Papillary Lesions of the Breast
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Papillary Lesions of the Breast

- Intraductal papilloma
- Papilloma with atypia (atypical papilloma)
- Papilloma with DCIS
- Papillary DCIS
- Encapsulated papillary carcinoma
- Solid papillary carcinoma
Papillary Lesions of the Breast

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Newer insights into encapsulated and solid papillary carcinomas

Implications of papillary lesions on core needle biopsy

Papillary Lesions of the Breast

The importance of myoepithelial cells and myoepithelial cell immunohistochemical markers in assessment of papillary lesions

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)
### Diagnostic Criteria for Papillary Lesions
adapted from Kraus and Neubecker, 1962

<table>
<thead>
<tr>
<th>Papilloma</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell types</strong></td>
<td>Epithelial and myoepithelial</td>
</tr>
<tr>
<td><strong>Cell orientation</strong></td>
<td>Haphazard</td>
</tr>
<tr>
<td><strong>Nuclei</strong></td>
<td>Normochromatic</td>
</tr>
<tr>
<td><strong>Stroma of papillae</strong></td>
<td>Prominent; fibrosis with epithelial entrapment</td>
</tr>
<tr>
<td><strong>Apocrine metaplasia</strong></td>
<td>Present</td>
</tr>
<tr>
<td><strong>Proliferation in adjacent ducts</strong></td>
<td>Hyperplasia</td>
</tr>
</tbody>
</table>

![Image of papillary lesion](image1)

![Image of papillary lesion](image2)

![Image of papillary lesion](image3)
Atypical Papillary Lesions

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

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
- Tavassoli: Proportion
  Atypical area > 1/3
- Elston, Ellis & Pinder: Qualitative
  "Overt features of malignancy, no matter what the proportion"

DCIS engrafted on pre-existing benign papilloma
The combination of an absence of CK5/6 staining and the presence of strong, diffuse ER staining is helpful in defining extent of atypia.
Cytokeratin 5 and Estrogen Receptor Immunohistochemistry as a Useful Adjunct in Identifying Atypical Papillary Lesions on Breast Needle Core Biopsy


- 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

Can additional immunohistochemistry staining replace the surgical excision for the diagnosis of papillary breast lesions classified as benign on 14-gage core needle biopsy?

Br Cancer Res Treat, 2013
### 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><strong>Cell types</strong></td>
<td>Epithelial and myoepithelial</td>
<td>Epithelial; myoepithelial cells absent or scant</td>
</tr>
<tr>
<td><strong>Cell orientation</strong></td>
<td>Haphazard</td>
<td>Uniform, perpendicular to fibrovascular stalks</td>
</tr>
<tr>
<td><strong>Nuclei</strong></td>
<td>Normochromatic</td>
<td>Hyperchromatic</td>
</tr>
<tr>
<td><strong>Stroma of papillae</strong></td>
<td>Prominent; fibrosis with epithelial entrapment</td>
<td>Delicate</td>
</tr>
<tr>
<td><strong>Apocrine metaplasia</strong></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Proliferation in adjacent ducts</strong></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

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
Immunohistochemistry for Myoepithelial Cells to Distinguish In Situ from Invasive Carcinomas

- Invasive Cancer
- No Myoepithelial Cells
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

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

Hill and Yeh, AJSP 2005
Collins et al, AJSP 2006
Esposito, AJCP 2009
Wynveen, AJSP 2010
Rakha AJSP 2011
Does the absence of a MEC layer define a lesion as being invasive rather than in situ?

What about the basement membrane?

Are Encapsulated Papillary Carcinomas of the Breast In Situ or Invasive?
A Basement Membrane Study of 27 Cases
Nicole Nicooro Esposti, MD, David J. Dehbi, MD, and Robert Buganza, MD

Intracystic Papillary Carcinoma of the Breast: An In Situ or Invasive Tumor? Results of Immunohistochemical Analysis and Clinical Follow-up
Christine A. Warren, MD,* Tatsuo Aoki-Ishibashi, BSc,* Martin A. Alron, MA, MS,* Mohammed Hazam, BSc,* Larry Norton, MD,* Kimberly L. Van Zeve, MS, MD,* and Edi Bregy, MD, PhD*

Am J Surg Pathol, 2010
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

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

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

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>
</thead>
<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>
</tr>
</tbody>
</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<0.0001)
- 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

Hill and Yeh, Am J Clin Pathol, 2005

Circumscribed Nodule of Papillary Carcinoma
No MEC Within or at Periphery
Encapsulated Papillary Carcinoma

Staging of EPCs is controversial

“In the absence of conventional invasive carcinoma, the consensus of the WHO Working Group was that EPCs should be staged and managed as Tis disease”

WHO, 2012
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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 hyalinized 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**  
In situ or Invasive Lesions?

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

"When there is doubt about the presence of invasion, solid papillary carcinomas should be regarded for staging purposes as a form of in situ carcinoma"

WHO, 2012

**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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philpots</td>
<td>6</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Liberman</td>
<td>4</td>
<td>0</td>
</tr>
<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>Kil</td>
<td>76</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Bernik</td>
<td>47</td>
<td>14 (36%)</td>
</tr>
<tr>
<td>Tseung</td>
<td>24</td>
<td>7 (29%)</td>
</tr>
<tr>
<td>Rizzo (2012)</td>
<td>234</td>
<td>31 (13%)</td>
</tr>
<tr>
<td>Linda (2012)</td>
<td>64</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Lu (2012)</td>
<td>66</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Fu (2012)</td>
<td>203</td>
<td>34 (17%)</td>
</tr>
<tr>
<td>Li (2012)</td>
<td>370</td>
<td>7 (2%)</td>
</tr>
</tbody>
</table>

Nonmalignant Breast Papillary Lesions at Core-Needle Biopsy: A Meta-analysis of Underestimation and Influencing Factors

Xin Wen, MD and Wen Cheng, PhD

- 34 studies
- 2,236 non malignant papillary lesions
- 346 upgraded to malignant
- Pooled underestimation rate of 15.7%
- Rate for benign papillomas =7.0% (5.6-8.3%)
- Rate for atypical papillomas =36.9% (29.5-44.3%)

Ann Surg Oncol 2013
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)

Micropapillomas

Microscopic Incidental Intraductal Papillomas on CNB

- What to do about micropapillomas?
- Lee AJR 2012
  - 17 microscopic papillomas
  - Could not determine if incidental or associated with imaging target
  - No upgrades to malignancy
- BIDMC experience
  - 10% of papillomas (12/121) on CNB represent incidental findings
  - 50% underwent excision with no upgrades to malignancy
All patients with benign papilloma on CNB require excision

Core Needle Biopsy Diagnoses for Atypical Papillary Lesions
• Atypical papillary lesion; excision recommended
• Papillary carcinoma, at least in situ; final categorization deferred to excision

Papillary Lesions of the Breast
• Implications and consequences of papillary lesions on core needle biopsy
• Papillary DCIS
• Encapsulated papillary carcinoma
• Solid papillary carcinoma
Consequences, Complications and Artifacts Related to Core Needle Biopsies

- Hemorrhage, granulation tissue, scarring and bx site
- Infarction
- Epidermoid cysts
- The missing cancer
- 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>
<th>Displaced epith.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youngson (1995)</td>
<td>43</td>
<td>12 (28%)</td>
</tr>
<tr>
<td>Diaz (1999)</td>
<td>352</td>
<td>114 (33%)</td>
</tr>
</tbody>
</table>
Displaced Epithelium Following Core Needle Biopsy

- Inversely related to CNB interval
- Increased with papillary lesions

Diaz, 1999; Nagi, 2005; Phelan, 2007

Displaced Epithelium Due to Benign Mechanical Transport

- Epithelial cells may reach SLN through benign mechanical transport
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

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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 (beware of consequences of CNB in papillary lesions)

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