543-1548. doi:10.1245/S10434-015-5041-Y

30. Wen B, Mousadoust D, Warburton R, et al. Phyllodes tumours of the breast: Outcomes and recurrence after excision. *Am J Surg*. 2020;219(5):790-794. doi:10.1016/J.AMJSURG.2020.02.048

31. Toussaint A, Piaget-Rossel R, Stormacq C, Mathevet P, Lepigeon K, Taffé P. Width of margins in phyllodes tumors of the breast: the controversy drags on?-a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2021;185(1):21-37. doi:10.1007/S10549-020-05924-8

32. Rashmi Kumar N, Burns J, Abraham J, et al. NCCN Guidelines Version 2.2022 Breast Cancer. Published online 2021. Accessed March 22, 2022. https://www.nccn.

33. Bogach J, Shakeel S, Wright FC, Hong NJL. Phyllodes Tumors: A Scoping Review of the Literature. *Ann Surg Oncol*. 2022;29(1):446-459. doi:10.1245/S10434-021-10468-2

34. Palassini E, Mir O, Grignani G, et al. Systemic treatment in advanced phyllodes tumor of the breast: a multi-institutional European retrospective case-series analyses. *Breast Cancer Res Treat*. Published online 2022. doi:10.1007/S10549-022-06524-4

35. Turunen M, Spaeth JM, Keskitalo S, et al. Uterine leiomyoma-linked MED12 mutations disrupt mediator-associated CDK activity. *Cell Rep*. 2014;7(3):654-660. doi:10.1016/J.CELREP.2014.03.047

36. Lim WK, Ong CK, Tan J, et al. Exome sequencing identifies highly recurrent MED12 somatic mutations in breast fibroadenoma. *Nat Genet*. 2014;46(8):877-880. doi:10.1038/ng.3037

37. Loke BN, Md Nasir ND, Thike AA, et al. Genetics and genomics of breast fibroadenomas. *J Clin Pathol*. 2018;71(5):381-387. doi:10.1136/JCLINPATH-2017-204838

38. Tan J, Ong CK, Lim WK, et al. Genomic landscapes of breast fibroepithelial tumors. *Nature Genetics*. 2015;47(11):1341-1345. doi:10.1038/ng.3409

39. Cani AK, Hovelson DH, McDaniel AS, et al. Next-Gen Sequencing Exposes Frequent MED12 Mutations and Actionable Therapeutic Targets in Phyllodes Tumors. *Mol Cancer Res*. 2015;13(4):613-619. doi:10.1158/1541-7786.MCR-14-0578

40. Yoshida M, Sekine S, Ogawa R, et al. Frequent MED12 mutations in phyllodes tumours of the breast. *Br J Cancer*. 2015;112(10):1703-1708. doi:10.1038/bjc.2015.116

41. Piscuoglio S, Murray M, Fusco N, et al. MED12 somatic mutations in fibroadenomas and phyllodes tumours of the breast. *Histopathology*. 2015;67(5):719-729. doi:10.1111/his.12712

42. Pareja F, Geyer FC, Kumar R, et al. Phyllodes tumors with and without fibroadenoma-like areas display distinct genomic features and may evolve through distinct pathways. *npj Breast Cancer*. 2017;3(1):40. doi:10.1038/s41523-017-0042-6

43. Ng CCY, Tan J, Ong CK, et al. MED12 is frequently mutated in breast phyllodes tumours: a study of 112 cases. *J Clin Pathol*. Published online May 27, 2015. doi:10.1136/jclinpath-2015-202896

44. Yoshida M, Ogawa R, Yoshida H, et al. TERT promoter mutations are frequent and show association with MED12 mutations in phyllodes tumors of the breast. *British Journal of Cancer*. 2015;113(8):1244-1248. doi:10.1038/bjc.2015.326

45. Piscuoglio S, Ng CKY, Murray M, 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):508-518. doi:10.1002/PATH.4672

46. Slodkowska E, Nofech-Mozes S, Xu B, et al. Fibroepithelial lesions of the breast: a comprehensive morphological and outcome analysis of a large series. *Mod Pathol*. 2018;31(7):1073-1084. doi:10.1038/S41379-018-0032-8

47. Lu Y, Chen Y, Zhu L, et al. Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. *Oncol*. 2019;26:1263-1275. doi:10.1245/s10434-018-07134-5

48. Mihai R, Callagy G, Qassid OL, et al. Correlations of morphological features and surgical management with clinical outcome in a multicentre study of 241 phyllodes tumours of the breast. *Histopathology*. 2021;78(6):871-881. doi:10.1111/HIS.14316

49. Chng TW, Lee JYH, Lee CS, Li H, Tan MH, Tan PH. Validation of the Singapore nomogram for outcome prediction in breast phyllodes tumours: an Australian cohort. *Journal of Clinical Pathology*. 2016;69(12):1124-1126. doi:10.1136/jclinpath-2016-203951

50. Chng TW, Gudi M, Li HL, Tan PH. Validation of the Singapore Nomogram for Outcome Prediction in Breast Phyllodes Tumors in a Large Patient Cohort. *Modern Pathol*. 2017;30(Suppl 2. Abstract: 106th Annual Meeting of the United States and Canadian Academy of Pathology (USCAP)):35A. doi:10.1038/modpathol.2016.241

51. Nishimura R, Tan PH, Thike AA, et al. Utility of the Singapore nomogram for predicting recurrence-free survival in Japanese women with breast phyllodes tumours. *J Clin Pathol*. 2014;67(8):748-750. doi:10.1136/jclinpath-2014-202215

52. Cristando C, Li HH, Almekinders M, Tan PH, Brogi E, Murray M . Validation of the Singapore Nomogram for Outcome Prediction in a US-Based Population of Women with Breast Phyllodes Tumors (PT). *Modern Pathology*. 2017;30(Suppl 2. Abstract: 106th Annual Meeting of the United States and Canadian Academy of Pathology (USCAP)):36A. doi:10.1038/modpathol.2016.241

53. Hench J, Vlajnic T, Soysal SD, Obermann EC, Frank S, Muenst S. An Integrated Epigenomic and Genomic View on Phyllodes and Phyllodes-like Breast Tumors. *Cancers (Basel)*. 2022;14(3). doi:10.3390/CANCERS14030667

54. Müller J. *Ueber Den Feinern Bau Und Die Formen Der Krankhaften Geschwülste*. G. Reimer; 1838.

55. Fiks A. Cystosarcoma phyllodes of the mammary gland--Müller's tumor. For the 180th birthday of Johannes Müller. *Virchows Arch A Pathol Anat Histol*. 1981;392(1):1-6. doi:10.1007/BF00430543

56. LOMONACO F. Phyllode tumors of the breast (cystosarcoma phyllodes of J. Muller). *Tumori*. 1960;46:156-184. doi:10.1177/030089166004600203

57. Krings G, Bean GR, Chen YY. Fibroepithelial lesions; The WHO spectrum. *Semin Diagn Pathol*. 2017;34(5):438-452. doi:10.1053/J.SEMDP.2017.05.006

58. Burga AM, Tavassoli FA. Periductal stromal tumor: a rare lesion with low-grade sarcomatous behavior. *Am J Surg Pathol*. 2003;27(3):343-348. Accessed April 6, 2017. http://www.ncbi.nlm.nih.gov/pubmed/12604890

59. Abbasi SL, Namara KM, Absar MS, Darlington A, Clucas F, Titi S. Periductal Stromal Tumor of Breast: A Case Report and A Review of Literature. *The Korean Journal of Pathology*. 2014;48(6):442-444. doi:10.4132/KoreanJPathol.2014.48.6.442

60. Zhao L, Komforti MK, Dawson A, Rowe JJ. Periductal Stromal Tumor of the Breast: One Institution's Review of 6 Tumors Over a 22 Year Period With Immunohistochemical Analysis. *Int J Surg Pathol*. Published online 2021. doi:10.1177/10668969211060482

61. Jacobs TW, Chen YY, Guinee, Jr DG, et al. Fibroepithelial lesions with cellular stroma on breast core needle biopsy: are there predictors of outcome on surgical excision? *Am J Clin Pathol*. 2005;124(3):342-354. doi:10.1309/5N2C-4N5X-CB8X-W8JL

62. 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(3):362-369. doi:10.1309/AJCPZUZ96RESGPUP

63. Resetkova E, Khazai L, Albarracin CT, Arribas E. Clinical and radiologic data and core needle biopsy findings should dictate management of cellular fibroepithelial tumors of the breast. *Breast J*. 2010;16(6):573-580. doi:10.1111/j.1524-4741.2010.01013.x

64. Lee AHS, Hodi Z, Ellis IO, Elston CW. Histological features useful in the distinction of phyllodes tumour and fibroadenoma on needle core biopsy of the breast. *Histopathology*. 2007;51(3):336-344. doi:10.1111/j.1365-2559.2007.02786.x

65. Jara-Lazaro AR, Akhilesh M, Thike AA, Lui PCW, Tse GMK, Tan PH. Predictors of phyllodes tumours on core biopsy specimens of fibroepithelial neoplasms. *Histopathology*. 2010;57(2):220-232. doi:10.1111/j.1365-2559.2010.03607.x

66. Jung J, Kang E, Chae SM, et al. Development of a Management Algorithm for the Diagnosis of Cellular Fibroepithelial Lesions From Core Needle Biopsies. *Int J Surg Pathol*. 2018;26(8):684-692. doi:10.1177/1066896918775525

67. Mohan SC, Tseng J, Marumoto A, et al. Upstaging of Fibroepithelial Lesions: A Single-Institution Experience. *Ann Surg Oncol*. 2022;29(4):2193-2199. doi:10.1245/S10434-021-10931-0

68. Dessauvagie BF, Lee AHS, Meehan K, et al. Interobserver variation in the diagnosis of fibroepithelial lesions of the breast: a multicentre audit by digital pathology. *J Clin Pathol*. 2018;71(8):672-679. doi:10.1136/JCLINPATH-2017-204977

69. Cheng CL, Md Nasir ND, Ng GJZ, et al. Artificial intelligence modelling in differentiating core biopsies of fibroadenoma from phyllodes tumor. *Laboratory Investigation 2021 102:3*. 2021;102(3):245-252. doi:10.1038/s41374-021-00689-0

70. Sim Y, Ng GXP, Ng CCY, et al. A novel genomic panel as an adjunctive diagnostic tool for the characterization and profiling of breast Fibroepithelial lesions. *BMC Medical Genomics*. 2019;12(1):1-14. doi:10.1186/S12920-019-0588-2/FIGURES/5

71. Md Nasir ND, Ng CCY, Rajasegaran V, et al. Genomic characterisation of breast fibroepithelial lesions in an international cohort. *J Pathol*. 2019;249(4):447-460. doi:10.1002/PATH.5333

72. Lee A, James J, Whisker L, Rakha EA, Ellis IO. Which lesions with a radiological or core biopsy diagnosis of fibroadenoma should be excised? *Ann R Coll Surg Engl*. Published online December 23, 2021. doi:10.1308/RCSANN.2021.0208

73. Tay TKY, Chang KTE, Thike AA, Tan PH. Paediatric fibroepithelial lesions revisited: pathological insights. *J Clin Pathol*. 2015;68(8):633-641. doi:10.1136/jclinpath-2015-202956

74. Amerson JR. Cystosarcoma phyllodes in adolescent females. A report of seven patients. *Annals of Surgery*. 1970;171(6):849. doi:10.1097/00000658-197006010-00005

75. Rajan PB, Cranor ML, Rosen PP. Cystosarcoma phyllodes in adolescent girls and young women: a study of 45 patients. *Am J Surg Pathol*. 1998;22(1):64-69. doi:10.1097/00000478-199801000-00008

76. Ross DS, Giri DD, Akram MM, Catalano J, van Zee KJ, Brogi E. Fibroepithelial lesions in the breast of adolescent females: A clinicopathological profile of 35 cases. *Modern Pathology*. 2012;25(Suppl.2).

77. Pareja F, da Cruz Paula A, Murray MP, et al. Recurrent MED12 exon 2 mutations in benign breast fibroepithelial lesions in adolescents and young adults. *J Clin Pathol*. 2019;72(3):258-262. doi:10.1136/JCLINPATH-2018-205570

78. Mohan SC, Tseng J, Angarita S, et al. Clinicopathologic Characteristics and Patient Outcomes of Phyllodes Tumors: A Single Institution Experience. *Am Surg*. 2021;87(10):1533-1538. doi:10.1177/00031348211051673

Tables

Table 1: Key histologic features diagnostic of PT in a fibroepithelial neoplasm (n = 205)

Histologic feature	Number of responses	Percentage
Increased stromal cellularity	173	84.4%
Stromal overgrowth	157	76.6%
Increased stromal mitoses	139	67.8%
Stromal atypia	126	61.5%
Stromal fronding	121	59.0%
Periductal stromal condensation	119	58.0%
Irregular tumour borders	95	46.3%
Lesional heterogeneity	69	33.7%

Table 2: Relative importance of histologic features in PT grading, ranked from most [5] to least important [1]*. A score of 0 indicates the factor is not considered by the respondent in PT grading.

Feature/ Rank	5	4	3	2	1	0
Mitotic activity	117 (55.5%)	40	25	22	6	1
Stromal overgrowth	114 (54.0%)	31	37	24	4	1
Stromal atypia	109 (51.9%)	33	44	17	5	2
Stromal cellularity	88 (41.7%)	36	43	25	18	1

Tumour border (circumscribed vs permeative)	82 (38.9%)	41	40	32	15	1

*Note: n = 211 for all Feature categories except "Stromal atypia" where n = 210.

Table 3: Epithelial malignancies encountered in PT (n = 99)

Epithelial malignancy	Number	Percentage
Ductal carcinoma in situ	42	42.4%
Invasive ductal carcinoma	24	24.2%
Lobular carcinoma in situ	21	21.2%
Invasive lobular carcinoma	10	10.1%
Others (not specified)	2	2.0%

Table 4: Most frequently encountered malignant heterologous element in PT (n = 170)

Heterologous element	Number	Percentage
Liposarcoma	53	31.2%
Chondrosarcoma	49	28.8%
Osteosarcoma	31	18.2%
Rhabdomyosarcoma	17	10.0%
Fibrosarcoma	2	1.2%
Sarcoma NOS	2	1.2%
Others (not specified)	16	9.4%

Figures

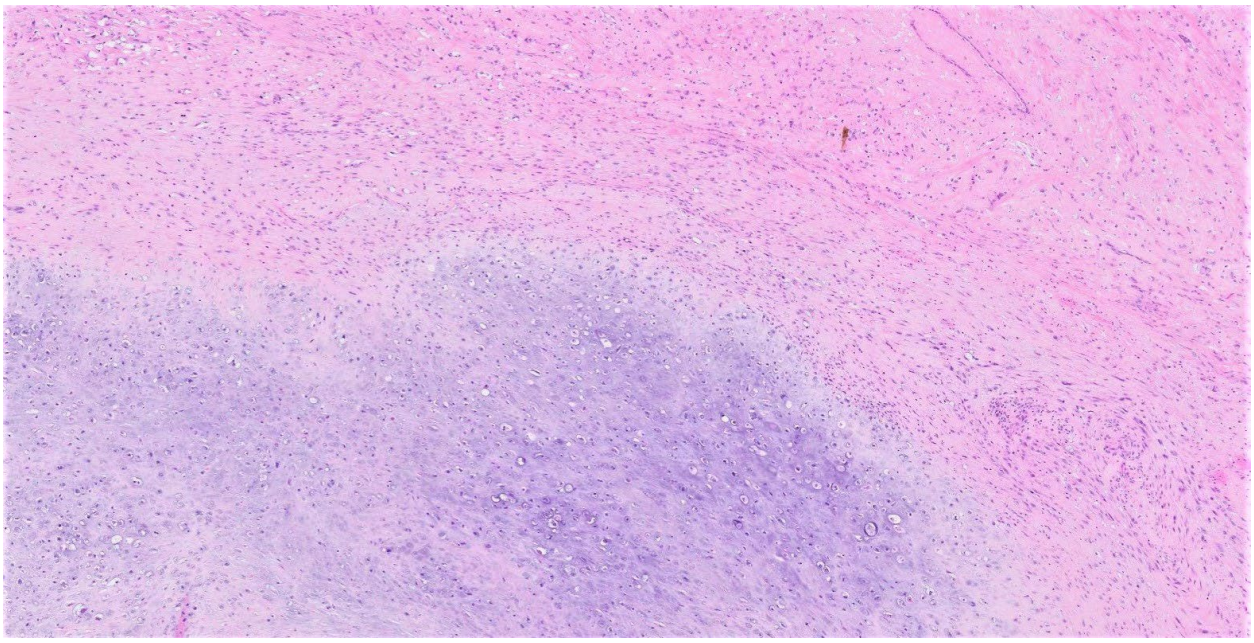

Figure 1. Chondrosarcomatous differentiation within a malignant PT.

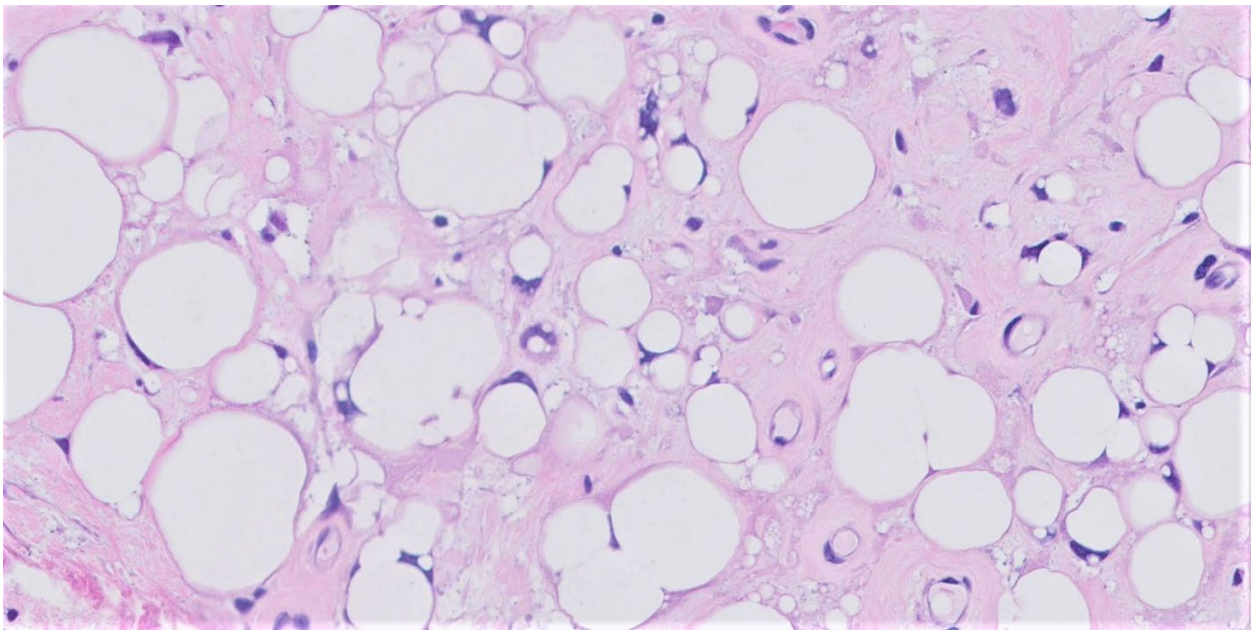

Figure 2. Well-differentiated liposarcoma in a PT; this finding, in the absence of other adverse histologic features, does not classify a PT as malignant, unlike the presence of other malignant heterologous elements.

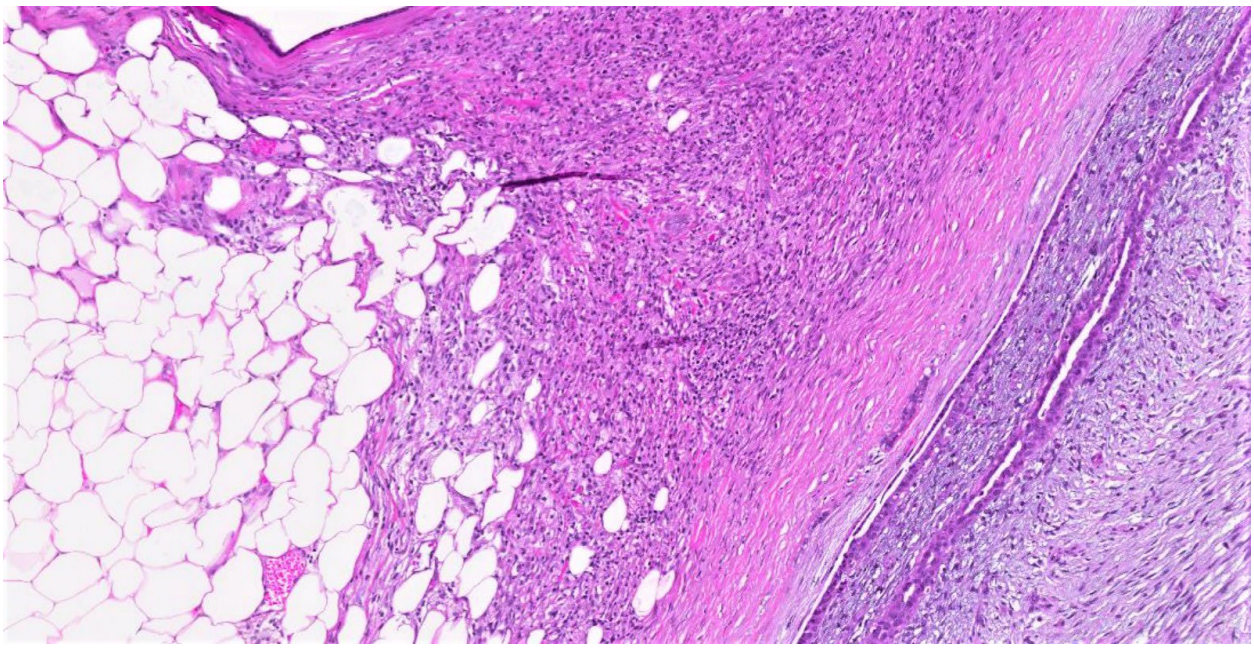

Figure 3. A PT of borderline grade, demonstrating irregular, permeative stromal infiltration into adjacent adipose tissue.

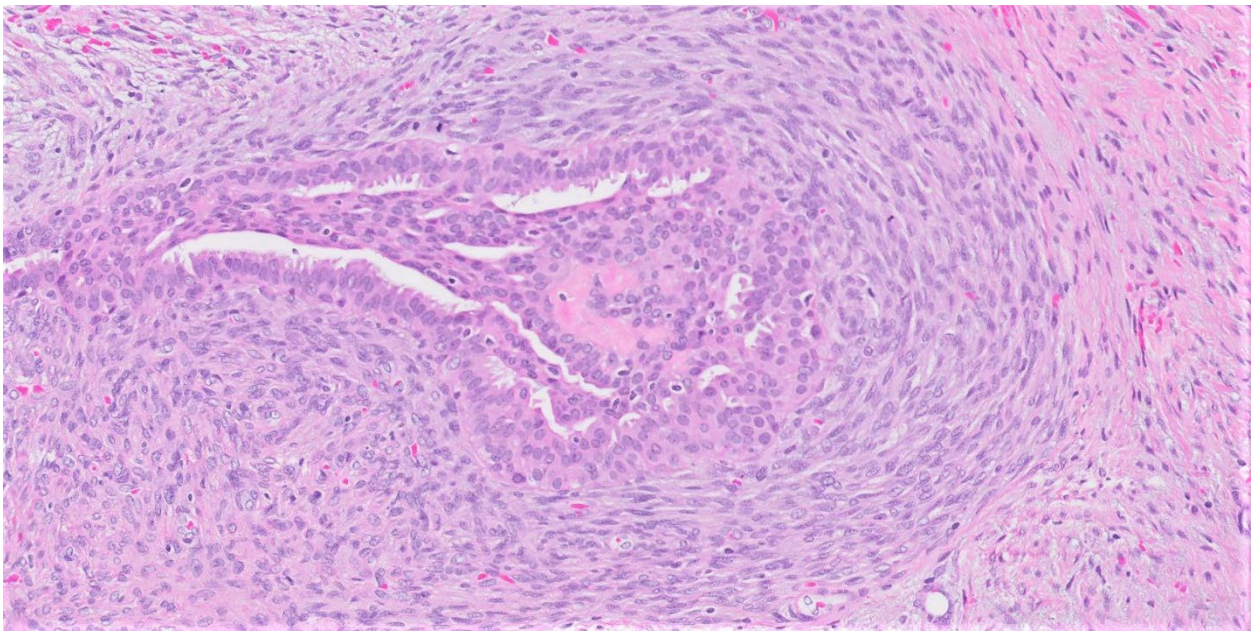

Figure 4. This borderline PT demonstrates accentuation of stromal cellularity around epithelial elements, and discernible mitotic activity (up to 5 mitoses/10hpf in this tumour).

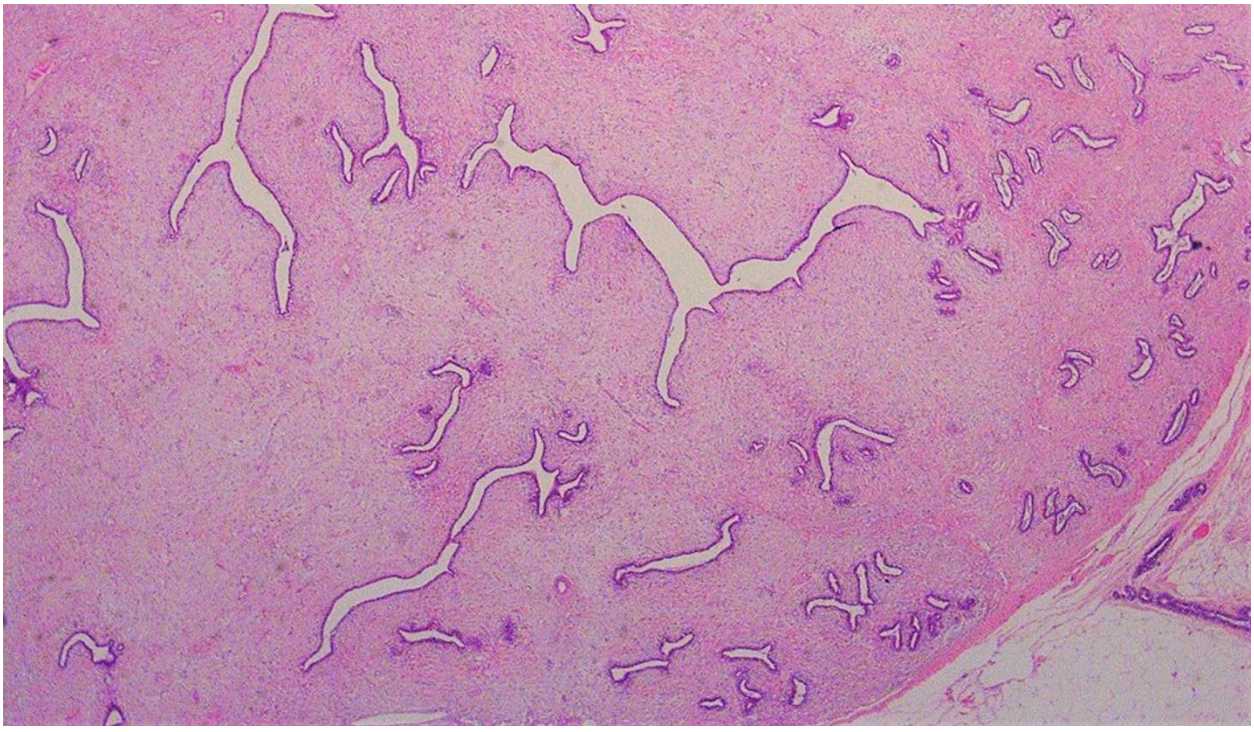

Figure 5. A "grey zone" lesion, with features borderline between that of a cellular FA and a PT. (Reprinted by permission from Springer: Tan, P.H., Sahin, A.A. (2017). Fibroepithelial Lesions. In: Atlas of Differential Diagnosis in Breast Pathology. Atlas of Anatomic Pathology. Springer, New York, NY. https://doi.org/10.1007/978-1-4939-6697-4_3)

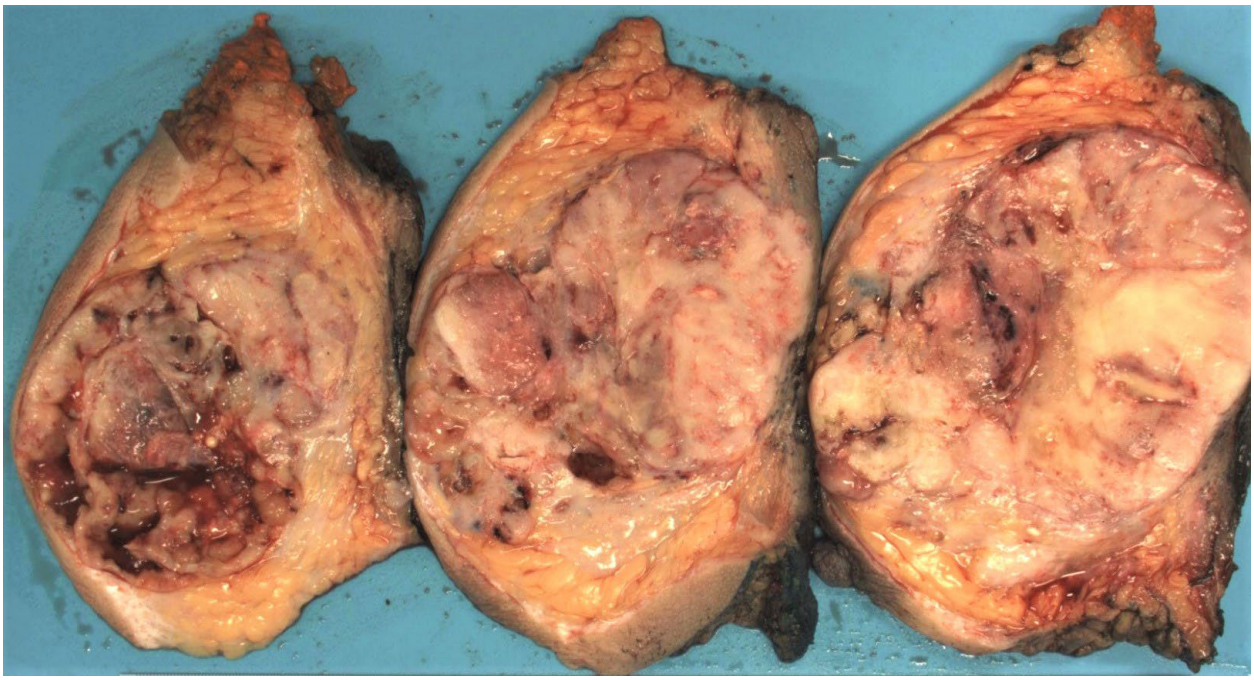

Figure 6. All grossly heterogeneous areas, as in this malignant PT, should be adequately sampled.