Practical Approach to Papillary Breast Lesions

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Overview of papillary lesions
- Benign intraductal papilloma vs papillary carcinoma
- Intraductal papilloma with atypia (ADH vs DCIS)
- Encapsulated (intracystic) papillary carcinoma
- Solid papillary carcinoma

Definition of papillary growth
- Branching fibrovascular skeleton lined by ductal epithelium
- Epithelium: benign or malignant

Intraductal Papillary Lesions
(Chapter 7; WHO 2012)

- Intraductal papilloma
  - with various benign alterations
  - with ADH involving papilloma (atypical papilloma)
  - with DCIS involving papilloma (DCIS arising in a papilloma)
- Intraductal papillary carcinoma (Papillary DCIS)
- Encapsulated (intracystic) papillary carcinoma
- Solid papillary carcinoma
Outline of Talk

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Papillary Intraductal Patterns

Papillary Carcinoma
(Papillary DCIS & Encapsulated papillary CA)

versus

Intraductal papilloma
Intraductal papilloma
Papilloma: Myoepithelial Markers

- Actin
- SMM
- p63
Myoepithelial markers, CK5/6 and ER--

IHC markers useful in distinguishing papilloma from papillary carcinoma

Papilloma vs Papillary carcinoma

Benign papilloma retains a continuous layer of ME cells along the fibrovascular cores
Papillary carcinoma lacks ME cells along the fibrovascular cores

Papilloma with UDH: CK5/6 +
CK5/6 negative
ER diffuse and strong

Papillary carcinoma: CK5/6 -

Benign Papilloma--
CK5/6 positive
ER patchy and variable
Pitfalls in Interpretation of MEC Markers

- SMM/calp: stain pericytes/myofibroblasts, mimic ME cells
- p63: may stain cancer cells, mimic ME cells
- CK5/6: does not stain pericytes/myofibroblasts or cancer cells, but not a consistent MEC marker
Pitfalls in Interpretation of MEC Markers

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Histologic features helpful in distinguishing benign papilloma from papillary carcinoma in situ

<table>
<thead>
<tr>
<th></th>
<th>Benign papilloma</th>
<th>Papillary DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue stroma</td>
<td>Prominent, variable fibrosis</td>
<td>Thin/delicate</td>
</tr>
<tr>
<td>Cell types</td>
<td>Epithelial and myoepithelial cells</td>
<td>Epithelial cells</td>
</tr>
<tr>
<td>Cytologic features</td>
<td>Heterogeneous population, normochromatic</td>
<td>Monotonous population, hyperchromatic</td>
</tr>
<tr>
<td>Cell organization</td>
<td>Haphazard (as in UDH)</td>
<td>Regular architecture: cribriform, rigid bar, solid, micropapillary (as in DCIS)</td>
</tr>
<tr>
<td>Apocrine metaplasia</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Adjacent ducts</td>
<td>Usual ductal hyperplasia</td>
<td>DCIS</td>
</tr>
</tbody>
</table>

(Adapted from Kraus and Neubecker, Cancer 1962;15:444-455)

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Papilloma with “Atypia”
Epithelial Proliferation in a Papilloma

- Benign (UDH) vs atypical

- Same criteria as in non-papillary lesions
  - UDH: heterogeneous cells, irregular architecture
  - Atypical: monomorphic cells, rigid architecture

- Adjunct IHC markers
  - UDH: strong/mosaic CK5/6, patchy ER
  - Atypical: negative CK5/6, diffuse ER

“Papilloma with Atypia”
Where to draw the line: How much is enough for DCIS?

- Page et al: Size
  Atypical area > 3mm  
  \((\text{Cancer} 1996;78:258)\)

- Tavassoli: Proportion
  Atypical area > 1/3  
  \((\text{Pathol of the Breast 2nd Ed,1999})\)

- Elston, Ellis & Pinder: Qualitative
  “Overt features of malignancy, no matter what the proportion”  
  \((\text{The Breast, 1998})\)

Papilloma with Atypia
Where to draw the line?

- ADH vs. DCIS cutoff >3mm

- Risk of subsequent breast CA:
  - Increased vs. papillomas without atypia (RR ~7.5x)

- Unlike ADH in parenchyma:
  - Ipsilateral and same site as original papilloma

- Risk between ADH in parenchyma and LG DCIS

\((\text{Cancer} 1996;78:258)\)
“Papilloma with Atypia”
Where to draw the line: How much is enough for DCIS?

- **Elston, Ellis & Pinder: Qualitative**
  “Overt features of malignancy, no matter what the proportion”  
  *(The Breast, 1998)*

- **Ellis: Qualitative**
  “ADH...less than 2 -3 mm. Larger foci are accepted if associated with ......a papilloma”  
  *(Modern Pathol, 2010)*

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**Papilloma with Atypia**
ADH vs. DCIS: WHO 2012

- **Size: Page et al.**
  Atypical area > 3mm

- **Proportion: Tavassoli**
  Atypical area > 1/3

- **Qualitative: Elston, Ellis & Pinder**
  “Overt features of malignancy, no matter what the proportion”

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**Papilloma with Atypia**
ADH vs. DCIS: WHO 2012

- **Size: Page et al.**
  Atypical area > 3mm

- **WHO disclaimer**
  “It is acknowledged that this is a pragmatic guideline and that scientific evidence for this size criterion to diagnose LG DCIS is lacking”
Papilloma with Atypia

Caution

- Only for ADH vs LG DCIS
- Not for intermediate or high grade DCIS (any amount is diagnostic)

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Intracystic Papillary Carcinoma of the Breast

After Mastectomy, Radiotherapy or Excisional Biopsy Alone

- Single cystic space/duct
- Often central
- Well circumscribed
- Fibrous capsule

Encapsulated/intracystic papillary carcinoma
Encapsulated/intracystic papillary carcinoma

- Single cystic space/duct
- Often central
- Well circumscribed
- Fibrous capsule
- Older women (average 65 yrs)
- Indolent behavior
- Traditionally = variant of DCIS

But...

Myoepithelial Cell Staining Patterns of Papillary Breast Lesions

From Intraductal Papillomas to Invasive Papillary Carcinomas

Cleri, B. P., Hill, M., and L. Tien Yeh, M.

AJCP 2005;123:36

Intracystic Papillary Carcinomas of the Breast: A Reevaluation Using a Panel of Myoepithelial Cell Markers


AJSP 2006;30:1002
Is encapsulated/intracystic papillary CA invasive?

Compressed Myoepithelium

Invaded Past Myoepithelium

? In-situ

Invasive

Controversial!

Encapsulated PC showing skeletal muscle invasion--
(h/o intracystic papillary ca, s/p mastectomy, chest wall nodule)

Encapsulated papillary ca metastatic to axillary LN

Encapsulated papillary ca in breast

Encapsulated papillary ca in breast

Encapsulated papillary ca metastatic to axillary lymph node
Although lymph node or even systemic metastasis can occur in patients with EPC, this is a very rare event!

Encapsulated Papillary CA Behavior

Regardless of whether these are in situ or invasive cancers, clinical outcome is excellent with adequate local therapy alone (akin to DCIS)

Encapsulated Papillary CA
11 Studies, 231 Patients
Mastectomy, Excision alone or with RT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Recurrence</td>
<td>2</td>
</tr>
<tr>
<td>Positive Axillary LN</td>
<td>1</td>
</tr>
<tr>
<td>Distant Metastases</td>
<td>1</td>
</tr>
<tr>
<td>Died of Disease</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted from Rakha, et al. Am J Surg Pathol 2011;35:1093 (Table 2)

Intracystic Papillary Carcinoma
A Review of 917 Cases
--California Cancer Registry --1988-2005

917 cases: 427 “CIS” 490 “Invasive”

Relative cumulative survival (specific)

<table>
<thead>
<tr>
<th>Intracystic Pap</th>
<th>Invasive Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yr 97.3%</td>
<td>83.2%</td>
</tr>
<tr>
<td>10 yr 95.6%*</td>
<td>74.6%</td>
</tr>
</tbody>
</table>
* CIS 96.8%, Invasive 94.4% (p = n.s.)

Encapsulated Papillary Carcinoma of the Breast: An Invasive Tumor With Excellent Prognosis
Emad A. Rakha, PhD, FRCPath,* cows, A.M.a, M.S. a, FRCPath, b, FRCPath, c, FRCPath, d, FRCPath, e, FRCPath, f, FRCPath, g, FRCPath, h
Carolyn H.M. van Dorenzen, PhD, S.0. A.M. Holmer, FRCPath, I, Louis Dunk, FRCPath, j
Andrew H.S. Lee, FRCPath, k, Douglas Macmillan, FRCPath, l, and Ian O. Ellis, FRCPath, m

- 208 encapsulated, 30 solid papillary
- 339 cases from review of literature
- Most lack myoepithelial layer → special type of invasive carcinoma:
  - Infrequent lymph node mets (~3%), infrequent local or distant recurrence
  - Indolent behavior, “extremely favorable prognosis”
- Local therapy adequate, no chemotherapy

Encapsulated Papillary CA
(WHO 2012, AJCC 7th Ed)

- Continue to manage as for DCIS
- Avoid over-diagnosis as frankly invasive papillary carcinoma
- Stage as pTis
- If associated with conventional invasive CA, staged by size of definite invasive CA
Evaluation of “invasion” in EPC

- Challenging
- Atypical glands or tumor nests beyond the capsule
- Typically IDC, nos

Encapsulated papillary ca with adjacent IDC

- Recognized pattern of invasive ca
- Invades beyond the fibrous capsule of EPC into adjacent stroma
When encapsulated PC associated with conventional invasive ca

Dx:
1. IDC, 0.7 cm; see comment
2. Encapsulated papillary ca, 2.1 cm
3. pT1b

➢ Tumor type and stage based on nonpapillary invasive component
➢ Report: associated with EPC, size, for clinical and imaging correlation

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➢ Solid papillary carcinoma

Solid Papillary Carcinoma

➢ Older women (average 70 yrs)
➢ Circumscribed nodule(s) of papillary carcinoma with a solid growth pattern and fine fibrovascular cores
➢ Special histologic and IHC features
➢ Traditionally, DCIS variant (in spectrum with endocrine or spindle cell DCIS)
➢ Associated invasion, often mucinous/endocrine features
➢ DDx: florid UDH in papilloma

Cross et al. Histopathology 1985;9:21
Maluf & Koerner. AJSP 1995;19:1237
Tsang & Chan. AJSP 1996;20:921
Nassar et al. AJSP 2006;30:501

Solid papillary carcinoma

➢ Predominantly solid growth pattern, subtle fibrovascular cores
➢ May not appear papillary at low power
**Solid papillary carcinoma**
- Papillary carcinoma with a solid growth pattern
- Well-circumscribed
- May be single or multiple nodules

**Histologic features of solid papillary carcinoma**
- Plasmacytoid cells
- Spindle cells

**Histologic features of solid papillary carcinoma**
- Mucinous features: extra and intracellular mucin

**Histologic features of solid papillary carcinoma**
- Pseudo-rosette around cores
- Neuroendocrine differentiation
- Chromogranin stain
Solid papillary carcinoma--
Spindle cells & streaming can mimic florid UDH in papilloma

Papilloma with UDH   vs   Solid papillary carcinoma

Papilloma with UDH   vs   Solid papillary DCIS
Papilloma with UDH--
- Heterogeneous, overlapping nuclei
- CK5/6 positive (mosaic)
- Patchy ER
- NE markers negative

Solid papillary ca--
- Monotonous; maybe spindle cells, plasmacytoid
- CK5/6 negative (residual non-neoplastic cells +)
- Diffuse/strong ER
- NE markers positive

Solid papillary carcinoma--
Invasive or in situ disease?

Heterogeneous group--
Myoepithelium may be present or absent in solid papillary carcinoma
Solid papillary ca: single nodule, no peripheral ME cells

In situ or invasive disease?

Solid papillary ca: multiple, geographic/jig-saw puzzle pattern

SPC--
- Multiple nodules
- Geographic/jig-saw puzzle pattern
- Negative MEC

Invasive SPC?

SPC showing LN metastasis

<table>
<thead>
<tr>
<th></th>
<th>SPC only (n = 19)</th>
<th>SPC + invasion (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LN metastasis</td>
<td>0% (0/12)</td>
<td>20% (6/30)</td>
</tr>
<tr>
<td>Local Recurrence</td>
<td>0% (0/18)</td>
<td>18% (5/28)</td>
</tr>
<tr>
<td>Die of disease</td>
<td>0% (0/18)</td>
<td>18% (5/28)</td>
</tr>
</tbody>
</table>

*mean follow-up 9.4 yrs

SPC have an indolent behavior


- 30 pure solid papillary CA:
  - No distant mets or death
  - 2 LN micromets (both had susp foci for mucinous CA)
  - 1 local recurrence as DCIS

- Outcome similar to pure encapsulated PC
- Characterized by indolent behavior and extremely favorable prognosis
- “Adequately treated with local therapy”
Solid Papillary Carcinoma--
WHO 2012

- When there is doubt about the presence of invasion, SPC should be regarded for staging purposes as a form of in situ carcinoma (Tis)
- Staged by size of definite invasive CA
- Presence of geographic jigsaw pattern with more ragged and irregular margins coupled with absence of myoepithelial cells may be considered by some authors as invasive disease

Molecular Profile of EPC and SPC

- Expression pattern of invasion-associated biomarkers: intermediate between DCIS and invasive cancer
- Luminal phenotype (ER/PR+, HER2-, basal CK-, EGFR-)
- High prevalence of PIK3CA mutation & low rate of p53 expression
- Similar genomic profile but less aberrations than grade- and ER-matched IDC of no special type

May explain the clinically indolent behavior


IHC for Papillary Lesions

<table>
<thead>
<tr>
<th>Category</th>
<th>MEC markers* around space</th>
<th>MEC markers* along stalks</th>
<th>CK5/6</th>
<th>ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papilloma + UDH</td>
<td>Positive</td>
<td>Positive (continuous)</td>
<td>Positive (mosaic)</td>
<td>Variably positive</td>
</tr>
<tr>
<td>Papilloma + ADH/DCIS</td>
<td>Positive</td>
<td>Patchy to negative in ADH/DCIS</td>
<td>Negative in ADH/DCIS</td>
<td>Uniformly positive in ADH/DCIS</td>
</tr>
<tr>
<td>Papillary DCIS</td>
<td>Positive (attenuated)</td>
<td>Negative</td>
<td>Negative</td>
<td>Uniformly positive</td>
</tr>
<tr>
<td>Encapsulated papillary ca</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Uniformly positive</td>
</tr>
<tr>
<td>Solid papillary ca</td>
<td>Positive or negative</td>
<td>Negative to patchy</td>
<td>Negative</td>
<td>Uniformly positive</td>
</tr>
</tbody>
</table>

*MEC (myoepithelial cell) markers: p63, SMM

Thank you!