FIBROEPITHELIAL LESIONS OF THE BREAST
UCSF Current Issues in Anatomic Pathology 2015
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Assistant Professor

OUTLINE

• FIBROADENOMA
• PHYLLODES TUMOR
• DIFFERENTIAL DIAGNOSIS
  — CELLULAR FIBROEPITHELIAL LESIONS
  — MALIGNANT PHYLLODES TUMORS
  — EXCISION VERSUS CORE NEEDLE BIOPSY
  — IMMUNOHISTOCHEMISTRY

FIBROADENOMA

• Very common
  — Most common fibroepithelial lesions
  — Most common benign tumors of the breast

• Broad age group
  — Incidence highest in women <30 years old
  — Can occur at any age (18.5% of women >40 years old in Breast Cancer Surveillance Consortium)

• Predisposing factors
  — No known inherited genetic alterations but risk in some families
  — Hormonal influence
    • Rare in men but associated with gynecomastia, exogenous hormones, drugs
    • Cyclosporin A (organ transplant)
    • Carney complex (myxoid fibroadenomas)

FIBROADENOMA

• Solitary, mobile, “rubbery” and painless palpable mass
• Non-palpable, mammographically detected
• Calcifications (hyalinized fibroadenomas)
• Rarely pain and/or bloody nipple discharge
  — Infarction
  — Pregnancy, prior aspiration procedure, spontaneous

• Often <3 cm but larger tumors not uncommon
• ‘Giant fibroadenomas’ up to 20 cm
  — Larger tumors in adolescents (juvenile fibroadenoma)
Intracanalicular Pericanalicular Mixed
Usual-type Hyalinized
Myxoid Mixed
Myxoid FA  Mucinous carcinoma

- Myxoid fibroadenoma may mimic invasive mucinous carcinoma
- Misdiagnosis on imaging
  - 16/17 myxoid fibroadenomas with rapid growth or size >3 cm misdiagnosed as mucinous carcinoma on ultrasound
  
  Yamaguchi Human Pathology 2011;42:419-423

- Misdiagnosis on FNA and core biopsy
  

COMPLEX FIBROADENOMA

- Sclerosing adenosis, papillary apocrine metaplasia, cysts >3mm or epithelial calcifications

Sklair-Levy M et al. AJR 2008;190(1):214-8

COMPLEX FIBROADENOMA

- Managed like typical FA in absence of atypia or rad-path discordance
- We do not use this term in diagnosis

Skair-Levy M et al. AJR 2008;190(1):214-8
CELLULAR FIBROADENOMA

- Focal or diffuse mildly increased stromal cellularity without stromal atypia
  - No threshold criteria for defining hypercellularity
  - Stromal atypia is subjective
- Stromal mitotic figures may be present (up to 2 MF/10 HPF typically acceptable)
- Overlapping features with benign phyllodes tumors
- Uniform cellularity and epithelial:stromal distribution

JUVENILE FIBROADENOMA

- More common in adolescents and women <20 years old
  - Usual-type fibroadenoma most common in all age groups
- May mimic phyllodes tumor
  - Rapid growth, large size, histologic features
- Cellular stroma with pericanalicular growth
- Stromal mitotic activity may be present
- No stromal cytologic atypia
- Uniform cellularity and epithelial:stromal distribution
- ‘Gynecomastoid’ usual ductal hyperplasia
- Excision with preservation of adjacent breast
Atypia or carcinoma may involve fibroadenomas primarily or secondarily:
- ALH/LCIS most common
- ADH/DCIS
- Invasive carcinoma

Phyllodes Tumors

- Rare
  - <1% primary breast tumors
  - <2.5% fibroepithelial lesions in tertiary centers

- Age 40-50 years (but wide range, adolescence to 90)
  - 15-20 years older than FA, on average
  - Tumors in adolescents often benign

- More common in Asian and Latina women
  - May present at younger age in this group

- Li-Fraumeni Syndrome (p53 mutations) predisposed
PHYLLODES TUMORS

- Present as mass lesion
  - Rapidly growing or accelerated growth of previously stable lesion

- 4-5 cm in size, but wide range (<3-20+ cm)
  - Smaller lesions increasingly detected by screening

- Not reliably distinguished from fibroadenoma by imaging

PHYLLODES TUMORS

“fibroepithelial neoplasms, histologically resembling intracanalicular fibroadenomas, characterized by a double-layered epithelial component arranged in clefts surrounded by a hypercellular stromal/mesenchymal component which in combination elaborate leaf-like structures”

PHYLLODES TUMOR DIAGNOSIS BASED ON A CONSTELLATION OF FEATURES

- Increased stromal cellularity*
- Leaf-like growth ± periductal stromal condensation
- Stromal heterogeneity
  - +/- mitotic activity*
  - +/- infiltrative border*
  - +/- stromal overgrowth*
  - +/- stromal cytologic atypia*
  - +/- malignant heterologous stroma*

* Used to establish grade

LEAF-LIKE GROWTH
INTRALOBULAR STROMAL COMPRESSION OF FIBROADENOMA

STROMAL HETEROGENEITY

GRADING PHYLLODES TUMORS

<table>
<thead>
<tr>
<th></th>
<th>BENIGN</th>
<th>BORDERLINE</th>
<th>MALIGNANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUMOR BORDER</td>
<td>Well-defined</td>
<td>Well-defined, may be focally infiltrative</td>
<td>Infiltrative</td>
</tr>
<tr>
<td>STROMAL CELLULARITY</td>
<td>Mild, non-uniform or diffuse</td>
<td>Moderate, non-uniform or diffuse</td>
<td>Marked, usually diffuse</td>
</tr>
<tr>
<td>STROMAL ATYPIA</td>
<td>None or mild</td>
<td>Mild or moderate</td>
<td>Marked</td>
</tr>
<tr>
<td>MITOTIC ACTIVITY</td>
<td>&lt;5 per 10 HPF</td>
<td>5-9 per 10 HPF</td>
<td>≥10 per 10 HPF</td>
</tr>
<tr>
<td>STROMAL OVERGROWTH</td>
<td>Absent</td>
<td>Absent or focal</td>
<td>Often present</td>
</tr>
<tr>
<td>MALIGNANT HETEROLOGOUS ELEMENTS</td>
<td>Absent</td>
<td>Absent</td>
<td>May be present</td>
</tr>
</tbody>
</table>

Adapted from WHO Classification of Tumours of the Breast, 4th ed. 2012
MALIGNANT PHYLLODES TUMOR

Stromal overgrowth (4x low power field) often diffuse

INFIltrATIVE BORDERS
MALIGNANT HETEROLOGOUS STROMA

Most commonly liposarcomatous

SATB2 is a useful marker of osseous differentiation

BORDERLINE PHYLLODES TUMOR

SATB2
Phyllodes tumor histologic grade predicts local recurrence

Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins

Phee Wee Tan1,2, Aue-An Y. Ooi3, Wai Jin Tan1, Min Min Myint Tha1,4, Inny Boonmee1, Hui Kua Li1, Wen Yee Choy2, Mei-Him Tan1,5. The Phyllodes Tumor Network Singapore

- 605 phyllodes tumors (diagnosed over 18 years, 1992-2010)
- 552 patients with clinical follow-up
- 29.8/24.6 months mean/median time to recurrence

Table 2 Relationship of grade of phyllodes tumour with recurrence (p<0.001)

<table>
<thead>
<tr>
<th>Grade of phyllodes tumour</th>
<th>Absent</th>
<th>Present</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>392 (98.1%)</td>
<td>48 (10.9%)</td>
<td>440 (100%)</td>
</tr>
<tr>
<td>Borderline</td>
<td>95 (85.6%)</td>
<td>16 (14.4%)</td>
<td>111 (100%)</td>
</tr>
<tr>
<td>Malignant</td>
<td>31 (70.4%)</td>
<td>15 (29.6%)</td>
<td>46 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>525 (88.8%)</td>
<td>88 (13.2%)</td>
<td>613 (100%)</td>
</tr>
</tbody>
</table>


Features predictive of phyllodes tumor recurrence

A. M.O.S. criteria

NOMOGRAM FOR PREDICTING PHYLLODES TUMOR RECURRENCE FREE SURVIVAL

A. 
M. 
O. 
S. 

* Positive margin status best predictor of recurrence*

NOMOGRAM FOR PREDICTING PHYLLODES TUMOR RECURRENCE FREE SURVIVAL

REQUIRES ADDITIONAL VALIDATION IN OTHER POPULATIONS

Tan PH et al J Clin Pathol 2012;65:69-76
**PHYLLODES TUMOR: HISTOLOGIC GRADE AND PROGNOSIS**

<table>
<thead>
<tr>
<th>Benign</th>
<th>Borderline</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence*</td>
<td>4-17%</td>
<td>14-25%</td>
</tr>
</tbody>
</table>

* Margin status remains the best predictor of local recurrence

- **PHYLLODES TUMOR: HISTOLOGIC GRADE AND PROGNOSIS**

<table>
<thead>
<tr>
<th>Benign</th>
<th>Borderline</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of phyllodes</td>
<td>65-70%</td>
<td>15-20%</td>
</tr>
<tr>
<td>Metastasis** (&lt;10% overall)</td>
<td>0%</td>
<td>0-4%</td>
</tr>
</tbody>
</table>

**Essentially only malignant tumors metastasize**

- **PHYLLODES TUMOR: HISTOLOGIC GRADE AND PROGNOSIS**

<table>
<thead>
<tr>
<th>Original tumour grade</th>
<th>Recurrent tumour grade</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>Benign</td>
<td>27</td>
</tr>
<tr>
<td>Benign</td>
<td>Borderline</td>
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<td>Borderline</td>
<td>Malignant</td>
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<tr>
<td>Borderline</td>
<td>Benign</td>
<td>4</td>
</tr>
<tr>
<td>Malignant</td>
<td>Malignant</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>73</td>
</tr>
</tbody>
</table>

21/48 (43.8%) initially benign tumors recurred as higher grade
2/16 (12.8%) initially borderline tumors recurred as malignant

- **PHYLLODES TUMOR: HISTOLOGIC GRADE AND PROGNOSIS**

**Phylloides Tumor:**

- **Histologic Grade and Prognosis**

  - * Margin status remains the best predictor of local recurrence
  - Other studies with similar results
    - 6-19% benign tumors reported to recur as malignant
  - Highlights importance of preventing local tumor recurrence

**Distant Phylloides Tumor Metastasis**

- Stromal overgrowth and malignant heterologous stromal elements are best predictors of distant spread
- Metastasis essentially always stromal component only
- Lung/pleura (>75%) and skeletal system most common sites
**Vulva**

**Lung**

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**PHYLLODES TUMOR TREATMENT**

- Excision with negative margins to minimize recurrence risk
  - 1 cm normal rim preferable (but no data to support this arbitrary margin width)
  - Rationale
    - Margin status primary predictor of recurrence
    - Recurrences may be of higher grade
    - Metastatic tumors may be preceded by local recurrences

- No routine role for radiation or chemotherapy

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**DIFFERENTIAL DIAGNOSIS OF FIBROEPITHELIAL LESIONS**

<table>
<thead>
<tr>
<th>Benign phyllodes</th>
<th>Fibroadenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>~45-50 (but any age)</td>
</tr>
<tr>
<td>Size</td>
<td>Few cm up to 20 cm</td>
</tr>
<tr>
<td>Growth</td>
<td>May be rapid; rapid growth of previously stable mass</td>
</tr>
</tbody>
</table>

**OVERLAP**

CLINICAL AND RADILOGIC FEATURES DO NOT RELIABLY DISTINGUISH BETWEEN PHYLLODES TUMOR AND FIBROADENOMA

<table>
<thead>
<tr>
<th>BENIGN PHYLLODES</th>
<th>FIBROADENOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaf-like architecture</td>
<td>Present, well-developed ± periductal condensation</td>
</tr>
<tr>
<td>Stromal heterogeneity</td>
<td>May be present</td>
</tr>
<tr>
<td>Distribution of epithelium and stroma</td>
<td>Often non-uniform</td>
</tr>
<tr>
<td>Stromal cellularity</td>
<td>Mild</td>
</tr>
<tr>
<td>Stromal mitoses</td>
<td>Few (0-4/10 HPF)</td>
</tr>
<tr>
<td>Cellular atypia</td>
<td>Mild</td>
</tr>
<tr>
<td>Squamous metaplasia</td>
<td>Rarely present</td>
</tr>
</tbody>
</table>
PITFALLS

1. Fibroadenomas may have focal leaf-like growth.
2. Phyllodes tumors may lack leaf-like growth.
3. Phyllodes tumors may be less cellular or mimic fibroadenomas in some areas due to heterogeneity.
4. Benign multinucleated stromal giant cells in fibroadenomas should not be mistaken for atypia.
5. Mitotic activity does not equate with phyllodes tumor.

FIBROADENOMA WITH FOCAL LEAF-LIKE GROWTH

PITFALLS

1. Fibroadenomas may have focal leaf-like growth.
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FIBROADENOMA WITH FOCAL LEAF-LIKE GROWTH
Juvenile fibroadenoma with focal leaf-like growth

PITFALLS

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2. Phyllodes tumors may lack leaf-like growth.
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4. Benign multinucleated stromal giant cells in fibroadenomas should not be mistaken for atypia.
5. Mitotic activity does not equate with phyllodes tumor.

PHYLLODES TUMOR WITHOUT LEAF-LIKE GROWTH
PITFALLS

1. Fibroadenomas may have focal leaf-like growth.
2. Phyllodes tumors may lack leaf-like growth.
3. Phyllodes tumors may be less cellular or mimic fibroadenomas in some areas due to heterogeneity.
4. Benign multinucleated stromal giant cells in fibroadenomas should not be mistaken for atypia.
5. Mitotic activity does not equate with phyllodes tumor.

PHYLLODES TUMOR HETEROGENEITY

* Adequate sampling required

CNB DIAGNOSIS: FIBROADENOMATOUS CHANGE
**PHYLLODES TUMOR HETEROGENEITY**

1. Fibroadenomas may have focal leaf-like growth.
2. Phyllodes tumors may lack leaf-like growth.
3. Phyllodes tumors may be less cellular or mimic fibroadenomas in some areas due to heterogeneity.
4. Benign multinucleated stromal giant cells in fibroadenomas should not be mistaken for atypia.
5. Mitotic activity does not equate with phyllodes tumor.

**PITFALLS**

- Benign multinucleated stromal giant cells
- Atypical stromal cells of phyllodes tumor

**PITFALLS**

1. Fibroadenomas may have focal leaf-like growth.
2. Phyllodes tumors may lack leaf-like growth.
3. Phyllodes tumors may be less cellular or mimic fibroadenomas in some areas due to heterogeneity.
4. Benign multinucleated stromal giant cells in fibroadenomas should not be mistaken for atypia.
5. Mitotic activity does not equate with phyllodes tumor.

- Overlap with cellular/juvenile fibroadenomas
21 pre-selected challenging cellular fibroepithelial lesions separately reviewed by 10 breast pathologists (1-2 slides per case)

- Uniform agreement in only 2 cases (9.5%): 1 fibroadenoma, 1 phyllodes
- 4 (19%) cases equally split between cellular fibroadenoma and phyllodes
- 43% of cases, diagnoses ranged from fibroadenoma to borderline phyllodes

- Some fibroepithelial lesions cannot be easily classified as fibroadenoma or phyllodes tumor

- “Diagnosis of fibroadenoma is preferable when there is histological ambiguity to avoid overtreatment”.

Our approach:

“Cellular fibroepithelial lesion; see comment.”

- Describe features and diagnostic difficulty/ambiguity
- Relate low recurrence potential, especially if margins frankly positive
Optimize cosmesis and avoid additional surgery

**PHYLLODES TUMOR**
- Excision with rim of normal tissue
- Recurrence potential

**FIBROADENOMA**
- Enucleation
- No (?) recurrence potential

Features of cellular fibroepithelial lesions on core biopsy that may predict phyllodes tumor???
- Increased stromal cellularity (marked>moderate)
- Increased mitotic activity (>2 MF/10 HPF)
- Stromal heterogeneity
- Tissue fragmentation
- Adipose tissue within lesional stroma
- Stromal expansion (no epithelium in 100x field)
- Ill-defined borders
- Stromal cell atypia
- Ki-67 index ≥5%
- Ki-67 6% (range 10-18%) in PT versus 1.6% (range 0-4.4%) in FA

-favor phyllodes tumor-

References:
Lee AHS et al. Histopathology 2007;51:336-244
Tsang AK et al. Histopathology. 2011;59(4):600-8
Features of cellular fibroepithelial lesions on core biopsy that may predict phyllodes tumor??

- Increased stromal cellularity (marked>moderate)
- Increased mitotic activity (>2 MF/10 HPF)
- Stromal heterogeneity
  - Tissue fragmentation
  - Adipose tissue within lesional stroma
  - Stromal expansion (no epithelium in 100x field)
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  - Ki-67 index ≥5%
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**REFERENCES**

Lee AHS et al. Histopathology 2007; 51: 336-244
Tsaung AK et al Histopathology. 2011;58(4):400-8

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**DIAGNOSTIC CRITERIA**

- No histologic features can reliably predict phyllodes tumor over cellular fibroadenoma on CNB
  - Cellularity and mitotic activity most useful
  - Stromal heterogeneity

- Constellation of features may favor phyllodes tumor in some cases

**DESCRIPTIVE DIAGNOSIS:**

FIBROEPITHELIAL LESION WITH CELLULAR STROMA

- Recommend excision for final classification
- 41% probability of PT on excision

**DIFFERENTIAL DIAGNOSIS:**

- Phyllodes Tumor
- Benign
- Borderline
- Malignant
- Fibroadenoma
- Adipose metaplasia
- Carcinoma
- Sarcoma

**MAY BE PROBLEMATIC IN EXCISIONS AND CORE BIOPSIES**
AMPLE TUMOR SAMPLING TO IDENTIFY EPITHELIAL COMPONENT
DIFFERENTIAL DIAGNOSIS

Metaplastic carcinoma
Phyllodes tumor
Sarcoma

Potential neoadjuvant chemotherapy
Sentinel lymph node
Surgical management
No sentinel lymph node
Sarcoma

KERATIN AND p63 EXPRESSION IN PHYLLODES TUMORS

<table>
<thead>
<tr>
<th></th>
<th>CK+ PT (%)</th>
<th>CK+ MPT (%)</th>
<th>No. CK antibodies</th>
<th>p63+ PT (%)</th>
<th>p63+ MPT (%)</th>
<th>PT (n)</th>
<th>Malignant PT (n)</th>
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<tr>
<td>Auger M (1989)</td>
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<td>14</td>
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<td>44</td>
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<td>0</td>
<td>109</td>
<td>9</td>
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<td>21</td>
<td>3</td>
<td>24</td>
<td>57</td>
<td>34</td>
<td>14</td>
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</tbody>
</table>

Focal (1-5% of stromal cells) CK and p63 staining in all cases

Phyllodes tumors may express cytokeratins and/or p63
- Expression is typically focal or patchy (<5%)

Cytokeratin or p63 expression, especially in core biopsies, cannot be used to exclude phyllodes tumor
- Strong, diffuse CK staining may favor metaplastic carcinoma
**CD34 in Fibroepithelial Lesions**

<table>
<thead>
<tr>
<th></th>
<th>FA</th>
<th>PT</th>
<th>Benign PT</th>
<th>Borderline PT</th>
<th>Malignant PT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverman (1996)</td>
<td>100 (10)</td>
<td>71 (7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen (2000)*</td>
<td>-</td>
<td>47 (29)</td>
<td>86 (7)</td>
<td>-</td>
<td>25 (13)</td>
</tr>
<tr>
<td>Moore (2001) **</td>
<td>100 (15)</td>
<td>100 (20)</td>
<td>100 (20)</td>
<td>100 (20)</td>
<td>100 (20)</td>
</tr>
<tr>
<td>Noronha (2011)***</td>
<td>-</td>
<td>76 (33)</td>
<td>86 (21)</td>
<td>190 (5)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Chia (2012)</td>
<td>-</td>
<td>73 (37)</td>
<td>79 (30)</td>
<td>67 (30)</td>
<td>45 (9)</td>
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<tr>
<td>Ko (2014)†††</td>
<td>-</td>
<td>34 (15)</td>
<td>88 (36)</td>
<td>83 (48)</td>
<td>6 (3)</td>
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<tr>
<td>Cimino-Mathews (2014)‡‡‡</td>
<td>100 (10)</td>
<td>22 (14)</td>
<td>100 (10)</td>
<td>100 (10)</td>
<td>57 (14)</td>
</tr>
</tbody>
</table>

* alternate grading scheme  
** patchy staining in all PT; median 40% cells staining in malignant PT vs 80% cells staining in benign/borderline PT  
*** TMA  
††† focal staining only (<5% cells)

**Spindle cell carcinoma are essentially always CD34 negative**

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**CD34**

**EXCISION – MALIGNANT PT**

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**MALIGNANT PHYLLODES TUMOR**
• CD34 positivity essentially excludes metaplastic carcinoma

• Malignant phyllodes tumors are often CD34 negative
  – CD34 expression is negatively correlated with phyllodes tumor grade
  – If positive, staining in malignant tumors is often focal or patchy (<5%)

Aberrant nuclear β-catenin can be seen in both phyllodes tumor and metaplastic carcinoma

  – 82-100% of mammary fibromatosis
  – 23% metaplastic carcinomas
  – 72-83% of phyllodes tumors

  • More common in benign than malignant PT
    – 94% benign vs 57% malignant PT (Lacroix-Triki et al. 2010)
    – 12.5% malignant PT (Sawyer et al. 2002)

Lacroix-Triki M et al. Modern Pathology;2010;23(11):1438-48

Excision – Malignant phyllodes tumor

Multiple keratins (AE1/3, Cam 5.2, MNF116, CK5/6) negative
SUMMARY

• **Fibroadenoma and variants**

• **Phyllodes tumor**
  – Diagnosis requires constellation of features
  – Pitfalls in diagnosis
  – Diagnosis and categorization has clinical significance
  – Some lesions may defy accurate categorization: err on conservative side

• **Core biopsy of cellular fibroepithelial lesions requires excision for definitive classification**

• **Malignant phyllodes tumor may mimic metaplastic carcinoma**
  – Additional sampling and/or immunohistochemistry may be useful
  – Core biopsy diagnosis of spindle cell neoplasm

---

### Table

<table>
<thead>
<tr>
<th>Feature</th>
<th>Phyllodes Tumor</th>
<th>Metaplastic Carcinoma</th>
<th>Fibromatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaf-like fronds</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Curvilinear ducts/epithelial clefts</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>DCIS/IDC</td>
<td>Absent (usually)</td>
<td>Maybe</td>
<td>Absent</td>
</tr>
<tr>
<td>Cytokeratin</td>
<td>Maybe (focal)</td>
<td>Maybe (focal or more diffuse)</td>
<td>Absent</td>
</tr>
<tr>
<td>p63</td>
<td>Maybe (focal)</td>
<td>Maybe (focal or more diffuse)</td>
<td>Absent</td>
</tr>
<tr>
<td>CD34</td>
<td>Maybe (benign &gt; malignant)</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Nuclear β-catenin</td>
<td>Maybe</td>
<td>Maybe (usually)</td>
<td></td>
</tr>
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