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LONG COURSE ARTICLE

Fibroepithelial lesions revisited: implications for diagnosis and management

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Abstract

Fibroepithelial lesions of the breast, comprising the fibroadenoma and phyllodes tumour, are a unique group of neoplasms that share histological characteristics but possess different clinical behaviour. The fibroadenoma is the commonest benign breast tumour in women, while the phyllodes tumour is rare and may be associated with recurrences, grade progression and even metastasis. The diagnosis of fibroadenoma is usually straightforward, with recognised histological variants such as the cellular, complex, juvenile and myxoid forms. The phyllodes tumour comprises benign, borderline and malignant varieties, graded using a constellation of histological parameters based on stromal characteristics of hypercellularity, atypia, mitoses, overgrowth and the nature of tumour borders. While phyllodes tumour grade correlates with clinical behaviour, interobserver variability in assessing multiple parameters that are potentially of different biological weightage leads to significant challenges in accurate grade determination and consequently therapy. Differential diagnostic considerations along the spectrum of fibroepithelial tumours can be problematic in routine practice. Recent discoveries of the molecular underpinnings of these tumours may have diagnostic, prognostic and therapeutic implications.

Introduction

Breast fibroepithelial lesions are biphasic neoplasms composed of both epithelial and stromal components, comprising the common fibroadenoma and the less frequently occurring phyllodes tumour [1].

While the diagnosis of fibroadenoma is made relatively often, especially in core biopsies, the phyllodes tumour is a less commonly encountered pathological conclusion, with particular challenges in grading as well as distinction from histological mimics. These differential diagnoses include the cellular fibroadenoma at the benign end of the phyllodes tumour spectrum, to metaplastic spindle-cell carcinoma and primary breast sarcoma at the borderline and malignant extreme.

In this review, the pathology of the fibroadenoma and phyllodes tumour is revisited, with emphasis on diagnostic and management implications. Molecular information that has emerged in recent years will also be highlighted especially in relation to diagnosis and prognosis.

Fibroadenoma

The fibroadenoma is the commonest benign tumour of the breast, occurring most frequently in women of reproductive age group. Clinically symptomatic patients present with round to ovoid painless breast lumps, which are smooth and rubbery in consistency, often slipping away during palpation, hence referred to as ‘breast mice’. Asymptomatic fibroadenomas are also often discovered in older women during mammographic screening, observed radiologically as masses or calcifications. Core biopsy or fine needle aspiration cytology confirmation of fibroadenoma allows avoidance of surgery, unless symptoms and/or rapid growth warrant removal.

Grossly, the fibroadenoma shows rounded to lobulated, variably encapsulated borders, with fibrous to myxoid cut

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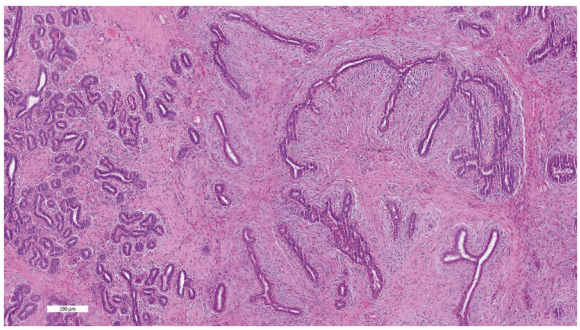

Fig. 1 Microscopic appearance of a fibroadenoma with both intracanalicular and pericanalicular growth patterns. In the right field, stroma grows against, compresses and stretches the epithelium (intracanalicular pattern), while in the left field, stroma surrounds patent tubules reflecting the pericanalicular pattern.

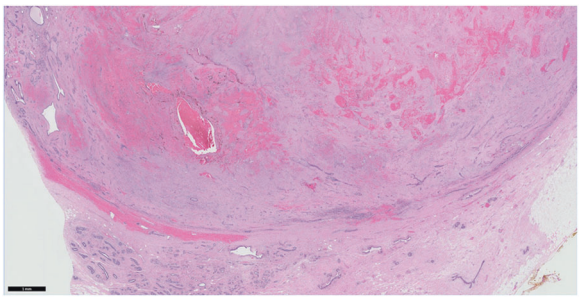

Fig. 2 Infarction in a fibroadenoma shows haemorrhage and loss of cellular detail. The circumscribed boundary of the fibroadenoma with adjacent breast tissue is seen in the lower half of the field.

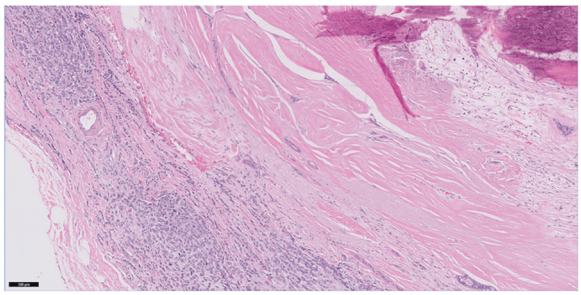

Fig. 3 Invasive carcinoma in a fibroadenoma. Invasive carcinoma is present within a hyalinised calcified fibroadenoma, observed near the periphery of the lesion as narrow trabeculae and short streams of invasive carcinoma cells (left field).

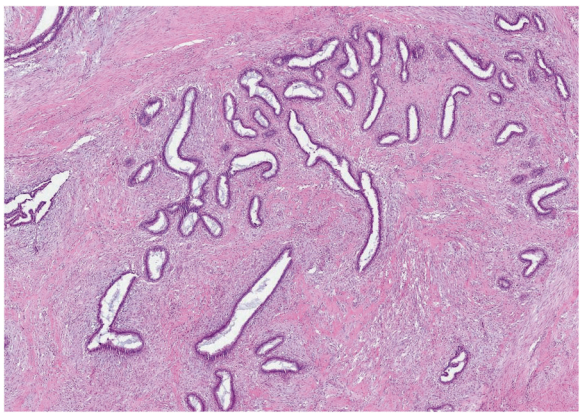

Fig. 4 Cellular fibroadenoma. Cellular fibroadenoma shows increased stromal cellularity around the epithelial compartment.

surfaces. Microscopically, it is a biphasic tumour with circumscribed and pushing contours, composed of an admixture of epithelial and stromal elements, with loss of lobular architecture due to the expansion of stroma between epithelial elements. The pericanalicular growth pattern refers to stromal growth around patent tubules, while the intracanalicular appearance comprises stroma pushing against epithelium creating arc-like epithelial shapes (Fig. 1). Both patterns are often seen in the same lesion, which are without clinical significance, apart from recent recognition that the *MED12* mutation is more frequently found in the intracanalicular fibroadenoma [2, 3].

A variety of histological changes can be seen in the fibroadenoma. Infarction may occur in pregnant patients and post-instrumentation (Fig. 2). The fibroadenoma stroma is usually of low cellularity, with myxoid, fibroblastic or hyalinised appearances. Stromal multinucleated cells [4–6], calcifications, ossification and pseudoangiomatous stromal hyperplasia (PASH) may be present. The epithelium can display usual ductal hyperplasia (UDH), reported to occur in 32.3% of cases (excluding mild hyperplasia) [7], apocrine metaplasia, sclerosing adenosis, atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), ductal carcinoma in situ, lobular carcinoma in situ and even invasive carcinoma [8] (Fig. 3), although the cancer rate in fibroadenoma is exceedingly rare, from 0.002 to 0.125% [9]. Carter et al. found a 0.81% prevalence of ALH or ADH in fibroadenomas, which when confined within the fibroadenoma, does not translate to a clinically meaningful increased risk of subsequent breast cancer development [10].

Fibroadenoma variants

Fibroadenoma variants include cellular, complex, juvenile and myxoid forms. The cellular variant shows increased density of stromal cells within the architecture of a typical fibroadenoma, without significant stromal atypia, excess stromal mitotic activity or accentuated intracanalicularity (Fig. 4). The main differential diagnosis of the cellular fibroadenoma, especially on core biopsy, is the phyllodes tumour, which is distinguished by the presence of well-formed stromal fronds. In a long-term follow-up study conducted on a series of cellular fibroepithelial lesions that included 35 cellular fibroadenomas, none of which were widely excised, it was concluded that the recurrence rate of these tumours was low, without any phyllodes tumours

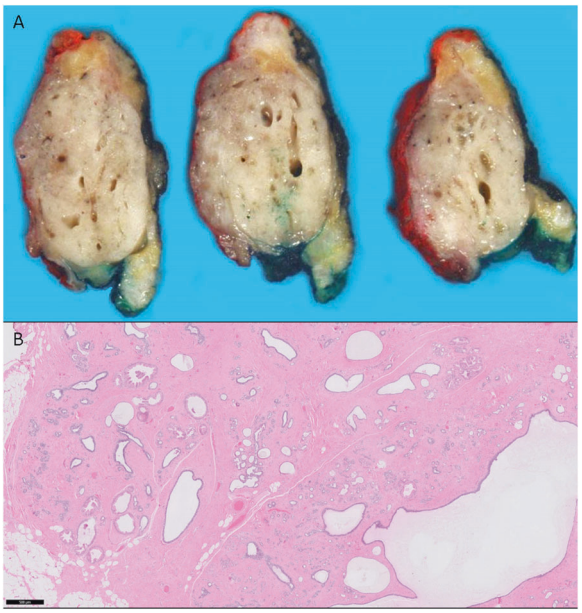

Fig. 5 Complex fibroadenoma. a Gross appearance of a complex fibroadenoma with a fibrous cut-surface displaying scattered cysts. **b** Microscopically, cysts larger than 3 mm are seen in the fibroadenoma. Apocrine metaplasia and adenosis are also present.

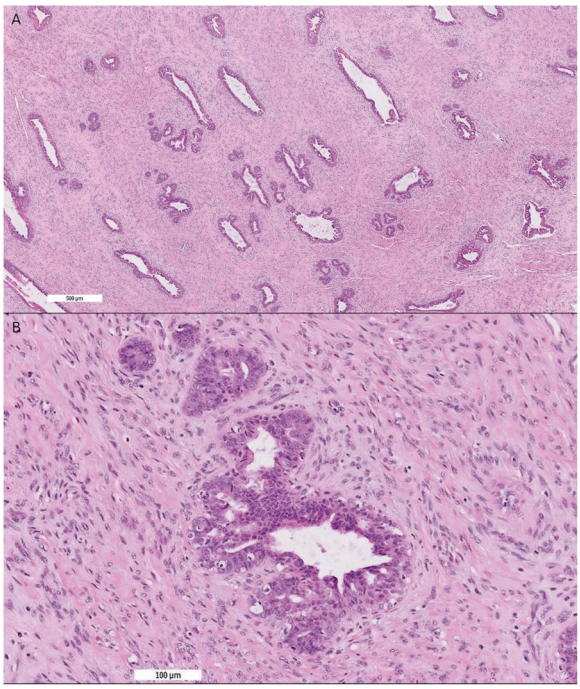

Fig. 6 Juvenile fibroadenoma. a The juvenile fibroadenoma shows a pericanalicular growth pattern with increased stromal cellularity. **b** The epithelium shows usual ductal hyperplasia with micropapillary epithelial tufts.

diagnosed among the recurrences [11]. Genomically, cellular fibroadenomas possessed similar rates of mutations in the most commonly mutated genes *MED12*, *KMT2D* and *RARA* (49%, 13% and 13%) as conventional fibroadenomas (44%, 15% and 8%), indirectly supporting their classification with conventional fibroadenomas [12]. In contrast, the mutation spectrum of benign phyllodes tumours with which they resemble disclosed 62%, 14% and 17% abnormalities in the same set of genes, with a significant difference in the *MED12* mutation rate. In addition, *TERT* promoter mutations were significantly higher in benign phyllodes tumours (32%) than in cellular (4%) and conventional (6%) fibroadenomas [12].

The complex fibroadenoma comprises 14.1–40.4% of all fibroadenomas [7, 13, 14]. It shows any of the following histological features: sclerosing adenosis, papillary apocrine metaplasia, cysts ≥3 mm in size and epithelial calcifications [15] (Fig. 5). Studies indicate a mildly increased risk of about 3× that of the general population of subsequent breast cancer development [13, 15], though it is uncertain if this higher probability is independent of epithelial proliferative changes within the fibroadenoma. This slight increase in risk associated with the complex fibroadenoma does not portend a clinically actionable management impact, further supported by a report that suggests that the complex fibroadenoma is not an independent risk marker for breast cancer [13].

The juvenile fibroadenoma is often described in children and adolescents, but may be diagnosed in women of any age. It can grow to a large size, with lesions exceeding 5 cm in size regarded as giant fibroadenomas [1]. The stroma tends to be cellular, displaying an interlacing fascicular arrangement of fibroblasts and myofibroblasts with a pericanalicular pattern (Fig. 6). The epithelium usually demonstrates moderate to florid UDH, the latter sometimes causing confusion with ADH. The epithelial proliferation may disclose gynaecomastoid features with fine filigree-like, narrow micropapillary epithelial protrusions. Four patterns, referred to as 'atypical epithelial proliferations' in juvenile fibroadenomas, were described decades ago: ductal-laciform, ductal-solid, cystic-papillary and lobular-terminal ductal; a conservative interpretation was recommended [16], and one would caution against over-diagnosing malignancy in these cases.

The myxoid fibroadenoma is typified by loose hypocellular stroma containing watery myxoid ground substance (Fig. 7), with some cases being part of the Carney's complex [17], an autosomal dominant disorder characterised by myxomas in different sites, spotty pigmentation and endocrine overactivity. Genomically, the myxoid fibroadenoma differs from the conventional fibroadenoma by its lack of *MED12* mutations [18].

Fibroadenomas in the paediatric population

Fibroadenomas in the paediatric population have not been extensively investigated pathologically. A radiological

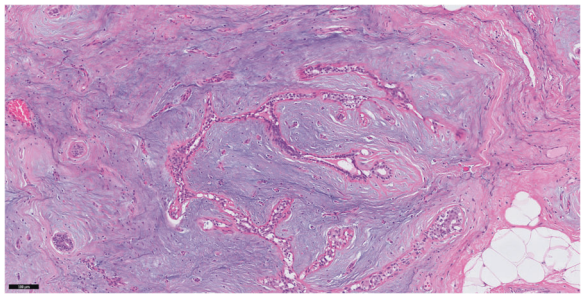

Fig. 7 Myxoid fibroadenoma. Myxoid fibroadenoma shows greyish-watery ground substance around the epithelial compartment.

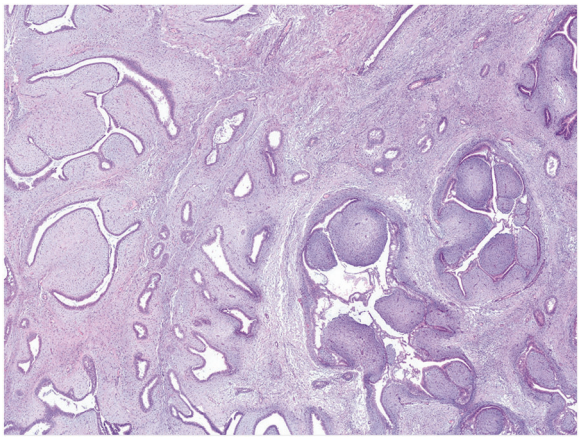

Fig. 8 Paediatric fibroadenoma. Fibroadenoma in a young patient shows small stromal fronds with areas of peri-epithelial 'shadowing' given by myxoid change and slight increase in stromal-cell density.

study concluded that fibroadenomas comprised 91% of all histologically evaluated solid breast masses among patients under 19 years of age [19]. Two major morphological studies reviewed microscopic findings with a note of increased stromal cellularity, which may be marked, especially in juvenile fibroadenomas [20], and mitoses that numbered up to 6 mitoses per 10 high-power fields in usual fibroadenomas [21]. Stromal fronds could also be identified [20] although they tended to be less well developed (Fig. 8), and were not associated with recurrences. Stromal nuclear atypia, up to moderate degree, was discovered [20]. It was acknowledged that traditional histological parameters and thresholds used for adult fibroepithelial tumours, when applied to lesions in young patients, could pose challenges. The juvenile fibroadenoma was the commonest form of fibroadenoma in the paediatric age group, with additional observations of slight stromal expansion and intratumoural heterogeneity without stromal atypia [21].

Both studies concurred that fibroadenomas in the young followed a benign course, without predisposition to phyllodes tumour or cancer development. Genomically, *TERT* promoter mutations which are found more frequently in phyllodes tumours, were not detected in paediatric fibroadenomas [22, 23]. A conservative and cautious approach is therefore recommended in the diagnosis and treatment of paediatric fibroepithelial tumours.

Core biopsy diagnosis

Core biopsy is a standard preoperative diagnostic procedure for breast lesions discovered clinicoradiologically. Fibroadenomas are commonly diagnosed on core biopsy material. A question that is sometimes raised is whether a conclusion of fibroadenoma on core biopsy is accurate and reliable, and whether there should be concern for undersampling of a phyllodes tumour. In a multicentre study incorporating routine diagnoses of fibroadenomas on core biopsies with follow-up, it was found that subsequent discovery of phyllodes tumour is extremely rare, with only 16 (0.38%) out of a total of 4163 cases [24]. These phyllodes tumours were categorised as benign in 14 cases and borderline in 2 cases. It was concluded that the main reason contributing to the core needle biopsy-excision discrepancies was phyllodes tumour heterogeneity with fibroadenoma-like areas, with such foci being discovered in 35.9% of phyllodes tumours in one study [25]. Unfortunately, there were no specific pathological features that were prospectively predictive of phyllodes tumour at excision, but that suspicious imaging features at the time of core needle biopsy or on follow-up should prompt consideration for surgical excision. In addition, all core biopsy diagnoses should be reviewed in the context of the triple approach with clinical and radiological input. Clinically symptomatic and large lesions, and rapid tumour growth are triggers for excision, obviating sampling issues. The key message from the study was that the diagnosis of fibroadenoma on core needle biopsy is reliable and safe in the setting of the triple approach.

Core biopsies of cellular fibroepithelial lesions represent a challenging area, with multiple studies having been conducted to determine factors that could predict phyllodes tumours on excision. Table 1 summarises the data from various publications, with a constellation of histological features including mitotic activity (suggested as 2 or more per 10 high-power fields), marked stromal hypercellularity, stromal overgrowth (variably defined in different studies), adipose infiltration, ill-defined lesional borders, heterogeneity, subepithelial condensation, stromal nuclear pleomorphism, tissue fragmentation, as well as older age group, that were correlated with a phyllodes tumour outcome [26–31]. Immunohistochemistry for proliferation markers Ki-67 and topoisomerase 2α was also described as being informative, though this has not been applied diagnostically as thresholds in individual cases are not yet determined [26, 29].

Table 1 Prediction of phyllodes tumour from core biopsy diagnosis of cellular fibroepithelial lesions.

No.	Authors	Reference	Key findings predicting phyllodes tumour
1	Jacobs et al. [26]	Am J Clin Pathol. 2005 Sep;124(3):342–54	Marked stromal cellularity, mitoses in moderate stromal cellularity, Ki-67 and topoisomerase IIα indices
2	Lee et al. [27]	Histopathology. 2007 Sep;51(3):336–44	Stromal cellularity ≥ 50% stroma, stromal overgrowth, fragmentation, adipose within stroma
3	Resetkova et al. [28]	Breast J. 2010 Nov-Dec;16(6): 573–80	No predictive value of clinical, radiological or pathological data. Suggested follow-up alone for a patient subset
4	Jara-Lazaro et al. [29]	Histopathology. 2010 Aug;57(2):220–32.	Marked stromal cellularity/atypia, stromal overgrowth, mitoses ≥ 2 per 10 HPF, ill-defined lesional borders, Ki-67 and topoisomerase IIα indices ≥ 5%, reduced CD34 staining
5	Yasir et al. [30]	Am J Clin Pathol. 2014 Sep; 142(3):362–9	Mitoses, stromal overgrowth, fragmentation, adipose infiltration, heterogeneity, subepithelial condensation and nuclear pleomorphism
6	Jung et al. [31]	Int J Surg Pathol. 2018 Dec;26(8):684–92	Age ≥ 40 years, stromal overgrowth and stromal cellularity

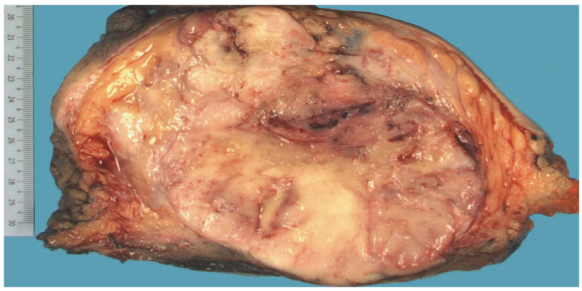

Fig. 9 Macroscopic pathology of phyllodes tumour. Gross appearance of a malignant phyllodes tumour shows a lobulated fleshy mass with partially circumscribed borders, areas of haemorrhage and necrosis.

With availability of molecular pathology, authors have attempted to use transcriptomic and genomic tools to assist in distinguishing fibroadenomas from phyllodes tumours on core biopsies. In the former, a 5-gene transcript was accurate in discriminating the two lesions in 92.6% of cases using a reverse-transcription polymerase chain assay [32] whereas in the latter, targeted sequencing of a 16-gene panel allowed development of a risk-scoring system that stratified core biopsies of fibroepithelial lesions into low and high risks of being a phyllodes tumour [33]. Application of digital pathology was unable to enhance diagnostic discrimination [34].

Phyllodes tumour

The phyllodes tumour of the breast is a biphasic neoplasm with an exaggerated, prominent intracanalicular growth pattern with leaf-like stromal fronds covered by benign bilayered epithelium (luminal and myo-epithelium) [1]. It affects females in their 5th decade or older, though it can occur in younger women, especially of Asian and Hispanic ethnicity. While the tumour tends to present symptomatically as a large mass which may exceed 10 cm and distort the breast, the average tumour size is 4–5 cm, with smaller tumours being detected radiologically.

Macroscopically, phyllodes tumours show circumscribed bosselated contours with a variety of appearances—whitish and whorled, grey and fleshy, soft and mucoid, with areas of necrosis and haemorrhage (Fig. 9). Cystic changes may also occur.

Microscopically, the key histological findings are broad patulous fronds of at least mildly cellular stroma covered by benign bilayered epithelium, forming protuberant projections into clefted compressed spaces. Once the diagnosis of phyllodes tumour is made, grading into benign, borderline and malignant categories is accomplished based on an assessment of a constellation of histological criteria—degree of stromal hypercellularity, stromal atypia, stromal mitoses,

Table 2 Histological features of phyllodes tumours (adapted from Breast Tumours, WHO Classification of Tumours 2019).

Histological feature	Phyllodes tumours		
	Benign	Borderline	Malignant
Tumour border	Well defined	Well defined, may be focally permeative	Permeative
Stromal cellularity	Cellular, usually mild, may be non-uniform or diffuse	Cellular, usually moderate, may be non-uniform or diffuse	Cellular, usually marked and diffuse
Stromal atypia	Mild or none	Mild or moderate	Marked
Mitotic activity	Usually low: <2.5 mitoses/mm^2 (<5 per 10 high power fields)	Usually frequent: 2.5 to <5 mitoses/mm^2 (5–9 per 10 high power fields)	Usually abundant: ≥5 mitoses/mm^2 (≥10 per 10 high power fields)
Stromal overgrowth	Absent	Absent (or very focal)	Often present
Malignant heterologous elements	Absent	Absent	May be present (liposarcoma excluded)

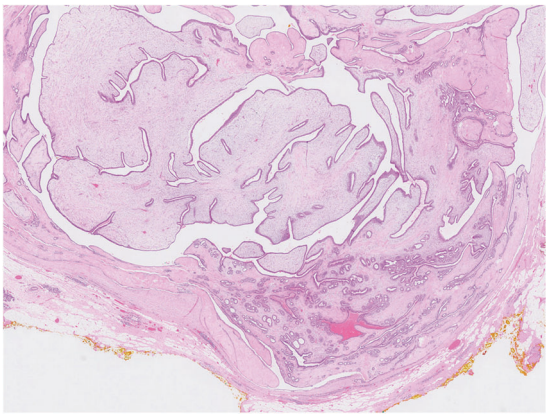

Fig. 10 Benign phyllodes tumour. At low magnification, the benign phyllodes tumour shows rounded pushing contours, broad stromal fronds and mild increase in stromal cellularity.

stromal overgrowth and the nature of the tumour borders (pushing or permeative) [1]. Like in the fibroadenoma, the epithelial component may display usual and atypical hyperplasia (both ductal and lobular), in situ and invasive carcinoma [35], with PASH more often encountered in the phyllodes tumour than in the fibroadenoma (personal observation). Among phyllodes tumours, PASH has also been noticed more frequently in the benign grade [36].

Grading of phyllodes tumours

Phyllodes tumours are graded into benign, borderline and malignant forms. Grade is important due to its correlation with clinical behaviour, in particular with local recurrences and metastases. Table 2 shows the histological grading parameters within the different grades.

The benign phyllodes tumour displays mild stromal hypercellularity with nil to mild stromal atypia, with scant mitoses numbering up to 4 per 10 high-power fields, without stromal overgrowth [1]. Borders are pushing and smooth contoured (Fig. 10). Peri-epithelial stromal condensation and elongated narrow epithelium-lined clefts may be seen (Fig. 11). The latter may be a clue to a phyllodes tumour diagnosis, with more characteristic phyllodal architecture found elsewhere in the tumour upon thorough search. At the other end of the grading spectrum is the malignant phyllodes tumour, which shows marked and diffuse stromal hypercellularity, marked stromal atypia, brisk mitotic activity exceeding 9 per 10 high-power fields, stromal overgrowth defined as one low-power field (×40 magnification, at ×4 objective with ×10 eyepiece) containing stroma only without any epithelial elements, as well as permeative borders (Fig. 12). Presence of malignant heterologous elements, except well differentiated liposarcoma, warrants a malignant grade even in the absence of other histological parameters indicating malignancy [1].

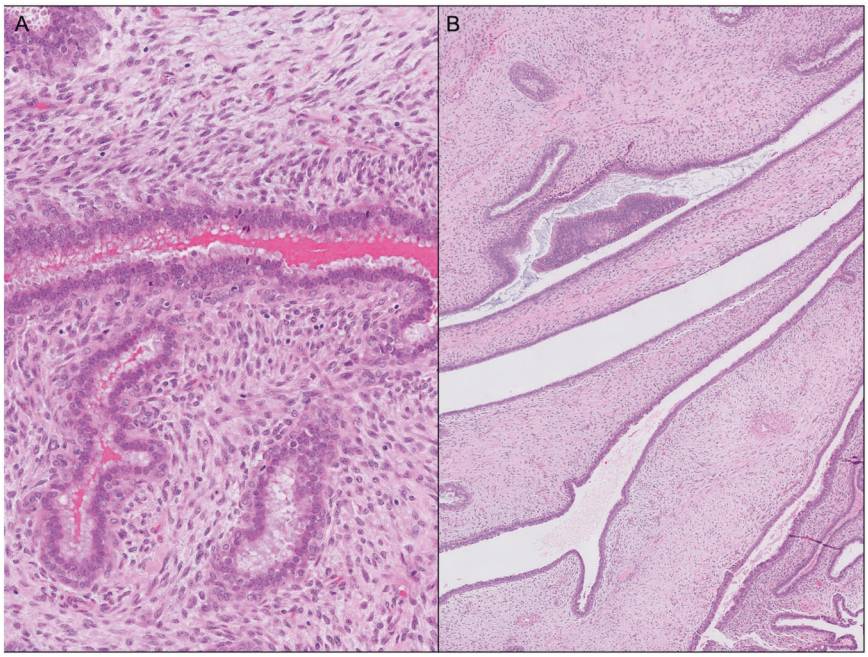

Fig. 11 Benign phyllodes tumour. a Peri-epithelial or subepithelial stromal condensation is seen as an aggregation of stromal cells hugging the epithelium, which at low magnification may be discerned as a 'shadow' around the epithelial component. **b** Elongated clefts lined by benign epithelium may be a clue to more diagnostic phyllodal areas.

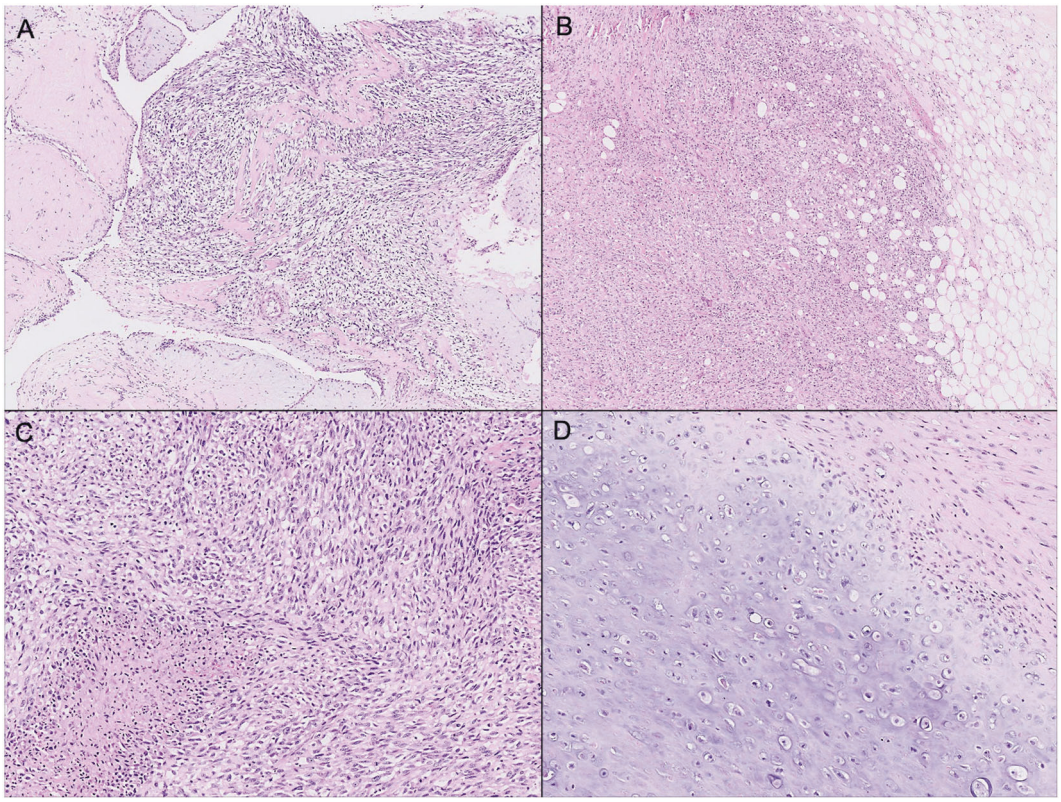

Fig. 12 Malignant phyllodes tumour. a Stromal fronds with increased cellularity. **b** Permeative border with malignant stromal cells percolating into the adjacent adipose tissue. **c** Necrosis within areas of stromal hypercellularity and atypia with brisk mitoses. **d** Malignant heterologous element of chondrosarcoma.

Straddling between the benign and malignant phyllodes tumours is the borderline grade, which shows moderate stromal hypercllularity, mild to moderate stromal atypia, 5–9 mitoses per 10 high-power fields and focally permeative borders. Stromal overgrowth can be present focally. No malignant heterologous elements are seen (Fig. 13).

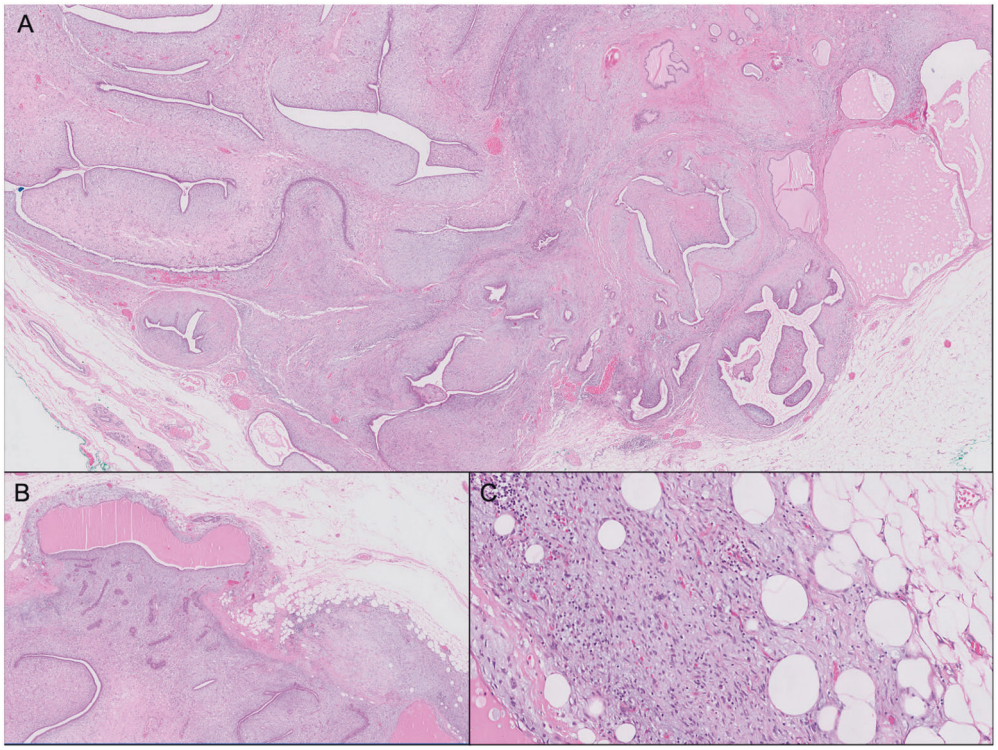

Fig. 13 Borderline phyllodes tumour. a Low magnification shows stromal fronds with mild to moderate stromal hypercellularity and generally pushing borders. **b** Part of the tumour shows stromal permeation into the surrounding adipose tissue. **c** High magnification of the stromal cells encircling adipocytes at the tumour periphery.

The exclusion of liposarcoma from the list of malignant heterologous elements that can individually indicate a malignant grade was a consensus decision made by the working group in the WHO 2019 breast tumour classification. It was the collective view that liposarcoma in the breast, and in particular the phyllodes tumour, did not harbour metastatic potential. This assessment was supported by the absence of *MDM2* and *CDK* amplifications in liposarcoma of phyllodes tumours [37–40], in contrast to their presence in extramammary liposarcoma, though there was one case with focal MDM2 immunopositivity [38]. In addition, genomic studies found that the non-heterologous component of malignant phyllodes tumours displayed more chromosomal aberrations than the liposarcoma element [37]. It is recommended that evaluation of other histological parameters is used to finalise the grade in phyllodes tumours harbouring liposarcoma. The presence of liposarcoma, however, tends to be associated with microscopic features of at least borderline grade (Fig. 14). It is important to recognise that benign adipocytic components can be seen in phyllodes tumours [41, 42] and do not impact grading. Focal fat necrosis may result in adipocytes and histiocytes with reactive nuclear atypia and cytoplasmic vacuolation that should not be interpreted as lipoblasts nor cause consternation for liposarcoma.

In order to rationalise terminology for cases where the final grade is determined as borderline rather than malignant based on other histological parameters, the liposarcoma foci could be referred to as 'lipoblast-like areas' to avoid using the term 'sarcoma' for phyllodes tumours that are not diagnosed as malignant. Presence of other malignant heterologous elements like osteosarcoma, chondrosarcoma and rhabdomyosarcoma remains diagnostic of malignant phyllodes tumours. As phyllodes tumours containing heterologous elements are rare, it would be helpful for their continued study to establish the true clinical significance. Koh et al. reported that large phyllodes tumours containing malignant heterologous elements, which included liposarcoma, were predictive of metastatic likelihood [43]. There are also anecdoctal reports of myxoid [44] and pleomorphic [45] liposarcoma in phyllodes tumours, which may be accompanied by aggressive behaviour [38].

Sampling of phyllodes tumours

Phyllodes tumours often display intratumoural heterogeneity. High grade areas may be focal within otherwise low-grade tumours, and stromal overgrowth may mask fibroepithelial architecture. Genomic heterogeneity parallels morphological diversity [46]. Adequate sampling is

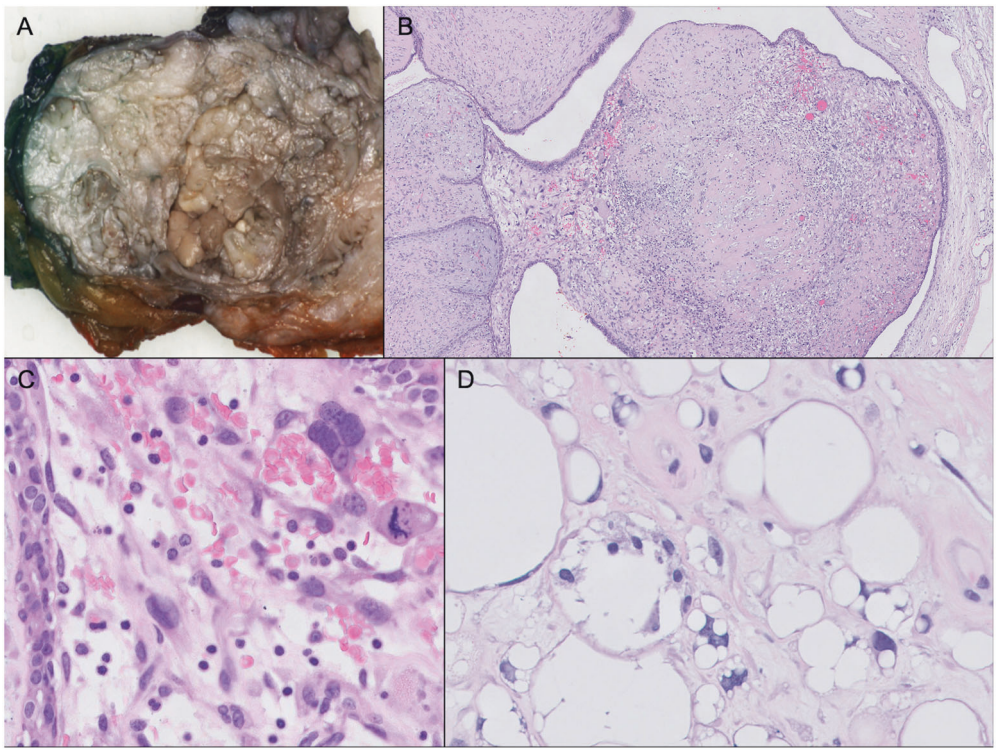

Fig. 14 Liposarcoma in phyllodes tumour. a Gross specimen of phyllodes tumour with whitish whorled and yellowish soft mucoid areas. Fronds and clefts are present. **b** Low magnification shows a hypercellular stromal frond with abnormal cells. **c** Marked stromal atypia and a mitosis. **d** Lipoblasts with hyperchromatic scalloped nuclei and vacuolated cytoplasm.

therefore important. One block per cm of maximum tumour dimension, with sampling of grossly heterogenous areas, is recommended.

Classification and grading challenges

Phyllodes tumour classification and grading are inherently imperfect, due to the need to amalgamate the assessment of multiple histological criteria, for which their relative importance to clinical outcome is not addressed in the current grading scheme. Each histological parameter also has several tiers of stratification and multiple combinational permutations, invariably leading to interobserver variability [47]. In order to circumvent these deficiencies, a study of 605 phyllodes tumours from a single institution was conducted to determine the relative impact of histological grading parameters to recurrence, with development of a formula that takes into account weighting of the criteria [47]. It was found that stromal atypia, mitotic activity, overgrowth and status of surgical margins were key parameters that correlated with recurrent likelihood (AMOS criteria). This Singapore nomogram has been validated in a few studies [25, 48–50], and may be accessed through an online calculator (https://mobile.sgh.com.sg/ptrra/), which can be used to counsel individual patients with phyllodes tumours.

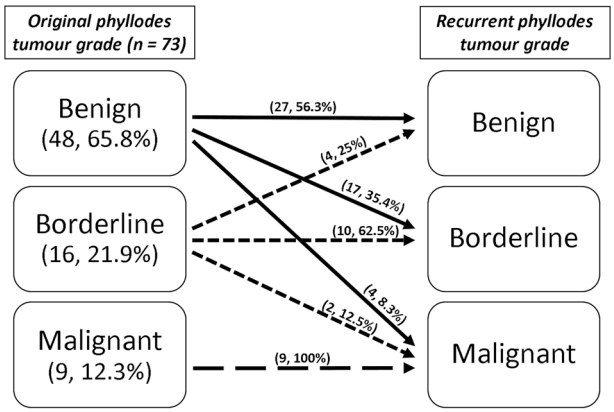

Fig. 15 Recurrences of phyllodes tumours and their corresponding grades.

Prognosis of phyllodes tumours

While grading of phyllodes tumours has its limitations, the benign, borderline and malignant grade groups are prognostically discriminatory with different recurrence rates. Local recurrence rates are 10–17%, 14–25% and 23–30%, respectively, for benign, borderline and malignant tumours [1], indicating greater recurrences with increasing tumour grades. Grade progression upon recurrence is shown in Fig. 15 with 43.7% of originally benign tumours recurring

at higher grades based on a study conducted on 605 cases [47] with a small handful (8.3%) progressing directly to malignancy from an initially benign tumour.

Metastases are reported to occur in 0.1%, 1.6% and 16.7% of benign, borderline and malignant phyllodes tumours, respectively [1]. The anecdotal case reports of metastases of benign tumours need to be critically appraised with regard to grading accuracy and tumour sampling [51]. While occasional borderline tumours are known to metastasise, whether such tumours were appropriately graded also requires review. Metastases are almost exclusively encountered in phyllodes tumours of malignant grade, occurring in up to 2% overall among all phyllodes tumours, with metastatic lesions comprising malignant stroma devoid of epithelium [1, 51, 52]. Predictors of metastases include age >50 years, stromal overgrowth, diffuse marked atypia, necrosis, mitoses ≥10/10 high-power fields [53]; large tumours (>9 cm) with heterologous elements [43]. Continued research into subsets of malignant tumours that are likely to metastasise will help in stratifying therapy.

Differential diagnosis

Diagnostic challenges revolve around the distinction of benign phyllodes tumour from the cellular fibroadenoma, while at the malignant end of the spectrum, separating malignant phyllodes tumour from spindle-cell metaplastic breast carcinoma and sarcoma. Other differential considerations include periductal stromal tumour, fibromatosis and metastases [54].

Benign phyllodes tumour and cellular fibroadenoma

The key histological feature that distinguishes these two entities is the presence of an exaggerated intracanalicular growth pattern, or prominent stromal fronds, in the phyllodes tumour. Both lesions show increased stromal cellularity and overlapping mitotic rates. While mild stromal atypia may be acceptable in the cellular fibroadenoma, greater degrees of atypia should raise consideration for phyllodes tumour. Stromal multinucleated cells may be observed in both lesions, and the general advice is not to overinterpret their presence, even when they appear bizarre as this may be of degenerative nature [5, 55] (Fig. 16). It would be prudent, however, to evaluate the non-multinucleated stromal-cell population in such cases, as lesions with significant stromal atypia including abnormal mitoses have been observed warranting at least a borderline grade (Fig. 17). Immunohistochemistry for Ki-67 and p53 may be useful in grading calibration [56–58].

In some cases, it may be very difficult to be absolutely certain if a tumour is a cellular fibroadenoma or benign phyllodes tumour, and in such circumstances, it may be appropriate to use the term 'benign fibroepithelial neoplasm' as a reflection of the overlapping histological features [51, 59].

Benign phyllodes tumour and periductal stromal tumour

The periductal stromal tumour differs histologically from phyllodes tumour by the absence of stromal leaf-like fronds [60]. These tumours are closely related [61], in that periductal stromal tumour-like areas are sometimes observed in phyllodes tumours, and some recurrences of periductal stromal tumours are diagnosed as phyllodes tumours [1, 59]. In addition, there is a genomic similarity of these lesions [46], with the latest WHO breast tumour classification regarding the periductal stromal tumour as a subtype of phyllodes tumour [1].

Borderline phyllodes tumour and fibromatosis

Stroma predominant phyllodes tumour, often in the setting of borderline grade, may resemble fibromatosis (Fig. 18). Finding stromal fronds on histology allows the correct diagnosis. Presence of periductal stromal condensation and narrow elongated clefted ducts should raise suspicion of a phyllodes tumour. Immunohistochemistry for CD34 generally shows stromal positivity in phyllodes tumours, with a higher rate in the benign grade [62–64], whereas it is negative in fibromatosis [65, 66]. Nuclear beta-catenin, often described as a diagnostic feature for fibromatosis, is also observed in phyllodes tumours, so it cannot be used for discriminating these two lesions [65, 67–69]. Fibromatosis-like metaplastic carcinoma (Fig. 19) is positive for epithelial markers on immunohistochemistry—nuclear beta-catenin can also be expressed [67, 70].

Malignant phyllodes tumour, metaplastic spindle-cell carcinoma and sarcoma

Malignant phyllodes tumours may have large areas of stromal overgrowth that overrun the epithelial compartment, effacing their characteristic stromal fronds, thus resembling spindle-cell metaplastic carcinoma and breast sarcoma histologically. Presence of accompanying in situ or invasive carcinoma, and immunohistochemical positivity for epithelial markers, support the diagnosis of metaplastic carcinoma. While immunostaining positivity is often diffuse, there can be variability observed for different antibodies, which highlights the need for using a panel rather than a single marker. Spindle-cell carcinoma invading into a fibroepithelial tumour may mimic a malignant phyllodes tumour (Fig. 20).

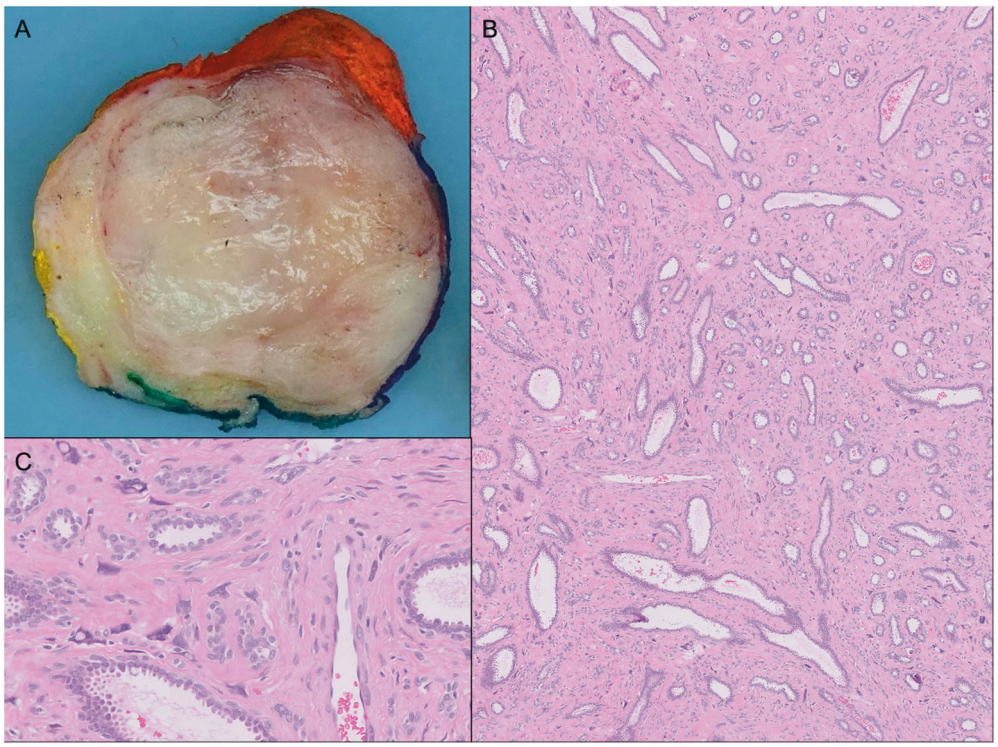

Fig. 16 Benign fibroepithelial tumour with hybrid tubular adenoma and fibroadenoma areas and bizarre multinucleated stromal cells. a Gross appearance of the benign tumour with circumscribed borders and a fibrous myxoid cut-surface. **b** Stroma in between the epithelial component shows low cellularity with scattered enlarged stromal cells. **c** High magnification of the abnormal stromal cells with multilobated nuclei and nuclear inclusions. Spindled stromal cells present are without atypia or mitoses.

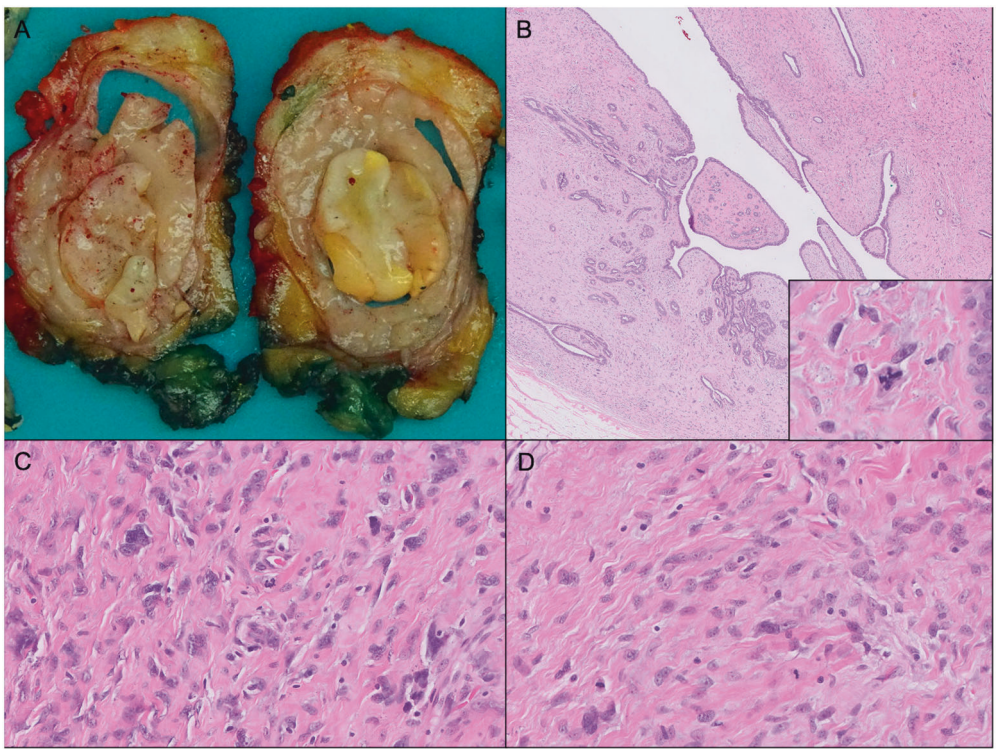

Fig. 17 Borderline phyllodes tumour with stromal giant cells. a Gross appearance of the phyllodes tumour with clefts and myxoid fronds. Yellowish areas correspond to infarction. **b** Low magnification shows phyllodal architecture with stromal fronds. Inset reveals a quadripolar mitosis. **c**, **d** Stromal cells among the giant forms display atypia and scattered mitoses.

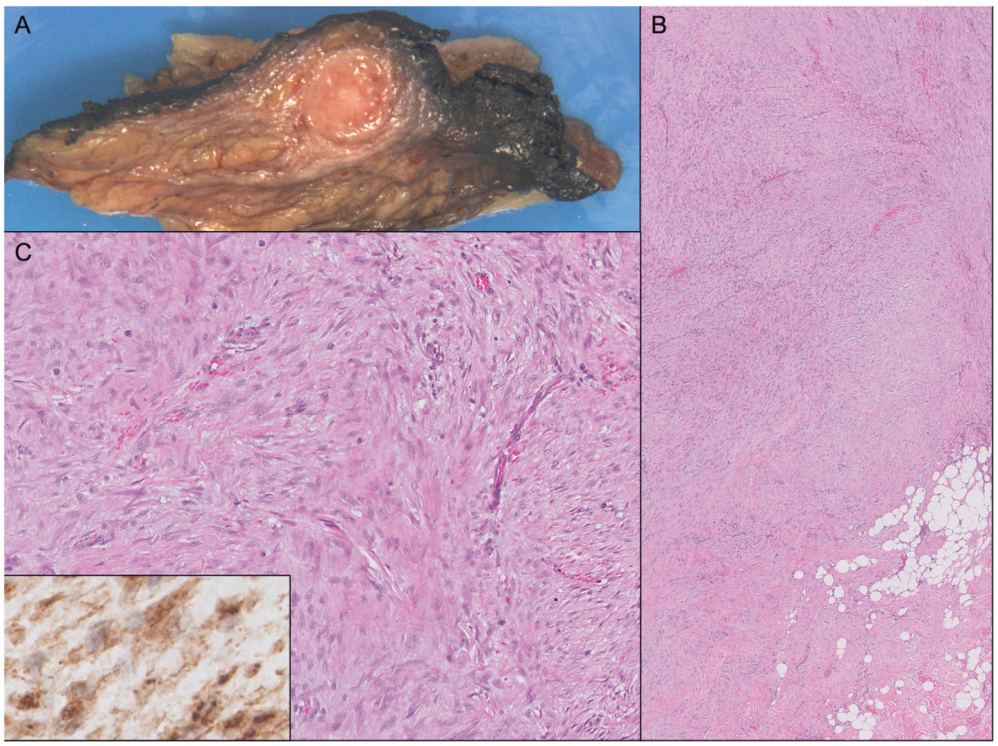

Fig. 18 Fibromatosis. a Gross appearance shows a rounded firm nodule within breast tissue. **b** Low magnification shows intersecting spindle-cell fascicles with an ill-defined border, which may resemble stroma predominant phyllodes tumour. **c**. High magnification shows bland spindle cells. Inset reveals immunohistochemical nuclear and cytoplasmic reactivity for beta-catenin, though phyllodes tumour stromal cells may also be positive for beta-catenin.

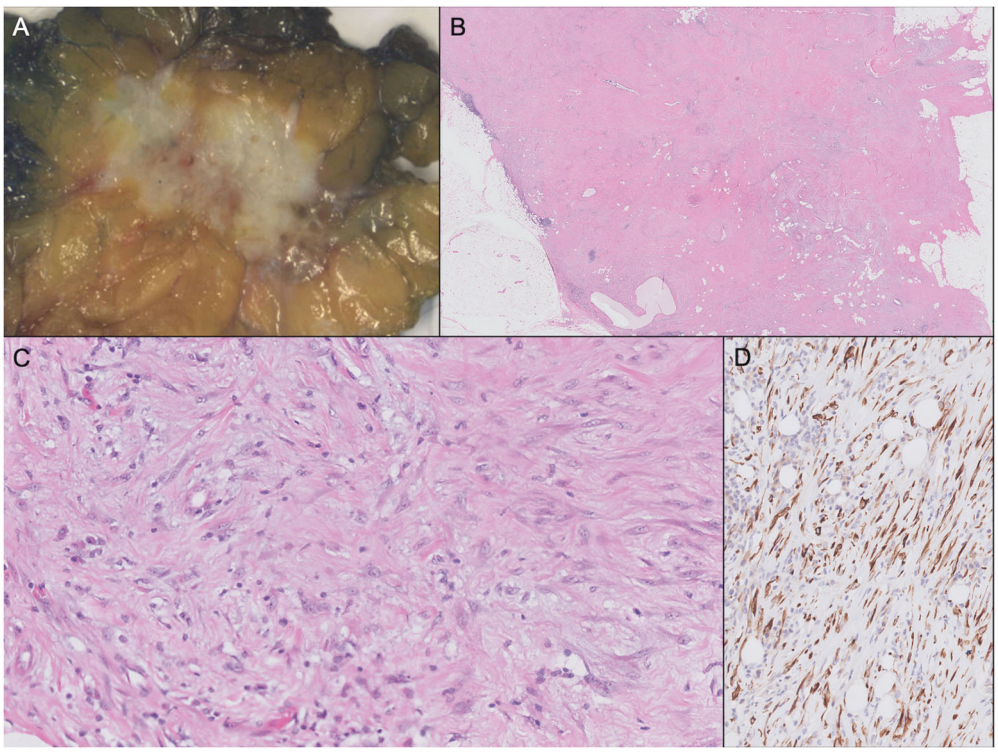

Fig. 19 Fibromatosis-like metaplastic carcinoma. a Irregular greyish-yellow tumour within the breast tissue. **b** Low magnification shows a fibrosclerotic lesion with ill-defined borders, with a few lymphocytic aggregates at the periphery. **c** High magnification shows plump-spindled cells within a collagenous background, with minimal atypia. **d** CK14 immunohistochemistry shows diffuse positivity of spindle cells, indicating epithelial differentiation.

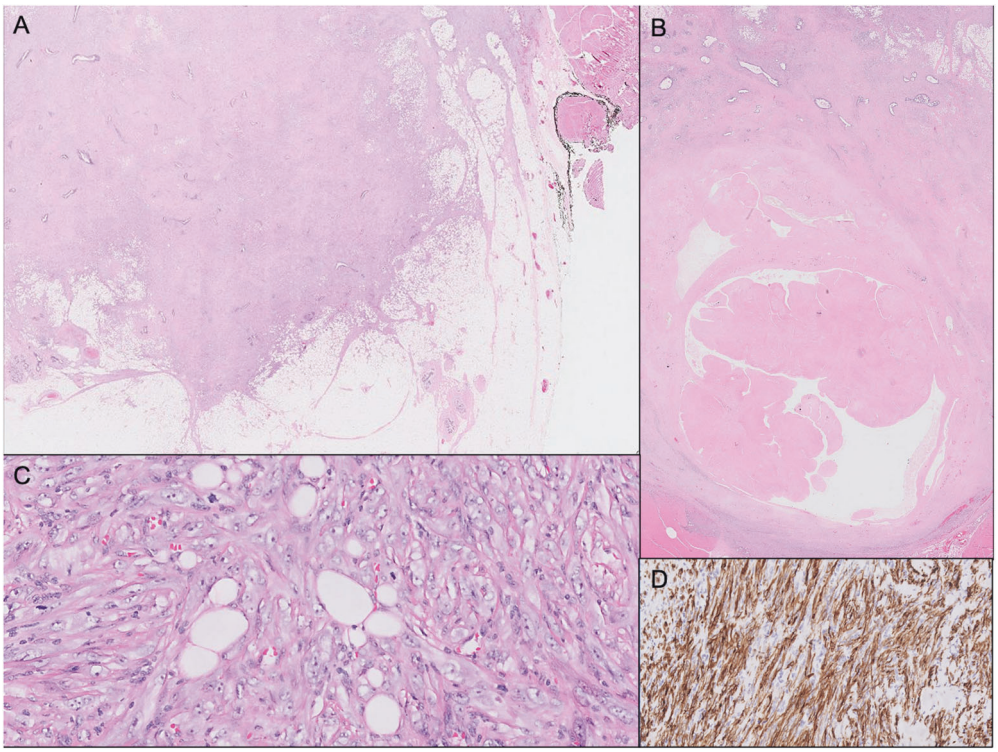

Fig. 20 Spindle-cell metaplastic carcinoma. a Low magnification of an irregular tumour composed of spindle cells. **b** Tumour encircles an infarcted fibroepithelial tumour. **c** High magnification of malignant spindle cells with obvious nuclear atypia and mitoses. **d** Immunohistochemistry for Cam5.2 shows diffuse positivity of the spindle cells.

The distinction between sarcoma and malignant phyllodes tumour may not be so critical in view of the overlapping biologic and genomic characteristics [71–73]. Primary breast sarcoma is extremely rare, and it is suggested that many of these are likely phyllodes tumours in which the epithelial component was not identified. Metastatic sarcoma is a rare occurrence, but an appropriate clinical history and workup should be able to alert one to the diagnosis. Rare entities like melanoma can be distinguished through a combination of morphological recognition and immunohistochemistry.

Pitfalls of immunohistochemistry

Epithelial markers, comprising a variety of keratins (MNF116, AE1/3, Cam5.2, 34βE12, CK5/6 and CK14), are relied upon to confirm the diagnosis of metaplastic spindle-cell carcinoma. Phyllodes tumours, however, have been discovered to express keratins as well, patchily and focally, especially in the malignant grade [74]. Similarly, p63 and p40 that are expressed in metaplastic carcinoma, are also found in malignant phyllodes tumours [75] (Fig. 21). These have implications on interpretation especially in small biopsy samples, where focal immunohistochemical expression of these markers should not automatically lead to a diagnosis of metaplastic carcinoma.

Surgical margins

The mainstay of treatment of breast phyllodes tumours is complete surgical excision with negative margins [51]. The questions often posed are whether all breast phyllodes tumours have to be widely excised, and if so, what is an optimal surgical margin width. Reports have used 1, 10 and >10 mm as surgical margin distances, and found variable correlation with recurrences [51]. A meta-analysis reported positive surgical margins to be associated with local recurrence in malignant phyllodes tumours, with a trend for increased local recurrence in benign and borderline tumours [76]. An overall local recurrence rate of 20.4% was documented for borderline and malignant phyllodes tumours that were subjected to breast conserving surgery with negative margins, when data of various studies were combined [77]. Hence, a direct association between margin status and local recurrence remains uncertain. There is increasing evidence that benign tumours may not need to be widely excised (Table 3), with low recurrence rates observed after

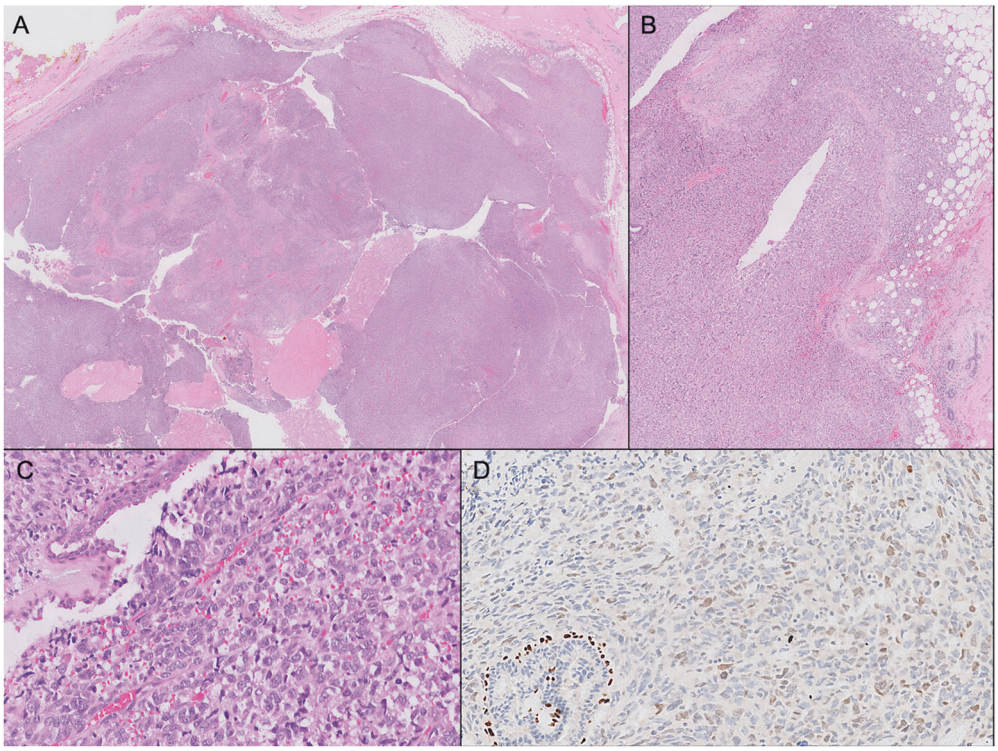

Fig. 21 Malignant phyllodes tumour with stromal p63 staining. a Low magnification of the tumour. **b** Malignant cells extending into adipose tissue. **c** High magnification of malignant stromal cells, with a short stretch of benign epithelium. **d** Immunohistochemistry for p63 shows patchy and weak nuclear reactivity in the stromal cells.

enucleation without negative margins [78–82]. Recurrent and malignant tumours, however, would require complete excision, and most authors would advocate that borderline tumours are widely excised as well. As there is no universal agreement on what constitutes a clear margin, a consensus review suggested that positive margins be regarded as tumour that extends to ink, or <1 mm away [51].

The role of adjuvant therapy is not established. While malignant and most borderline tumours may be offered radiotherapy, administration of systemic chemotherapy is considered on individual cases.

Molecular genetics

In 2014, recurrent *MED12* mutations were reported in a series of fibroadenomas, found only within the stromal component [83]. Prior to this discovery, fibroadenomas were regarded as genomically quiescent with only sporadic reports of molecular changes [84]. *MED12* mutations were subsequently soon documented in phyllodes tumours (Table 4) [2, 3, 12, 22, 23, 33, 37, 83, 85–103]. *MED12* mutations were previously described only in the uterine leiomyoma, a benign tumour that is hormonally linked, extrapolating to a possible hormonal aetiology for the fibroadenoma and phyllodes tumour as well. *MED12* is a gene located on the X chromosome, whose functions are shown in Fig. 22 [104, 105].

The studies led to a proposed pathogenesis for phyllodes tumours through the *MED12* pathway, whereby mutations in the *MED12* gene initiate the development of fibroadenoma, and progressive acquisition of additional gene abnormalities leads to the formation of phyllodes tumours, with cancer driver gene derangements being associated with borderline and malignant tumours. A *MED12* wild-type progression pathway is also proposed (Fig. 23). The event triggering the progression from fibroadenoma to phyllodes tumour is exceptionally rare, in light of the frequency of fibroadenomas and the rarity of phyllodes tumours.

Apart from insights into pathogenesis, these genomic discoveries augment grading of phyllodes tumours and have potential clinical relevance by enhancing diagnoses. Phyllodes tumour may be differentiated from fibroadenoma with the presence of *TERT* promoter mutations [93], which are rarely encountered in fibroadenoma. The separation from other spindle-cell tumours may also be assisted through molecular interrogation, with presence of *MED12* mutations leaning towards phyllodes tumour and away from metaplastic carcinoma [106, 107]. Discovery of candidate therapeutic targets in borderline/malignant phyllodes tumours such as *PIK3CA* activating mutations and *EGFR*

Table 3 Summary of studies on surgery and margin status, with particular reference to benign phyllodes tumours (PTs).

Author (Ref.)	No. of cases	Summary of key findings
Tan et al. [78]	$N = 37$ (Benign = 22, borderline = 9, malignant = 6)	• Tumour grade was not associated with age, tumour size, surgical margins, number of recurrences, time interval to recurrence or probability of malignant recurrence. • Histology of recurrent tumour was similar to primary tumour in most cases. Upstaging to malignant PT occurred in 19% of patients but no significant predictive factor was found. • It may be satisfactory for benign and borderline PTs to be excised without sufficient surgical margins, but not for malignant PTs.
Borhani-Khomani et al. [79]	$N = 479$ (Benign = 354, borderline = 89, uncertain = 6, possibly PT = 30)	• No correlation between resection margins and risk of recurrence for benign and borderline PTs. • About 13% of benign and borderline PTs did not have clear margins, but less than 10% experienced local recurrence. • 30 (6.3%) cases recurred, of which 23 were similar or lower grade compared with the primary PT. • Wide local excision may not be necessary for non-malignant PTs.
Cowan et al. [80]	$N = 90$ (Benign = 52, borderline = 19, FA with phyllodal features = 19)	• Cases of FA with phyllodal features were more likely to have positive. surgical margins but less likely to undergo re-excision compared with benign or borderline PT. • No significant association between surgical margins and recurrence rates. • No significant difference in recurrence rates of cases with initial negative margins and those with positive margins regardless of whether re-excision was performed for positive margins. • Length of positive margins did not predict recurrence. • Low-grade FELs had low risk of recurrence regardless of margin status and most may be conservatively managed with close follow-up and timely re-excisions.
Moutte et al. [81]	$N = 76$ (Benign = 67, borderline = 9)	• Of 72 patients with margin information, 7 had positive margins. No further surgery was performed except in three patients who relapsed. • Among 65 with negative margins, 46 had margins <1 mm. No further surgery was performed to widen margins. • Local recurrence rate (4%) did not surpass what was reported in literature. • Re-excision for close/positive margins can be omitted for carefully selected patients with benign PTs but instead followed up closely.
Moo et al. [82]	$N = 246$ (Benign = 216, borderline/malignant = 30)	• For benign PTs, of the 152 with close or positive margins, 67 (44%) underwent re-excision while 85 (56%) were put under observation. There was no statistically significant difference in recurrence rates between these groups. • All recurrences were benign and underwent wide excision. • Routine re-excision for wider margins may not be required for benign PTs but instead be followed up closely.

FA fibroadenoma, *FEL* fibroepithelial lesions.

Table 4 Summary of publications on MED12 in fibroepithelial tumours.

No.	Author, journal	No. of cases	Assay	Findings
1	Lim et al. Nat Genet. [83]	98 FAs	Exome and targeted sequencing	Highly frequent *MED12* exon 2 mutations (58/98, 59%) in FAs, with 71% of mutations occurring in codon 44. Mutations present in stromal but not epithelial mammary cells.
2	Cani et al. Mol Cancer Res. [85]	15 PTs	Targeted sequencing	*MED12* was mutated in 10/15 samples. There was no significant difference in the presence of *MED12* mutations between tumours of different histologic grade (benign 4/5, borderline 4/5, malignant 2/5, Fisher's exact test, $p = 0.5$).
3	Yoshida et al. Br J Cancer. [86]	58 FAs 46 PTs	Sequencing	*MED12* mutations were detected in 37 out of 46 PTs (80%). The prevalence of *MED12* mutations was similar among benign (15/18, 83%), borderline (12/15, 80%) and malignant tumours (10/13, 77%). *MED12* mutations were also identified in 36 of 58 FAs (62%). The mutations were frequent among intracanalicular-type (24/32, 75%) and complex-type lesions (4/6, 67%), but were significantly less common among the pericanalicular-type lesions (8/20, 40%).
4	Mishima et al. Breast Cancer Res Treat. [2]	58 FAs 27 PTs	Targeted sequencing	Frequency of *MED12* mutant tumours was significantly higher ($p = 0.016$) in PTs (74.1%) than in FAs (46.6%). As for FAs, this frequency was significantly higher ($p = 0.001$) for intracanalicular type (69.0%) than for other histological subtypes such as pericanalicular, organoid and mastopathic types (24.1%). Stromal cells, but not epithelial cells, harboured *MED12* mutations.
5	Nagasawa et al. Cancer Med. [87]	9 FAs 11 PTs	Sanger sequencing	Six mutations in FAs (6/9, 67%), and five mutations in PTs (5/11, 45%) were observed.
6	Pfarr et al. Genes Chromosomes Cancer. [3]	39 FELs	Sanger sequencing	62% of FAs harboured mutated *MED12*, with intracanalicular FAs being the most frequently mutated histological subtype (82%). 8/11 of benign PTs had *MED12* mutations while only 1/5 of malignant phyllodes tumours showed mutations in exon 2 of *MED12*.
7	Ng et al. J Clin Pathol. [88]	112 PTs	Targeted sequencing	There were 66 benign, 32 borderline and 14 malignant tumours, with 43 (65.1%), 21 (65.6%) and 6 (42.8%) disclosing *MED12* mutations respectively. Patients with PTs that harboured *MED12* mutations experienced improved disease-free survivals, with higher recurrence likelihood in those without *MED12* mutations (HR 9.99, 95% CIs 1.55–64.42, $p = 0.015$).
8	Yoshida et al. Br J Cancer. [89]	58 FAs 46 PTs	Sequencing	*TERT* promoter mutations were detected in 30 of 46 PTs (65%) and in 4 of 58 FAs. All but one *TERT* promoter-mutated tumour also contained *MED12* mutations. All four FAs with *TERT* promoter mutations also possessed *MED12* mutations.
9	Tan et al. Nat Genet. [90]	100 FELs	Exome and targeted sequencing	Frequent mutations of *MED12* (73%) identified in all subtypes (81%, 82% and 62% of FAs, benign, borderline and malignant PTs, respectively).
10	Piscuoglio et al. Histopathology. [91]	26 FAs 25 Benign PTs 9 Borderline PTs 13 Malignant PTs	Sanger sequencing	*MED12* exon 2 somatic mutations were found in 65%, 88%, 78% and 8% of FAs, benign PTs, borderline PTs and malignant PTs, respectively.
11	Lien et al. Histopathology. [92]	121 PTs and FAs	Direct sequencing	*MED12* mutations were found in 71.4% of PTs, and in 47.1%, 52.6% and 50.0% of complex FAs, juvenile FAs and tubular adenomas, respectively, and the frequency and mutation patterns were similar between FA variants and usual FAs.

Table 4 (continued)

No.	Author, journal	No. of cases	Assay	Findings
12	Piscuoglio et al. J Pathol. [93]	6 Benign PTs 6 Borderline PTs 13 Malignant PTs	Targeted sequencing	Recurrent *MED12* mutations were found in 56% of PTs.
13	Yoon et al. Genes Chromosomes Cancer. [94]	176 PTs: 49 Benign 49 Borderline 78 Malignant	Sanger sequencing and IHC	Significant difference in the frequency of *MED12* mutations was found according to histologic grade (71.4% of benign PTs, 51% of borderline PTs, 26.9% of malignant PTs; $p < 0.001$). MED12 protein expression was not correlated with *MED12* mutation status. Patients with malignant PTs that harboured *MED12* mutations demonstrated improved disease-free survival (DFS) compared with those without *MED12* mutation ($p = 0.07$).
14	Tan et al. J Clin Pathol. [95]	100 FAs 132 PTs	IHC	*MED12* mutation was significantly associated with high MED12 protein expression (H-score > 150) in the stroma ($p = 0.029$), but not in the epithelium. It was not associated with ERα and ERβ protein expression in both stroma and epithelium. MED12 protein expression was significantly correlated with ERα in epithelial ($p = 0.007$) and ERβ in stromal ($p = 0.049$) components. MED12 was not significantly different between FAs and PTs.
15	Liu et al. Mod Pathol. [37]	10 Malignant PTs	Targeted sequencing	30% of malignant PTs harboured *MED12* mutations (3/10).
16	Piscuoglio et al. NPJ Breast Cancer. [96]	Occurring in same patient: 3 FAs 1 Benign PT 1 Malignant PT	Targeted sequencing	One FA and the benign PT harboured a *MED12* Gly44Val mutation, whereas another FA and the malignant PT displayed a *MED12* Gly44Asp mutation. The remaining FA had an independent distinct *MED12* Gly44Cys mutation. A formal clonality analysis suggested a clonal relationship between the FELs with identical *MED12* mutations ($p < 0.05$).
17	Laé et al. Oncotarget. [97]	10 FAs 83 PTs	Sanger sequencing and IHC	High prevalence of *MED12* mutations in 49.4% (41/83) of PTs and 70% (7/10) of FAs. *MED12* mutations were more frequent in benign (14/24, 58.3%) and borderline PTs (19/30, 63.3%) compared with malignant PTs (8/29, 27.6%) ($p = 0.0036$). Nuclear expression of MED12 protein was observed in the stromal-cell component of 46/57 PTs (80.7%). No correlation was observed between *MED12* mutation status and *MED12* in the stroma, and ER and PR in the epithelial component of PTs.
18	Nozad et al. Breast Cancer Res Treat. [98]	24 Malignant PTs	Targeted sequencing	Frequency of *MED12* mutations was 45.8%.
19	Pareja et al. NPJ Breast Cancer. [99]	16 Borderline/ malignant PTs	Targeted sequencing	Seven PTs with FA-like areas and nine PTs without FA-like areas were previously subjected to sequencing. *MED12* exon 2 mutations were significantly more frequent in tumours with FA-like areas (71 vs. 11%).
20	Garcia-Dios et al. Br J Cancer. [100]	19 FAs 26 Benign PTs 22 Borderline PTs 27 malignant PTs	Sanger sequencing	*MED12* mutations occurred in 21%, 54%, 27% and 22% of FAs, benign, borderline and malignant PTs, respectively. *MED12* mutations were more common in benign PTs compared with malignant/borderline ($p = 0.02$, Fisher's Exact Test).
21	Kim et al. Transl Oncol. [101]	3 Benign PTs 1 Borderline PT 13 Malignant PTs	Targeted sequencing	*MED12* mutations were frequently detected (11 of 17, 64.7%).

Table 4 (continued)

No.	Author, journal	No. of cases	Assay	Findings
22	Tay et al. Histopathology. [22]	43 FAs	Targeted sequencing	Twenty-five conventional and seventeen juvenile fibroadenomas were studied, with *MED12* mutations found in 53.8% and 35% of the tumours, respectively. Tumours with *MED12* mutations incidentally had a significantly higher stromal mitotic count compared with those without.
23	Darooei et al. J Cell Biochem. [102]	80 FAs 20 IBCs	Sanger sequencing	40% of FAs had *MED12* mutations encompassing exon 2.
24	Pareja et al. J Clin Pathol. [23]	21 FAs 8 Benign PTs	Sanger sequencing	*MED12* exon 2 mutations were identified in 62% and 88% of FAs and benign PTs in juvenile patients, respectively, and no *TERT* promoter hotspot mutations. Majority were in-frame deletions (60%).
25	Xie et al. Cancer Med. [103]	12 FAs	Exome sequencing	Six nonsynonymous/frameshift somatic *MED12* mutations and one CNV were detected.
26	Sim et al. BMC Med Genomics. [33]	167 FAs 24 Benign PTs 14 Borderline PTs 6 Malignant PTs	Targeted sequencing	*MED12* was mutated in 45% of FAs and 61% of PTs (67% of benign, 64% of borderline and 33% of malignant PTs, respectively, $p = 0.063$).
27	Md Nasir et al. J Pathol. [12]	303 FAs 493 PTs: 322 Benign 117 Borderline 54 Malignant	Targeted sequencing	45% of FAs and 56% of PTs harboured *MED12* mutations (62% of benign, 50% of borderline and 37% of malignant PTs, respectively, $p = 0.0017$).

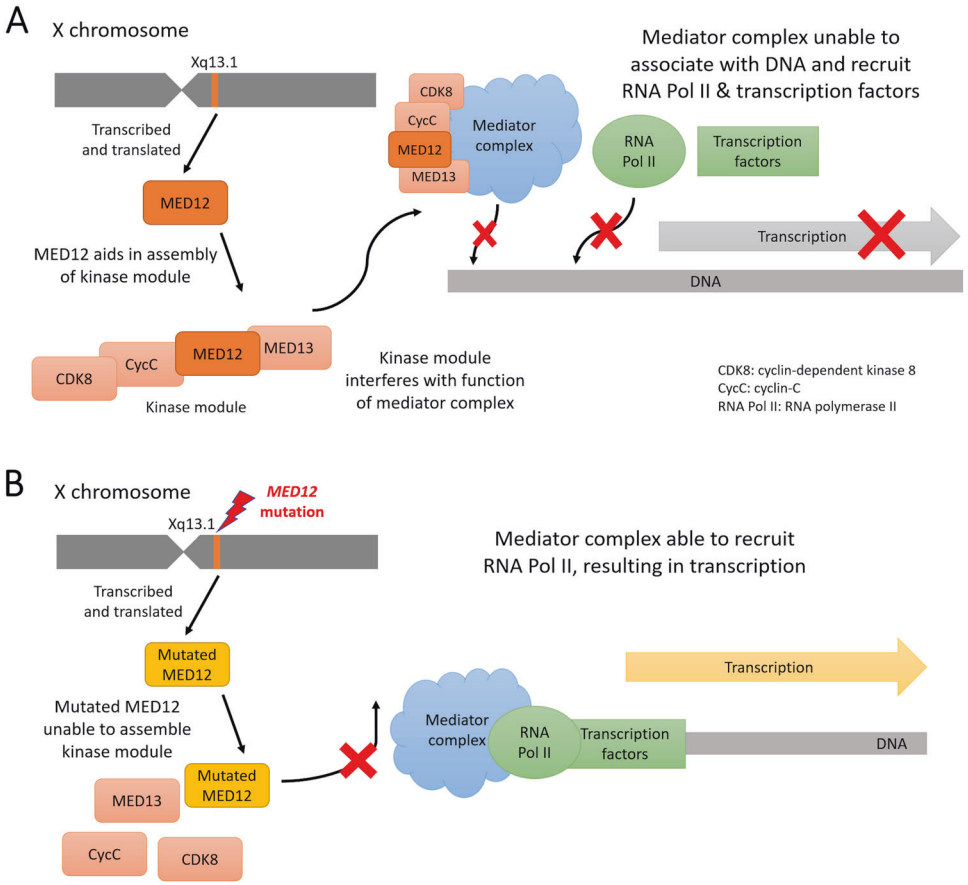

Fig. 22 Structure and function of wild-type and mutant *MED12* gene. a The Mediator complex initiates transcription through binding with DNA and recruiting transcription factors and RNA polymerase II (RNA Pol II). A kinase module comprising cyclin-dependent kinase 8 (*CDK8*), *Cyclin C*, *MED12* and *MED13* regulates the Mediator complex by interfering in its association with RNA Pol II to repress transcription. *MED12* is essential for assembly of the kinase module, binding *Cyclin C-CDK8* to core Mediator and stimulating kinase activity. **b** Mutation in *MED12* leads to transcriptional misregulation as *Cyclin C-CDK8* binding and activation are compromised.

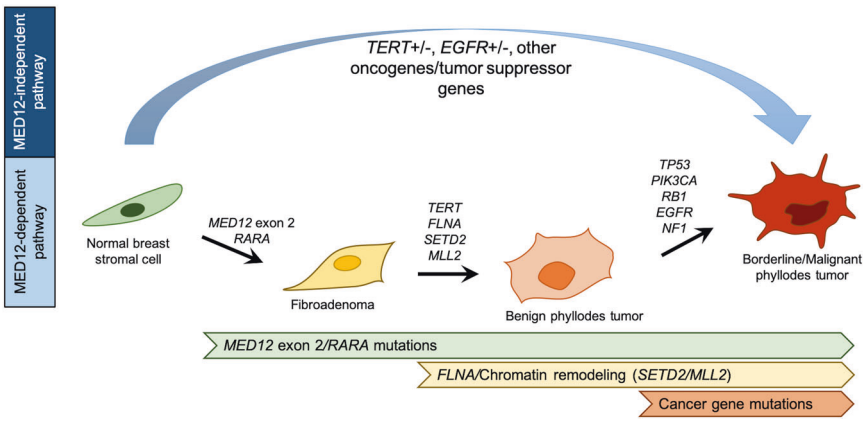

Fig. 23 *MED12*-dependent and -independent progression pathways of fibroepithelial tumours.

amplifications may open additional treatment avenues. Prognostically, *MED12* mutations are correlated with improved disease-free survival [88, 94].

Conclusion

In summary, fibroadenomas and phyllodes are a fascinating group of fibroepithelial tumours that share not only morphological appearances but also genomic changes that underpin their pathogenesis. Continued work to refine the prediction of recurrences, identify which tumours would recur with grade progression, as well as triggers of metastases, is warranted. Distinction from histological mimics requires a combination of morphological and adjunctive studies. The roles of the epithelium and epithelial–stromal interaction in the aetiology and pathogenesis remain relatively unexplored. As phyllodes tumours are uncommon, especially borderline and malignant grades, collective international efforts for combining knowledge will go a

long way towards bridging information gaps for effective treatment.

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Compliance with ethical standards

Conflict of interest The author declares no conflict of interest in this review.

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