Papillary Lesions of the Breast
Laura C. Collins, M.D.
Department of Pathology
Beth Israel Deaconess Medical Center and
Harvard Medical School, Boston, MA

Question 1
Given the low power image provided on the next slide, how is this papillary lesion best classified?

a) Benign intraductal papilloma
b) Atypical papilloma
c) Papillary DCIS
d) Encapsulated papillary carcinoma

e) Solid papillary carcinoma

Question 2
Given the single image provided on the next slide, how is this papillary lesion best classified?

a) Benign intraductal papilloma
b) Atypical papilloma
c) Papillary DCIS
d) Encapsulated papillary carcinoma
e) Solid papillary carcinoma
Question 3
Which of the following statements about the papillary breast lesion depicted on the next slide is false?

a) It is most common in elderly women
b) It is associated with a high risk of lymph node metastasis
c) It may present with nipple discharge
d) It may be adequately treated with local therapy alone
e) Myoepithelial markers may be of value in arriving at the correct diagnosis

Question 4
The photograph on the next slide demonstrates an immunostain performed on an encapsulated papillary carcinoma. Which myoepithelial cell marker is depicted in this image?

a) Smooth muscle actin
b) p63
c) Smooth muscle myosin heavy chain
d) Calponin
e) Cytokeratin 5/6
Question 5
Given the images provided on the next slide, how is this papillary lesion best classified?

a) Benign intraductal papilloma
b) Atypical papilloma
c) Papillary DCIS
d) Encapsulated papillary carcinoma
e) Solid papillary carcinoma
Papillary Lesions of the Breast

- Intraductal papilloma
- Papilloma with atypia (atypical papilloma)
- Papilloma with DCIS
- Papillary DCIS
- Encapsulated papillary carcinoma
- Solid papillary carcinoma

Newer insights into encapsulated and solid papillary carcinomas
Consequences of core needle biopsy

Intraductal Papilloma

- Solitary (central) or multiple (peripheral)
- Any age; most common 50-60 yrs
- Nipple discharge and/or palpable mass
- Subsequent breast cancer risk similar for other proliferative lesions without atypia (~1.5-2x)

The importance of myoepithelial cells and myoepithelial cell immunohistochemical markers in assessment of papillary lesions
### Diagnostic Criteria for Papillary Lesions
adapted from Kraus and Neubecker, 1962

<table>
<thead>
<tr>
<th></th>
<th>Papilloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell types</td>
<td>Epithelial and myoepithelial</td>
</tr>
<tr>
<td>Cell orientation</td>
<td>Haphazard</td>
</tr>
<tr>
<td>Nuclei</td>
<td>Normochromatic</td>
</tr>
<tr>
<td>Stromal changes</td>
<td>Prominent; fibrosis with epithelial entrapment</td>
</tr>
<tr>
<td>Apocrine</td>
<td>Present</td>
</tr>
<tr>
<td>Metaplasia</td>
<td>Hyperplasia</td>
</tr>
</tbody>
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**Image Description:**
- **Image 1:** Histological image of a papillary lesion showing typical features such as papillae with fibrovascular cores and epithelial lining.
- **Image 2:** Another histological view highlighting the characteristic papillary architecture and epithelial proliferation.
Atypical Papillary Lesions

- Papilloma with atypia (atypical papilloma)
- Papilloma with DCIS
- Papillary DCIS
Atypical Papillary Lesions

The importance of myoepithelial cells and MEC markers in assessment of papillary lesions

Papilloma with Atypia

Papilloma with foci of ADH

Papilloma with limited area(s) of non-high grade DCIS

Papilloma with Atypia vs. Papilloma with DCIS

- Page et al: Size
  Atypical area > 3mm (Cancer 1996;78:258)
- Tavassoli: Proportion
  Atypical area > 1/3 (Pathol of the Breast 2nd Ed, 1999)
- Elston, Ellis & Pinder: Qualitative
  "Overt features of malignancy, no matter what the proportion"
  (The Breast, 1998)

WHO Working Group Recommendation 2012
Use size/extent criteria
- <3mm ADH
- >3mm LG DCIS
• Absence of CK 5/6 staining can help define extent of atypia

• Presence of strong, diffuse ER staining also helpful in defining extent of atypia

• ER-high/CK5-low profile predicts atypia
• ER-low/CK5-high profile characterizes non-Atypical papillary lesions

• Pitfalls:
  – Apocrine cells
  – Basal-like DCIS
  – Columnar cell change

Tse, 2010, questioned accuracy of this approach
### Diagnostic Criteria for Papillary Lesions
adapted from Kraus and Neubecker, 1962

<table>
<thead>
<tr>
<th></th>
<th>Papilloma</th>
<th>Papillary DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell types</td>
<td>Epithelial and myoepithelial</td>
<td>Epithelial; myoepithelial cells absent or scant</td>
</tr>
<tr>
<td>Cell orientation</td>
<td>Haphazard</td>
<td>Uniform, perpendicular to fibrovascular stalks</td>
</tr>
<tr>
<td>Nuclei</td>
<td>Normochromatic</td>
<td>Hyperchromatic</td>
</tr>
<tr>
<td>Stroma of papillae</td>
<td>Prominent; fibrosis with epithelial entrapment</td>
<td>Delicate</td>
</tr>
<tr>
<td>Apocrine metaplasia</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Proliferation in adjacent ducts</td>
<td>Hyperplasia</td>
<td>DCIS</td>
</tr>
</tbody>
</table>

### Papilloma with DCIS vs. Papillary DCIS

- **Papilloma with DCIS**
  - Underlying structure of benign papilloma
  - Papillae themselves not neoplastic

- **Papillary DCIS**
  - Papillae themselves part of the neoplastic process
Papillary Lesions of the Breast

- Intraductal papilloma
- Papilloma with atypia (atypical papilloma)
- Papilloma with DCIS
- Papillary DCIS
- Newer insights into encapsulated and solid papillary carcinomas

Encapsulated Papillary Carcinoma

- Considered to be a variant of DCIS
- Older women (mean age, mid 60s)
- ~50% central
- Mass, nipple discharge/bleeding
- Rounded, lobulated, circumscribed lesions on mammography
- Grossly well circumscribed
- Mean size, 2-3cm
- ~50% have adjacent DCIS (assoc. with increased local recurrence risk)
- ~1/3 of reported cases had associated invasive ca
Questions Raised

- Are “intracystic” papillary carcinomas an exception to this principle?
- Does this tell us something about the nature of lesions we have traditionally considered to be “intracystic” papillary carcinomas?
- What does this mean for clinical practice?

Myoepithelial Markers in EPC

Several studies have now demonstrated an absence of MECs in encapsulated papillary carcinomas

- Hill and Yeh, AJSP 2005
- Collins et al, AJSP 2006
- Esposito, AJCP 2009
- Wynveen, AJSP 2010
- Rakha AJSP 2011
Possible explanations

• MEC attenuated in EPCs
  – MEC demonstrated in papillomas of similar size
• MEC protein expression altered in EPCs
  – Multiple antibodies to a variety of MEC components evaluated
• EPCs are really invasive lesions
  – May be circumscribed, “encapsulated” invasive carcinomas rather than in situ carcinomas

What about the basement membrane?

Does the absence of a MEC layer define a lesion as being invasive rather than in situ?
Myoepithelial Markers in EPC

- Both studies showed reduced/absent MECs in EPC
- Both studies showed presence of collagen IV (basement membrane), albeit reduced in many cases
- ?Carcinoma in transition to invasive carcinoma


Outcome Studies

Older studies of EPCs
- Many large, requiring mastectomy
- Some pts had lymph node and/or distant metastases and/or died of disease
- At least some invasive

Metastatic Potential of Encapsulated (Intracystic) Papillary Carcinoma of the Breast: A Report of Two Cases with Axillary Lymph Node Micrometastases

Anna Marie Malligan, MB, MRCPath, and Frances P. O'Malley, MB, FRCPath

- 2 cases of encapsulated papillary carcinoma
  - 1 case with 3 micrometastatic foci in a sentinel node
  - 1 case with micrometastases in 2 of 11 axillary nodes
Outcome Studies

More recent f/u studies

Clinical outcome excellent with adequate local therapy alone (akin to DCIS)

Outcome of Patients with EPC/SPC

11 Studies, 231 patients*

<table>
<thead>
<tr>
<th>Outcome Parameter</th>
<th>#</th>
</tr>
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<tbody>
<tr>
<td>Positive ALN</td>
<td>1</td>
</tr>
<tr>
<td>Local Recurrence</td>
<td>2</td>
</tr>
<tr>
<td>Distant Mets</td>
<td>1</td>
</tr>
<tr>
<td>Died of Disease</td>
<td>0</td>
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</table>

*treatment included mastectomy, excision+RT, and excision alone; from Rakha, Am J Surg Pathol, 2011

Survival of Breast Intracystic/Solid Papillary Carcinoma compared to DCIS

Elavathil, USCAP, 2011

- 34 women with ICP/SPC (compared with 206 women with DCIS)
- Median f/u 73 months
- Among age, size, nuclear grade, necrosis, margin and treatment status, only age showed significant effect on overall survival (HR 5.2, p<0001)
- After adjusting for age, no difference in survival between the two groups

Encapsulated Papillary Carcinoma of the Breast: An Invasive Tumor with Excellent Prognosis


- Reviewed 208 pure EPCs and 30 solid papillary carcinomas
- Absent MEC layer found in majority of PC but not papillary DCIS
- Represent a special type of invasive carcinoma with indolent behavior and extremely favorable prognosis
- Adequately treated with local therapy
Recommendations

Regardless of whether these are truly in situ or invasive lesions, continue to manage as for DCIS

Avoid over-diagnosis as frankly invasive papillary carcinoma!!!

Terminology

Intracystic Papillary Carcinoma
Encysted Papillary Carcinoma

Encapsulated Papillary Carcinoma

Papillary Lesions of the Breast

- Intraductal papilloma
- Papilloma with atypia (atypical papilloma)
- Papilloma with DCIS
- Papillary DCIS
- Encapsulated papillary carcinoma
- Solid papillary carcinoma
Solid Papillary Carcinoma

- Considered to be a variant of DCIS
- Older women (mean age, early 70s)
- Mass, nipple discharge/bleeding
- Grossly well circumscribed
- Single or multiple circumscribed nodules of neoplastic cells, solid pattern
- Delicate to hyalized fibrovascular stromal network
- Endocrine differentiation common ("E-DCIS")
- Intra- and extra-cellular mucin production
- Frequently associated with invasive mucinous ca and IDC
Solid Papillary Carcinoma: No MEC

- No myoepithelial cells at periphery
- Perineural invasion
- Lymph node metastases
- Excellent prognosis with adequate local therapy
- Are at least some low grade invasive carcinomas?
### Papillary Lesions of the Breast

- Implications of papillary lesions on core needle biopsy (papilloma)
- Papilloma with DCIS
- Papillary DCIS
- Encapsulated papillary carcinoma
- Solid papillary carcinoma

### Management Problems

**To Excise or Not to Excise?**

### Intraductal Papilloma on Core Needle Biopsy

**What to Do?**

- Definitive classification of papillary lesions may be difficult in limited material afforded by CNB
- Representative - otherwise benign papillomas may harbor foci of ADH or DCIS
- Limited data available

### Benign Papilloma on CNB with Excision Follow-up

<table>
<thead>
<tr>
<th>Author</th>
<th># with excision f/u</th>
<th>CA on excision</th>
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<tbody>
<tr>
<td>Philpots</td>
<td>6</td>
<td>1 (17%)</td>
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<tr>
<td>Liberman</td>
<td>4</td>
<td>0</td>
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<tr>
<td>Ivan</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Renshaw</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Mercado</td>
<td>36</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Kii (2008)</td>
<td>76</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Bernik (2008)</td>
<td>47</td>
<td>14 (36%)</td>
</tr>
<tr>
<td>Tseng (2008)</td>
<td>24</td>
<td>7 (29%)</td>
</tr>
<tr>
<td>Rizzo (2008)</td>
<td>125</td>
<td>30 (24%)</td>
</tr>
<tr>
<td>Amidayeh (2009)</td>
<td>29</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Rizzo (2012)</td>
<td>234</td>
<td>21 (9%)</td>
</tr>
<tr>
<td>Linda (2012)</td>
<td>64</td>
<td>4 (6%)</td>
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</table>
Intraductal Papilloma on Core Needle Biopsy
What to Do?

- Excise if there is discordance between histologic findings and imaging studies
- ? No need to excise if imaging studies are consistent with dx of benign papilloma
- ? Excise all
- ? Micropapillomas (Lee 2012)

All patients with benign papilloma on CNB require excision

Papillary Lesions of the Breast

- Intraductal papilloma
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- Solid papillary carcinoma

Consequences of core needle biopsy
Consequences, Complications and Artifacts Related to Core Needle Biopsies

- Hemorrhage, granulation tissue, scarring and bx site
- Infarction
- Epidermoid cysts
- The missing cancer
- Epithelial displacement

Consequences, Complications and Artifacts Related to Core Needle Biopsies

- Infarction
Consequences, Complications and Artifacts Related to Core Needle Biopsies

- Epithelial displacement

Epithelial Displacement

- Benign epithelium, ductal carcinoma in situ: stroma or vascular spaces
- Invasive carcinoma: vascular spaces
- ?Displacement/transport of benign epithelium, DCIS or invasive cancer to axillary nodes
Frequency of Displaced Epithelium Following Core Needle Biopsy

<table>
<thead>
<tr>
<th>Study</th>
<th>#cases</th>
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<tbody>
<tr>
<td>Youngson</td>
<td>43</td>
<td>12 (28%)</td>
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<tr>
<td>(1995)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diaz</td>
<td>352</td>
<td>114 (33%)</td>
</tr>
<tr>
<td>(1999)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Displaced Epithelium Following Core Needle Biopsy

- Inversely related to CNB interval
- Increased with papillary lesions
To Avoid Overdiagnosis of Stromal Invasion

- Look for invasion away from biopsy site
- Look for recognized type of invasive cancer
To Avoid Overdiagnosis of Vascular Space Invasion

• Be extremely conservative if there is only DCIS or a benign lesion
• In cases of invasive carcinoma, look for vascular involvement away from biopsy site

Displaced Epithelium Due to Benign Mechanical Transport

• Epithelial cells may reach SLN through benign mechanical transport
• Dermal angiolympathic epithelial aggregates secondary to the same phenomenon in patient with DCIS

(Diaz et al, Hum Pathol 2005)

Displaced Epithelium in Axillary Lymph Nodes

• Theoretically possible
• Associated hemosiderin-laden macrophages and damaged RBCs favor mechanical displacement (Carter, AJCP 2000)

Displaced Epithelium in Axillary Lymph Nodes

• Epithelial cell clusters of < 0.2mm more frequent in SLN of patients undergoing pre-SLN biopsy breast massage (Diaz, Am J Surg Pathol 2004)
• CK positive SLN in which the IHC characteristics differed from the primary tumor (Bleiweiss, J Clin Oncol 2006)
Displaced Epithelium in Axillary Lymph Nodes

- If invasive cancer is present in breast biopsy, neoplastic cells in a node should be considered a metastasis.
- Be more circumspect without demonstrable invasion.
Question 1
Given the low power image provided on the next slide, how is this papillary lesion best classified?

a) Benign intraductal papilloma
b) Atypical papilloma
c) Papillary DCIS
d) Encapsulated papillary carcinoma

The low power impression of a “pink” lesion is conferred by the broad fibrovascular cores and fibrosis often seen in benign papillomas. There is a lack of epithelial proliferation in this lesion too. Of course, examination at high power is required to ensure there is no cytologic atypia, but the low power examination suggests a benign papilloma.

Question 2
Given the single image provided on the next slide, how is this papillary lesion best classified?

a) Benign intraductal papilloma
b) Atypical papilloma
c) Papillary DCIS
d) Encapsulated papillary carcinoma
e) Solid papillary carcinoma
Question 2
2e: Solid papillary carcinoma

This intermediate power image depicts a monotonous proliferation of atypical epithelial cells arranged in circumscribed, solid nests. Within the solid nests a fine network of fibrovascular cores is appreciated. In the top left of the image, there is the suggestion of a second tumor nodule. Taken together, these features are consistent with a diagnosis of solid papillary carcinoma.

Question 3
Which of the following statements about the papillary breast lesion depicted on the next slide is false?

a) It is most common in elderly women
b) It is associated with a high risk of lymph node metastasis
c) It may present with nipple discharge
d) It may be adequately treated with local therapy alone
e) Myoepithelial markers may be of value in arriving at the correct diagnosis
Answer 3: b) It is associated with a high risk of lymph node metastasis is false

This is an example of an encapsulated papillary carcinoma. These lesions typically present in elderly women as a palpable mass and/or with nipple discharge. Contemporary outcome studies indicate that these lesions are rarely associated with lymph node metastases and have an excellent prognosis with adequate local therapy alone. Whether these lesions represent variants of DCIS or circumscribed nodules of low grade invasive carcinoma is a controversial issue.

Question 4

The photograph on the next slide demonstrates an immunostain performed on an encapsulated papillary carcinoma. Which myoepithelial cell marker is depicted in this image?

a) Smooth muscle actin  

b) p63  

c) Smooth muscle myosin heavy chain  

d) Calponin  

e) Cytokeratin 5/6

Answer 4: b) p63

Smooth muscle actin, smooth muscle myosin heavy chain, calponin, cytokeratin 5/6 and p63 are all useful myoepithelial cell markers. The first four stain myoepithelial cell cytoplasm; only p63 stains myoepithelial cell nuclei as shown on the slide from this question. Encapsulated papillary carcinomas have been shown in a number of recent studies to lack a peripheral myoepithelial cell layer.
Question 5
Given the images provided on the next slide, how is this papillary lesion best classified?

a) Benign intraductal papilloma  
b) Atypical papilloma  
c) Papillary DCIS  
d) Encapsulated papillary carcinoma  
e) Solid papillary carcinoma

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Question 5c: Papillary DCIS

The images show multiple ducts with a monotonous appearing papillary proliferation. The presence of cytologic atypia readily identified in the high power image (nuclear atypia, monotonous nuclei, arranged perpendicular to the fibrovascular cores) put this lesion in the "carcinoma" category. An absence of myoepithelial cells along the fibrovascular cores also supports this interpretation. The p63 stain confirms the presence of myoepithelial cells at the periphery of the ducts (and the absence within) enabling classification of this lesion as papillary DCIS.
Summary

Papillary lesions of the breast may be benign, atypical, in situ or invasive
And perhaps even somewhere in between!

Papillary lesions on core needle biopsy need excision

Important to communicate with our clinical colleagues the nature of the lesion excised; in particular whether myoepithelial cells are present or absent at the periphery of circumscribed nests of papillary carcinoma